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47 Antiviral Drugs Against Hepatitis Viruses

Jules L. Dienstag

SHORT VIEW SUMMARY

ANTIVIRALS FOR HEPATITIS B (SEE TABLE 47.1)

Pegylated ([Polyethylene Glycol]; PEG) Interferon (IFN)- α2a (Has Largely Supplanted IFN-α2b)

- PEG IFN-α2a is administered subcutaneously, with hepatitis B e antigen (HBeAg) seroconversion in 32% of patients.
- Toxicities include flulike symptoms, cytopenia, emotional lability, and autoimmune events.
- Included in treatment guidelines as first-line therapy, but its use pales in comparison to that of the first-line oral agents.

Lamivudine (Epivir)

- Orally administered and well tolerated but has a low barrier to resistance
- Supplanted by entecavir

Adefovir (Hepsera)

- Orally administered at low doses (10 mg/day) to avoid nephrotoxicity
- Less potent and slower activity than other anti–hepatitis B virus (HBV) drugs
- Supplanted by tenofovir

Entecavir (Baraclude)

- Orally administered and well tolerated
- High barrier to resi:stance
- Currently, first-line therapy for hepatitis B

Telbivudine (Tyzeka)

- Orally administered and generally well tolerated
- Elevated creatine phosphokinase, myopathy, and peripheral neuropathy can occur
- Frequent development of resistance and toxicities limit its use; now discontinued

Tenofovir Disoproxil Fumarate (TDF) (Truvada)

- Orally administered, 300 mg
- Can cause nephrotoxicity and reduced bone density, but rarely encountered in hepatitis B studies
- Active against human immunodeficiency virus and HBV
- High potency and high barrier to resistance against HBV
- Currently, first-line therapy for hepatitis B

Tenofovir Alafenamide (TAF) (Vemlidy)

- Orally administered, 25 mg, prodrug of tenofovir, activated in target organ (liver), >90% reduction in systemic exposure
- Reduced nephrotoxicity and bone density decline
- Active against human immunodeficiency virus and HBV
- High potency and high barrier to resistance against HBV
- Currently, first-line therapy for hepatitis B in patients with evidence for proximal tubular injury, with reduced bone density, with risk of renal disease, and with age older than 60 years (per the European Association for the Study of the Liver [EASL])

ANTIVIRALS FOR HEPATITIS C (SEE TABLE 47.1)

- The availability of highly potent, well-tolerated, orally administered, direct-acting antivirals (DAAs) has supplanted the use of PEG IFN and first-generation protease inhibitors for treatment of hepatitis C. The September 2017 treatment recommendations by the Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) are presented in Chapter 117.

PEG IFN-α2a or PEG IFN-α2b Plus Ribavirin

- Initial treatments historically; now supplanted by other drugs
- Was still recommended with first-generation protease inhibitors and with sofosbuvir (SOF) and ribavirin (RBV) until supplanted by pangenotypic DAA combinations

Boceprevir (Victrelis)

- First-generation inhibitor of hepatitis C virus (HCV) nonstructural 3 (NS3) protease (supplanted by other drugs, discontinued December 2015)
- Most active against HCV genotype 1; limited activity against and not approved for genotypes 2 and 3
- Orally administered with food and metabolized by cytochrome P3A4 (CYP3A4) system, resulting in multiple drug-drug interactions
- Main toxicity from bone marrow suppression additive to PEG IFN/RBV

Telaprevir (Incivek)

- First-generation inhibitor of NS3/NS4A protease (supplanted by other drugs, discontinued October 2014)
- Active against HCV genotype 1; limited activity against and not approved for genotypes 2 and 3
- Orally administered with fatty meal; metabolized by CYP3A4 system, resulting in multiple drug-drug interactions
- Toxicities primarily are anemia, rash, and rectal burning.

Simeprevir (Olysio)

- Inhibitor of NS3/NS4A protease
- Active against HCV genotype 1
- Orally administered once daily with food; metabolized by CYP3A4 system
- Toxicities primarily rash, hyperbilirubinemia
- Supplanted by improved, pangenotypic DAA combinations but still considered an alternative combination regimen along with SOF for genotype 1; should not be used as monotherapy because of emergence of resistance
- In patients with HCV genotype 1a, requires testing for Q80K polymorphism, which is predictive of nonresponse

Sofosbuvir (Sovaldi)

- Nucleoside inhibitor of NS5B polymerase
- Active against HCV genotypes 1 to 6
- Orally administered once daily with or without food; metabolized in the liver to form the active uridine triphosphate
- Negligible toxicity
- Sofosbuvir is a component for recommended DAA regimens as part of combination therapy with simeprevir or daclatasvir and as first-line treatment in combination with ledipasvir, velpatasvir (VEL), and VEL/voxilaprevir (VOX) (see later).

Ledipasvir/Sofosbuvir (Harvoni)

- Fixed-dose combination of ledipasvir (NS5A inhibitor) and SOF (NS5B inhibitor)
- Recommended as first-line regimen for treatment of genotypes 1 and 4 to 6
- Orally administered once daily with or without food
- Well tolerated with very mild side effects of fatigue, headache, nausea, diarrhea, and vomiting
- High rates of sustained virologic response (SVR) in treatment of naïve and experienced patients, both with and without cirrhosis
- Approved in patients with decompensated cirrhosis (genotypes 1 and 4), not for patients with advanced renal insufficiency

Paritaprevir/Ritonavir/Ombitasvir Plus Dasabuvir (Viekira Pak) and Paritaprevir/Ritonavir/Ombitasvir Without Dasabuvir (Technivie)

- Viekira Pak is a fixed-dose combination of paritaprevir (NS3/4A protease inhibitor), ritonavir (pharmacokinetics booster), ombitasvir (NS5A inhibitor), and dasabuvir

SHORT VIEW SUMMARY—cont'd

(nonnucleoside inhibitor of NS5B). Available without dasabuvir (Technivie).
- Was recommended for treatment of genotypes 1a and 1b but is no longer a recommended first-line treatment.
- Technivie (does not include dasabuvir) plus RBV recommended for treatment of genotype 4 but is no longer a recommended first-line treatment.
- Paritaprevir/ritonavir/ombitasvir is given orally once daily, and dasabuvir is given orally twice daily; RBV is given orally twice daily, with or without food.
- Well tolerated but commonly associated with mild nausea, pruritus, insomnia, and asthenia. As with all DAAs that include a protease inhibitor, hepatic decompensation and failure have been reported with both Viekira Pak and Technivie; they should not be used in patients with decompensated cirrhosis.
- Paritaprevir and ritonavir are metabolized by the CYP3A system, resulting in multiple drug-drug interactions. High rates of SVR in treatment of naïve and experienced patients both with or without cirrhosis.

Elbasvir/Grazoprevir (Zepatier)
- Fixed-dose combination of elbasvir, an NS5A inhibitor, and grazoprevir, an NS3/4A protease inhibitor
- Approved and recommended as first-line treatment of genotypes 1 and 4 infection
- Administered orally once daily with or without food
- No dosage adjustments required for renal insufficiency or mild hepatic impairment
- Elbasvir and grazoprevir are substrates of CYP3A, and drug-drug interactions should be considered
- Generally well tolerated, and most common adverse events were fatigue, headache, and nausea
- Highly effective in treatment of genotypes 1 and 4 in treatment-naïve and treatment-experienced patients, with and without cirrhosis
- A preferred regimen in patients with advanced renal insufficiency but cannot be used in decompensated cirrhosis

Daclatasvir (Daklinza)
- Daclatasvir is an inhibitor of HCV NS5A used in combination with SOF.
- Approved for treatment of genotypes 1 and 3 infection and also recommended by AASLD/IDSA for genotype 4 (see Table 47.1). In treatment-naïve and treatment-experienced patients, daclatasvir is no longer approved as a first-line treatment, except in patients with decompensated cirrhosis (genotypes 1–4) and after liver transplantation (genotypes 2 and 3).
- Standard dose is oral administration of one tablet with or without food plus SOF. RBV may be added for decompensated cirrhosis with genotypes 1 to 4 and after liver (genotypes 1–6) or kidney transplantation (genotypes 2, 3, 5, and 6).
- Dosage does not need to be adjusted for renal or hepatic impairment (because daclatasvir is taken along with SOF, the combination cannot be used in patients with severe renal impairment [creatinine clearance < 30 mL/min]).
- Daclatasvir is a substrate for CYP3A and is a moderate inhibitor of organic anion-transporting polypeptide 1B1 (OATP1B1) and OATP1B3. Drug-drug interactions need to be considered.
- Daclatasvir is generally well tolerated. When administered with SOF, most common adverse events were fatigue, headache, nausea, and diarrhea.
- Highly effective in treatment of genotypes 1 to 3 infection. Also recommended for genotype 4. Somewhat less effective in patients with advanced liver disease; recommended as first-line treatment (genotypes 1–4) in combination with SOF and RBV for 12 weeks in patients with decompensated cirrhosis or for 24 weeks without RBV.

Velpatasvir/Sofosbuvir (Epclusa)
- Fixed-dose combination of ledipasvir (NS5A inhibitor) and SOF (NS5B inhibitor)
- Pangenotypic DAA recommended as first-line treatment of genotypes 1 to 6
- Orally administered once daily with or without food
- Well tolerated with very mild side effects of headache, fatigue, nausea, asthenia, and insomnia
- High rates of SVR in treatment of naïve and experienced patients, both with and without cirrhosis
- Recommended in patients with decompensated cirrhosis (genotypes 1–4 and 6), not for patients with advanced renal insufficiency

Glecaprevir/Pibrentasvir (Mavyret)
- Fixed-dose combination of glecaprevir, a high-potency, pangenotypic protease inhibitor and the HCV NS5A inhibitor pibrentasvir.
- Pangenotypic DAA recommended for treatment of genotypes 1 to 6
- Well tolerated with very mild side effects of headache, fatigue, diarrhea, and nausea
- High rates of SVR in treatment of naïve and experienced patients, both with and without cirrhosis
- Like DAA combinations containing a protease inhibitor, this combination is not recommended in patients with decompensated cirrhosis
- A preferred regimen in patients with advanced renal insufficiency

Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi)
- Fixed-dose combination of ledipasvir (NS5A inhibitor), SOF (NS5B inhibitor), and VOX (protease inhibitor)
- Recommended for retreatment in treatment-experienced patients with genotypes 1 and 3 to 6 and for treatment-naïve cirrhotic patients with genotype 3
- Orally administered once daily with food
- Well tolerated with very mild side effects of fatigue, headache, nausea, and diarrhea
- High rates of SVR in treatment of naïve and experienced patients, both with and without cirrhosis
- Not recommended in patients with decompensated cirrhosis, nor for patients with advanced renal insufficiency

Antiviral drugs for viral hepatitis are reviewed in this chapter and in Chapter 117.

HEPATITIS B

Overview

The first antiviral agent applied to the treatment of chronic hepatitis B was interferon-α (IFN-α), supplanted eventually by pegylated (polyethylene glycol) interferon (PEG IFN; see Chapters 117 and 145). Although IFNs have immunomodulatory properties, data to support a direct immunologic effect of IFN in its antiviral efficacy against hepatitis B virus (HBV) are lacking. Instead, the effect of IFN in HBV infection may be mediated by direct virus inhibition, for instance, by such factors as protean interference at multiple points in the viral life cycle; by stimulation of the IFN signal-transduction pathway, culminating in antiviral activity; and by overcoming the effect of viral infection on suppression of IFN-stimulated genes. IFN therapy, although free of antiviral drug resistance, requires frequent subcutaneous injections and intensive clinical and laboratory monitoring, and tolerability is limited by adverse side effects, including sometimes disabling flulike symptoms, marrow suppression, emotional/psychiatric responses, autoimmune disorders, and a variety of miscellaneous reactions. Currently, potent (micromolar to nanomolar effective concentration for 50% of isolates [EC_{50}], with a high therapeutic index), well tolerated, direct-acting oral nucleoside/nucleotide analogues that inhibit HBV DNA polymerase are the dominant agents used to treat chronic hepatitis B; the most successful have been agents with high genetic barriers to resistance (Table 47.1). These nucleoside analogues require metabolic activation within the cell by phosphorylation (to a nucleoside analogue triphosphate or nucleotide analogue diphosphate). To date, efforts to develop antivirals that target other events in the HBV life cycle remain embryonic.

In chronic hepatitis B, oral antiviral agents can suppress viral replication by up to approximately 4 to 7 $\log_{10}$, which, in turn, translates to immediate biochemical (return to normal of aminotransferase activity), histologic (improvement in grade of necroinflammatory activity and

TABLE 47.1 Antiviral Agents of Established Therapeutic Effectiveness in Hepatitis B and C

DRUG	ROUTE	USUAL ADULT DOSAGE
Chronic Hepatitis B		
IFN-α2b	SC/IM	5 MU/day or 10 MU 3 times weekly for 16 wk
PEG IFN-α2a	SC	180 μg weekly for 48 wk
Lamivudine[a]	PO	100 mg/day
Adefovir	PO	10 mg/day
Entecavir	PO	0.5 mg/day (1.0 mg if lamivudine resistant)
Telbivudine	PO	600 mg/day
Tenofovir disoproxil fumarate (TDF)	PO	300 mg/day
Tenofovir alafenamide (TAF)	PO	25 mg/day
Chronic Hepatitis C[b]		
PEG IFN-α2a *or*	SC	180 μg weekly for 48 wk
PEG IFN-α2b *plus* RBV	SC PO	1.5 μg/kg weekly for 48 wk 800–1400 mg/day, depending on weight and genotype
Boceprevir	PO	800 mg tid (with meals) with PEG IFN plus RBV for up to 44 wk after 4 wk of lead-in therapy with PEG IFN plus RBV (no longer recommended for therapy; see text)
Telaprevir	PO	750 mg tid (with fatty meal) with PEG IFN plus RBV for 12 wk, followed by another 12–36 wk of PEG IFN plus RBV (no longer recommended for therapy; see text)
Simeprevir	PO	150 mg once daily with sofosbuvir ([SOF], 400 mg). Supplanted by improved, pangenotypic DAA combinations but still considered an alternative combination regimen along with SOF for genotype 1; should not be used as monotherapy because of emergence of resistance
Sofosbuvir	PO	400 mg plus simeprevir (150 mg) once daily. SOF is a component for recommended DAA regimens as part of combination therapy with simeprevir or daclatasvir and as first-line treatment in combination with ledipasvir, velpatasvir (VEL), and VEL/voxilaprevir (VOX) (see later).
Ledipasvir/sofosbuvir	PO	Ledipasvir (90 mg)/SOF (400 mg) daily for 12 wk for genotypes 1, 4, 5, and 6
Paritaprevir/ritonavir/ombitasvir and dasabuvir[b]	PO	Paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) once daily and dasabuvir (250 mg) twice daily or 12 wk for genotypes 1a with RBV, 1b without RBV (compensated cirrhotic patients with genotype 1a require 24 wk plus RBV). Genotype 4 is treated without dasabuvir (Technivie) without cirrhosis or with compensated cirrhosis Supplanted as first-line agents and are considered alternative regimens
Elbasvir/grazoprevir	PO	Elbasvir (50 mg) combined with grazoprevir (100 mg) for 12 wk for genotypes 1 and 4 without cirrhosis or with compensated cirrhosis
Daclatasvir	PO	60 mg plus SOF (400 mg) for 12 wk Approved for treatment of genotypes 1 and 3 and also recommended for genotype 4 No longer approved as a first-line treatment, except in patients with decompensated cirrhosis (genotypes 1–4) and after liver transplantation (genotypes 2 and 3)
Velpatasvir/sofosbuvir	PO	100 mg combined with SOF (400 mg) for 12 wk in genotypes 1 to 6, with or without compensated cirrhosis. Not recommended in advanced renal insufficiency; recommended in decompensated cirrhosis (genotypes 1–4, 6)
Glecaprevir/pibrentasvir	PO	Glecaprevir 300 mg combined with pibrentasvir 120 mg. A *first-line* treatment for hepatitis C (genotypes 1–6) in treatment-naïve, treatment-experienced, noncirrhotic, and cirrhotic patients, including patients with severe renal impairment (chronic kidney disease, stages 4 and 5, creatinine clearance (CrCl) <30 mL/min) but not patients with decompensated cirrhosis
Sofosbuvir/velpatasvir/voxilaprevir	PO	SOF 400 mg combined with velpatasvir 100 mg and voxilaprevir 100 mg × 12 wk Recommended in noncirrhotic and compensated cirrhotic patients with genotypes 1–6 but not in patients with decompensated cirrhosis or in patients with severe renal impairment (chronic kidney disease, stages 4 and 5, CrCl <30 mL/min). In noncirrhotic and compensated cirrhotic patients with hepatitis C, SOF/VEL/VOX is a *first-line* treatment for (1) treatment-experienced patients with genotypes 1 to 6 and (2) DAA treatment-naïve (not PEG IFN/RBV–naïve) patients with genotype 3. Among treatment-experienced patients, SOF/VEL/VOX is recommended for patients with failed prior protease inhibitor/PEG IFN/RBV treatment who have genotypes 3 to 6; for patients who failed prior SOF but not an NS5A and who have genotypes 1 and 3 to 6; and for patients who failed prior NS5A treatment and who have genotypes 1 to 6.

[a]Dosage in children ≥2 years of age is 3 mg/kg/day to a maximum of 100 mg/day.
[b]US Food and Drug Administration warning letter issued in October 2015 that hepatic decompensation and failure have been reported with paritaprevir/ritonavir/ombitasvir with or without dasabuvir.
DAA, Direct-acting antiviral; *IFN,* interferon; *IM,* intramuscular; *MU,* million units; *PEG,* polyethylene glycol (pegylated); *PO,* oral; *RBV,* ribavirin; *SC,* subcutaneous; *tid,* three times daily.
Note: Please consult text and manufacturer's product prescribing information for dosage adjustments in renal or hepatic insufficiency and in other circumstances.
See recommendations in September 2017 American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines for testing, managing, and treating hepatitis C (see Chapter 117: Table 117.9).

grade of fibrosis), and serologic (seroconversion from hepatitis B e antigen [HBeAg] to antibody to HBeAg [anti-HBe, clinical status of an inactive carrier] or, more rarely, from hepatitis B surface antigen [HBsAg] to antibody to HBsAg [anti-HBs, serologic pattern of recovery from infection]) effects, and to long-term improvement in the natural history of disease (progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma [HCC], and death). The more profound the suppression of viral replication and the lower the level of residual viremia, the more frequent the immediate outcomes of therapy and, conversely, the lower the likelihood of antiviral resistance. Combination antiviral therapy is the standard of care in human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection but not in HBV infection. Whereas

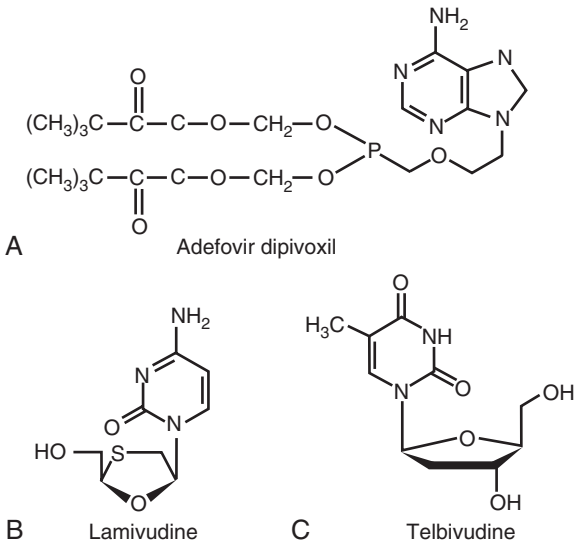

FIG. 47.1 Chemical structures of adefovir (A), lamivudine (B), and telbivudine (C).

combination drug therapy is required for the older, lower-resistance-barrier oral agents after the emergence of resistance, monotherapy suffices in almost all instances with the more potent, high-resistance-barrier agents (entecavir, tenofovir). In addition, although replication must be suppressed to undetectable in patients with HIV and HCV infections, in patients with HBV infection, suppression to a threshold of less than 10^3 IU/mL is usually sufficient to achieve a meaningful clinical change, for instance, from chronic hepatitis to inactive carriage. In practice, HBV DNA can be suppressed to undetectable levels (as determined by sensitive amplification assays) in 70% to 90% of patients treated with current-generation potent oral antivirals.

Individual drugs for hepatitis B are discussed in alphabetic order as follows.

Adefovir

Also see Chapter 128.

Spectrum and Mechanism of Action

Adefovir dipivoxil (9-[2-phosphonomethoxyethyl]adenine; bis-POM, PMEA; Hepsera) is a diester prodrug of adefovir, an acyclic phosphonate nucleotide analogue of adenosine monophosphate (Fig. 47.1A). It is active in vitro against a range of DNA and RNA viruses, including hepatitis B, HIV, poxviruses, and herpesviruses.[1,2] In cell culture, inhibitory concentrations for HBV range from 0.2 to 1.2 µM, whereas concentrations inhibiting growth of uninfected cells are generally greater than 100 µM. Adefovir retains activity against lamivudine-resistant HBV strains and shows dose-dependent inhibition of hepadnavirus replication in animal models.[1] Combinations of adefovir with lamivudine or penciclovir show enhanced antihepadnavirus activity in vitro.[3]

After intracellular transport, adefovir is converted by cellular enzymes to the diphosphate, which acts as a competitive inhibitor of viral DNA polymerases and reverse transcriptases with respect to deoxyadenosine triphosphate and serves as a chain terminator of DNA synthesis.[3,4] Its selectivity relates to higher affinity for HBV DNA polymerase than for host cell polymerases. The prodrug is taken up intracellularly much more readily than the parent. The intracellular half-life ($T_{½}$) of the diphosphate is prolonged, ranging from 5 to 18 hours in different cells, which makes once-daily dosing feasible.[4]

Resistance

Adefovir resistance in HBV is difficult to develop in the laboratory, and no resistant variants have been detected during 48 to 60 weeks of use in chronically infected patients.[5–10] After 144 weeks of dosing, 3.9% of patients show a novel HBV DNA polymerase mutation (N236T or A181V) that confers reduced susceptibility.[6–9] The nucleoside analogues lamivudine, telbivudine, and entecavir are inhibitory for such variants (see Chapter 117).

TABLE 47.2 Dosage Adjustments of Adefovir Dipivoxil in Renal Impairment

CREATININE CLEARANCE (mL/min)	ORAL DOSE (mg)	INTERVAL
≥50	10	q24h
30–49	10	q48h
10–29	10	q72h
Hemodialysis	10	q7 days after dialysis

Note: Dosage is based on manufacturer's recommendations.

Pharmacology/Pharmacokinetics

Adefovir has low oral bioavailability (<12%).[4,11] In contrast, oral adefovir dipivoxil is rapidly absorbed and hydrolyzed to the parent compound by esterases in the intestine or blood or both, with liberation of pivalic acid. The bioavailability of adefovir ranges from approximately 30% to 60%, and after 10-mg doses of adefovir dipivoxil, peak serum concentrations average 0.02 µg/mL. No intact prodrug is detectable in the blood, and ingestion with food does not affect bioavailability. Adefovir has low protein binding (<5%), and has a volume of distribution approximating body water (≈0.4 L/kg).

Adefovir is eliminated unchanged by renal excretion through a combination of glomerular filtration and tubular secretion. After intravenous (IV) dosing, greater than 98% is recovered in urine within 24 hours.[11] After oral administration of adefovir dipivoxil, about 30% to 45% of the dose is recovered within 24 hours, and the serum elimination half-life ($T_{½elim}$) is approximately 5 to 7.5 hours. HIV-infected children have higher clearance than adults. Peak plasma levels increase and clearance decreases with decreasing renal function; therefore dosage reductions are indicated (Table 47.2). Adefovir is removed by hemodialysis (≈35% of the dose during a 4-hour session), and a once-a-week dose after dialysis is recommended, but the effects of peritoneal dialysis are unknown. The pharmacokinetics of adefovir in patients with moderate-to-severe hepatic insufficiency (unrelated to hepatitis B) are not altered.

Interactions

No clinically important drug interactions have been recognized, although drugs that reduce renal function or compete for active tubular secretion could decrease adefovir clearance. Ibuprofen increases adefovir exposure, but no interactions with lamivudine, acetaminophen, or trimethoprim-sulfamethoxazole have been found. An increased risk for lactic acidosis and steatosis may exist when used in conjunction with nucleoside analogues or other antiretrovirals.

Toxicity

Nephrotoxicity at higher doses was the primary adverse event leading to discontinuation of HIV clinical studies in 1999. Adefovir is efficiently transported into tubular epithelium by a probenecid-sensitive human organic anion transporter, and inhibitory effects of the diphosphate on renal adenyl cyclase may contribute to nephrotoxicity. In HIV trials with dosages of 60 mg daily, a Fanconi-like disorder with elevations of serum creatinine, decreases in serum phosphorus and bicarbonate, glycosuria, and proteinuria developed gradually after 20 weeks of dosing. Such nephrotoxicity was generally mild to moderate in severity and usually reversible after a median duration of 4 months. Older age and preexisting renal insufficiency appeared to be risk factors.

In studies of chronic hepatitis B, a lower dose (10 mg daily) has been associated with few adverse events (headache, abdominal discomfort, diarrhea, asthenia) and minimal renal toxicity compared with a higher dose (30 mg).[5,10] Adverse events lead to premature discontinuation in about 2% of patients. At 96 weeks of dosing the estimated risks of an increase in serum creatinine of 0.3 or greater and of an increase of

0.5 mg/dL or greater are 10% and 2%, respectively, but the risk is substantially higher in patients with preexisting renal insufficiency. During therapy, marked increases in aminotransferase levels (>10 times the upper limit of normal) occur less often in adefovir recipients (10%) than in patients taking placebo. Acute, sometimes severe, exacerbations of hepatitis can occur in patients who stop adefovir or other anti-HBV therapies. Close monitoring is necessary after cessation of therapy, and the threshold for resumption of therapy should be low for posttreatment viremia and/or biochemical evidence for reactivation, especially in patients with histologically or clinically advanced liver disease (cirrhosis, advanced fibrosis, borderline hepatic decompensation).

Pivalic acid, a product of adefovir dipivoxil metabolism, can esterify free carnitine and cause reduced free carnitine levels. Although L-carnitine was administered in some HIV studies, supplementation is generally not recommended at the dosages used in chronic hepatitis B.

In preclinical studies, adefovir was genotoxic, and high doses caused renal tubular nephropathy, hepatotoxicity, and toxicity to lymphoid tissues in animals. Carcinogenicity studies in rodents were negative. Adefovir dipivoxil is not associated with reproductive toxicity, although high IV doses of adefovir cause maternal toxicity and embryotoxicity with fetal malformations in rats. Adefovir is classified as pregnancy category C.

Clinical Studies

A detailed discussion of the clinical uses of adefovir dipivoxil in hepatitis B is presented in Chapter 117. Adefovir dipivoxil is approved for treatment of chronic hepatitis B and causes dose-dependent inhibition of HBV replication within 1 week of starting administration. In patients with chronic hepatitis B and who are positive for HBeAg, adefovir (10 mg daily for 48 weeks) results in improved hepatic histology in 53%, reduced serum HBV DNA levels (>3.5 $\log_{10}$ copies/mL), normal aminotransferase levels in 48%, and a 12% rate of HBeAg seroconversion.[10] Continued therapy is associated with sustained viral suppression and increasing frequencies of normalization of aminotransferase and HBeAg loss and seroconversion.[6,7] Similarly, in patients with HBeAg-negative chronic hepatitis B (precore or core promoter mutants), adefovir dipivoxil (10 mg daily for 48 weeks) is associated with significant reductions in HBV DNA (nearly 4 $\log_{10}$), normalization of aminotransferase levels in 72%, and histologic improvement in 64%.[5] Regression of cirrhosis may occur in some patients.[6,7] In addition, adefovir reduces HBV DNA levels comparably across all genotypes,[12] and potential differences in clinical and serologic responses between different genotypes have not been found.

In patients with lamivudine-resistant HBV infections, adefovir dipivoxil monotherapy results in sustained reductions in serum HBV DNA levels comparable to reductions seen with the combination of adefovir and lamivudine, whereas lamivudine monotherapy is ineffective.[13–15] Still, in the face of lamivudine resistance, rather than switching from lamivudine to adefovir, adefovir should be added to lamivudine to reduce the likelihood of biochemical exacerbation and adefovir resistance. In patients with dual HIV and lamivudine-resistant HBV infections, adefovir dipivoxil (10 mg daily) causes sustained decreases in HBV DNA levels.[16] Adefovir dipivoxil has also been used successfully in patients with lamivudine-resistant HBV infections before and after liver transplantation,[17] in whom approximately 4 $\log_{10}$ reductions in HBV DNA levels, improved biochemical markers, and stable or improved histology have been observed.

Although adefovir formerly had an important role in therapy of lamivudine-resistant HBV infection, it has several important limitations. Adefovir is the least potent and slowest acting of the anti-HBV drugs and is ineffective in many patients.[18] Adefovir has been supplanted by tenofovir (see "Tenofovir") and is no longer recommended as a first-line agent.[19,20]

Entecavir

Spectrum and Mechanism of Action

Entecavir (Baraclude) is a cyclopentyl 2′-deoxyguanosine nucleoside analogue that potently and selectively inhibits hepadnaviruses (Fig. 47.2C) and is approved as a first-line drug for the treatment of chronic hepatitis B infection. Entecavir is inhibitory for HBV replication at

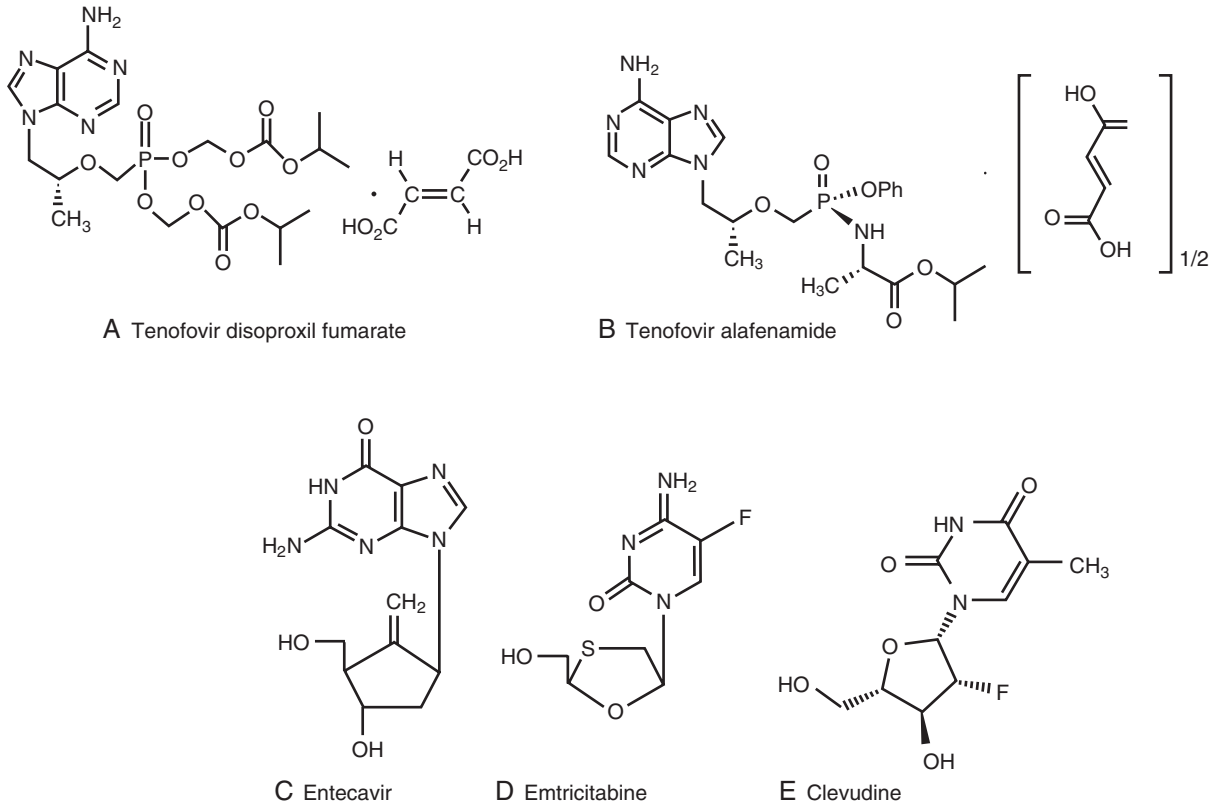

FIG. 47.2 Chemical structures of tenofovir disoproxil fumarate (A) and tenofovir alafenamide (B), entecavir (C), emtricitabine (D), and clevudine (E).

nanomolar concentrations and is 30-fold to greater than 1000-fold more active than lamivudine in cell culture.[21–23] Entecavir is also inhibitory for lamivudine-resistant HBV variants possessing M550I or M550V/L526M mutations, although at 20-fold to 30-fold or higher concentrations.[21,22] After intracellular phosphorylation by cellular enzymes, the triphosphate inhibits several viral DNA polymerase functions, including priming, reverse transcription, and synthesis of positive-strand DNA. The triphosphate accumulates intracellularly at approximately 10-fold to 30-fold higher concentrations relative to extracellular entecavir levels and persists with a $T_{1/2}$ of approximately 15 hours. Oral entecavir is active in several animal models of hepadnavirus infection; prolonged administration for 3 years in hepatitis virus–infected woodchucks resulted in sustained viral suppression without emergence of resistance, in reductions in hepatocyte covalently closed circular (ccc) DNA levels, and in partial protection against HCC.[24] Entecavir inhibits HIV-1 isolates at EC_{50} values ranging from 0.026 to greater than 10 μM. Because its anti–HIV-1 activity can result in development of the M184V mutation, the drug should not be used as monotherapy in HIV-positive patients.[25]

Resistance

Entecavir has a high barrier to resistance; resistance requires the emergence of a YMDD (tyrosine-methionine-aspartate-aspartate) mutation and a second mutation in polymerase domain B, C, or D.[26] In treatment-naïve patients receiving entecavir at 0.5 to 1 mg/day, resistance has rarely been encountered in the first years of therapy and has not exceeded 1.2% after 6 years.[27–30] In patients with previous lamivudine resistance, entecavir is effective, but a higher daily dose (1 mg/day) is required, and resistance to entecavir occurs in 7% at year 1 to 43% at year 4. Therefore, although approved for lamivudine-resistant HBV infection, entecavir has not been adopted for this indication by the treating community; tenofovir is used instead (see "Resistance" under "Tenofovir").

Pharmacology/Pharmacokinetics

Oral administration of entecavir is essentially 100% bioavailable and results in peak plasma concentrations in 0.5 to 1.5 hours. After multiple doses of 1 mg/day, maximum drug concentration (C_{max}) was 8.2 ng/mL, and C_{trough} was 0.5 ng/mL.[31] Administration with food results in a 0.25- to 0.75-hour delay in absorption; therefore, ideally, entecavir should be administered on an empty stomach. The drug has an estimated $T_{1/2}$ of 24 hours and is predominantly (62%–73%) eliminated by the kidneys, probably by glomerular filtration and tubular secretion. Dosage reductions should be undertaken with a creatinine clearance (CrCl) of <50 mL/min (Table 47.3).[32] For patients with liver impairment, the higher 1-mg dose is recommended, but pharmacokinetics are not altered, and dosage reductions are not necessary.

Interactions

Entecavir is not a substrate, inhibitor, or inducer of cytochrome P (CYP) isoenzymes and is not affected by drugs that are metabolized or otherwise affected by that system. Drugs that affect renal function may also affect serum levels of entecavir. Because of its low-level anti-HIV activity, entecavir monotherapy is contraindicated in patients with HBV-HIV coinfection who are candidates for anti-HBV therapy.[33]

TABLE 47.3 Dosage Adjustments of Entecavir in Renal Impairment

CREATININE CLEARANCE (mL/min)	ORAL DOSE (mg)	INTERVAL
≥50	0.5	q24h
30–50	0.5 q48h or 0.25 q24h	q24h or q48h, respectively
10–30	0.5 q72h or 0.15 q24h	q24h or q72h, respectively
<10 or hemodialysis	0.5 once/wk or 0.05 q24h	q7days after dialysis

[a]Doses shown are for treatment-naïve patients; for lamivudine-refractory patients or patients with decompensated liver disease, all doses should be doubled.
Note: Dosage is based on manufacturer's recommendations.

Toxicity

Entecavir is generally well tolerated at dosages of 0.5 to 1 mg/day[34,35] and has a safety profile similar to that of lamivudine. Preclinical toxicity identified hepatic, pulmonary, and brain tumors in rodents but not in other animal species; such toxicity has not been encountered in clinical trials or in postapproval surveillance. In clinical trials the following adverse events were reported: hematuria (9% of patients); glycosuria (4%); and elevations of amylase (8%), lipase (3%), and bilirubin (3%).[32] As is the case for other nucleoside/nucleotide analogues for hepatitis B, a black box warning for entecavir has been issued by the US Food and Drug Administration (FDA) for lactic acidosis and steatosis in patients treated with nucleoside analogues with or without antiretrovirals and for acute exacerbations of hepatitis B when therapy is stopped. Entecavir is classified as pregnancy category C.

Clinical Studies

Short-term administration (0.05–1 mg daily for 4 weeks) is associated with approximately a 2 to 3 $\log_{10}$ suppression of serum HBV DNA levels and at higher doses (0.5 mg and 1 mg) a delay in return of levels to baseline.[36] Entecavir (0.1 mg or 0.5 mg once daily for 24 weeks) reduces HBV DNA levels by more than 4 $\log_{10}$ copies/mL or about 10-fold more than lamivudine.[37] When evaluated in phase III trials against lamivudine as a comparator, entecavir, 0.5 mg/day for 48 weeks, was superior to lamivudine in both HBeAg-positive chronic hepatitis B (HBeAg seroconversion in 21%, 6.9 $\log_{10}$ reduction in HBV DNA, undetectable HBV DNA in 69%, normal alanine aminotransferase [ALT] activity in 68%, improved histology in 72%) and HBeAg-negative chronic hepatitis B (5.0 $\log_{10}$ reduction in HBV DNA, undetectable HBV DNA in 90%, normal ALT in 78%, improved histology in 70%).[35,37,38] Sustained inhibition of lamivudine-resistant HBV infections occurs at dosages of 0.5 mg or 1 mg given daily for 48 weeks[23,39]; however, in this population of lamivudine-experienced/refractory patients, the rate of emerging entecavir resistance becomes prohibitive (reaching 43% at 4 years), rendering entecavir a poor choice for lamivudine-resistant HBV infection.[26,39] Continuation of entecavir for 2 to 5 years or more is well tolerated and is followed by increased HBeAg seroconversion (40% at year 5) and HBsAg loss (5%–6% at years 2–5, respectively).[27,40] Entecavir is effective as well in patients with HBV reinfection after liver transplantation.[23]

The clinical use of entecavir is discussed in more detail in Chapter 117. Because of its efficacy and excellent resistance profile, entecavir is recommended as first-line therapy for chronic hepatitis B.[19,20]

Interferons

The classification, mechanism of action, and pharmacokinetic properties of IFNs are reviewed in Chapter 48. Clinical studies of IFNs in hepatitis B are discussed as follows and in Chapters 117 and 145.

For patients with chronic hepatitis B, parenteral administration of various recombinant IFNs is associated with loss of HBV DNA, loss of HBeAg and development of antibody to HBeAg (anti-HBe), and biochemical and histologic improvement in about 25% to 40% of patients.[41,42] Lasting responses require moderately high IFN dosages and prolonged administration (5 MU/day or 10 MU three times a week for at least 16 weeks).

Responses with seroconversion to anti-HBe are usually associated with aminotransferase elevations and often a hepatitis-like illness during the second or third month of therapy, presumably related to immune clearance of infected hepatocytes. An increased risk for clinical deterioration exists in patients with poor or decreasing hepatic synthetic function, and lower dosages have been suggested for such patients. Factors associated with reduced response rates include high plasma HBV DNA, long-standing infection, male sex, low aminotransferase levels, inactive histology, immunosuppressive therapy, and HIV infection.

Remissions in chronic hepatitis B induced by IFN are sustained in more than 80% of patients, and are frequently followed by later loss of HBsAg and improved long-term clinical outcomes.[43–46] Patients with

precore mutants of HBV may have higher relapse rates.[47] IFN-γ is less effective than IFN-αs and IFN-βs, and combinations do not seem to enhance antiviral effects.[48,49] Combinations of IFNs and lamivudine were not shown to provide consistently greater antiviral effects or clinical benefits than monotherapy.[50,51]

IFN has been covalently linked to a PEG moiety (pegylation) that renders the drug more stable, with a longer half-life, and less immunogenic. PEG IFN-α2a at doses of 180 μg/wk and 270 μg/wk was more efficient than standard IFN-α2a at a dose of 4.5 MU three times per week, which was half the standard dose used in registration trials.[52] The higher dose (270 μg) was associated with more side effects but with no greater efficacy. Large-scale trials of 48 weeks of PEG IFN-α2a (180 μg/wk), lamivudine (100 mg orally daily), or combinations of lamivudine and PEG IFN-α2a showed potent levels of HBV DNA suppression and HBeAg seroconversion in all three groups.[53] Because of the convenience of administration and the results of comparisons in clinical trials, PEG IFN supplanted standard IFN for this indication (see Chapter 117). IFN may improve HBV-associated nephrotic syndrome and glomerulonephritis in some patients.[54]

Standard doses of IFN-α seem to be ineffective against chronic hepatitis D. Longer duration of therapy (12 months) at doses of 9 MU three times a week resulted in return to normal aminotransferase activity and improvement in histology in two-thirds of patients, although reactivation of disease occurred in many patients after therapy was discontinued.[55] PEG IFN has also been shown to have efficacy in chronic hepatitis D infection (see Chapter 146).[56,57]

Lamivudine

Spectrum and Mechanism of Action

Lamivudine (3TC; Epivir) is an L-configuration deoxycytidine analogue with a β-oxathiolane ring that is inhibitory for HIV and HBV (see Fig. 47.1B). It is approved for treatment of HIV (at 150 mg twice daily) and chronic hepatitis B (at 100 mg daily) infection. Its use as an HIV reverse-transcriptase inhibitor is discussed in more detail in Chapter 128, and its use as an anti–hepatitis B drug is discussed in Chapter 117. The triphosphate moiety is a potent inhibitor of the DNA polymerase–reverse transcriptase of HBV, which results in chain termination, and oral lamivudine is active in animal models of hepadnavirus infection. Lamivudine shows enhanced antiviral activity in combination with adefovir or penciclovir against hepadnaviruses.[3]

Resistance

Point mutations in the YMDD motif of HBV DNA polymerase (M550I/V and others) result in 40-fold to 10^4-fold reduction in in vitro susceptibility.[21,58,59] Lamivudine resistance confers cross-resistance to related agents, such as emtricitabine and clevudine (see later), and is often associated with an additional non-YMDD mutation at codon L526M that confers cross-resistance to famciclovir.[60,61] Lamivudine-resistant HBV retains susceptibility to adefovir, tenofovir, and, to a lesser extent, entecavir.[8,22,61,62]

The frequency of lamivudine-resistant variants increases progressively with continued drug administration; cumulative frequencies of 14% to 32%, 38%, 53%, and 67% were observed after 1, 2, 3, and 4 years, respectively, of treatment in chronic hepatitis B.[8,62] Most lamivudine-resistant variants possess L526M/M550V mutations, followed by M550I and L526M/M550I.[22] The risk is higher in posttransplantation infections, and patients coinfected with HIV and HBV have 50% and 90% frequencies of resistance at 2 and 4 years, respectively, of lamivudine therapy.[63,64]

Viruses bearing YMDD mutations are less replication competent in vitro than wild-type HBV and may be associated with lower HBV DNA levels in patients on lamivudine therapy[62]; however, eventually, the antiviral benefit of continued lamivudine therapy degrades. Lamivudine resistance is associated with an increase in HBV DNA levels, decreased likelihood of HBeAg loss or seroconversion, biochemical and histologic deterioration, and graft failure in liver allograft recipients.[58,65,66] Moreover, in patients with histologically advanced chronic hepatitis B, lamivudine resistance reduces the beneficial impact of lamivudine resistance on preventing hepatic decompensation.[67] Emergence of resistant variants may be associated with hepatitis exacerbations in 67% of patients[68] and with rapid clinical deterioration and progressive hepatic fibrosis.

Toxicity

At the dosages used for chronic hepatitis B, lamivudine is well tolerated, including by children; adverse event and laboratory abnormalities are similar to those of placebo.[69] Increases in aminotransferase activity after therapy occur more often in lamivudine recipients, and substantial posttreatment aminotransferase elevations (>500 IU/mL) occur in about 15% of patients after drug cessation.[62] Among the oral antiviral agents for hepatitis B, lamivudine has been used most widely during pregnancy and has an excellent safety record, but the FDA classifies lamivudine as pregnancy category C.

Clinical Studies

(See also Chapter 117.)

In adults with chronic hepatitis B, lamivudine is associated with dose-related, reversible decreases in serum HBV DNA levels.[70] Dosages of 100 mg/day for 1 year suppress HBV DNA levels by a median of 5.5 $\log_{10}$, normalize aminotransferase levels in 40% to 75% or more of patients, and reduce hepatic inflammation in 52% to 56%.[35,62,66] Seroconversion from HBeAg to anti-HBe occurs in only 15% to 17% of adults after 1 year but increases with each year of resistance-free therapy, reaching approximately 50% at 5 years.[71] In children 2 to 17 years of age, lamivudine (3 mg/kg daily for 1 year) is associated with HBeAg loss in 26%, HBeAg seroconversion in 22%, and normalization of aminotransferase levels in 55%.[69] In cases without emergence of YMDD variants, prolonged therapy is associated with sustained suppression of HBV DNA, normalization of aminotransferase activity, continued histologic improvement, and an increase in the proportion of patients experiencing a virologic response (loss of HBeAg and undetectable HBV DNA).[65] In patients coinfected with HIV, higher lamivudine dosages are associated with reductions of HBV replication, reversal of hepatic decompensation, and, in a few patients, HBeAg seroconversion.[63] Administration before and after liver transplantation is useful in preventing or suppressing recurrent HBV infection.[72] Indefinite lamivudine treatment is required until serologic responses are achieved (HBeAg loss/seroconversion in HBeAg-positive patients, HBsAg loss/seroconversion in HBeAg-negative patients), followed by a consolidation period of at least 6 to 18 months of additional therapy. Lamivudine was the first oral antiviral drug introduced against hepatitis B, and, in the absence of other antivirals, lamivudine therapy was continued after YMDD mutations emerged. Currently, newer, more potent, and less resistance-prone anti–hepatitis B drugs are available; therefore lamivudine has been largely supplanted (see Chapter 117 for further details) by entecavir (see earlier) and tenofovir (see later) and is no longer recommended as first-line therapy.[19,20]

Telbivudine

Spectrum and Mechanism of Action

Telbivudine is a synthetic thymidine nucleoside analogue (β-L-2′-deoxythymidine, Tyzeka) (see Fig. 47.1C) that was approved in 2006 in the United States for the treatment of chronic hepatitis B infection.[73] A highly selective inhibitor of HBV, telbivudine is not active against HIV-1. This antiviral agent is phosphorylated by cellular kinases to the active 5′ triphosphate, which competitively inhibits HBV DNA polymerase and causes DNA chain termination.[73,74] Telbivudine inhibits first-strand and second-strand DNA synthesis but may inhibit second-strand synthesis preferentially. The mean EC_{50} against HBV in HCC cell lines is 0.2 μm.

Resistance

Telbivudine is generally cross-resistant with lamivudine and other L-nucleosides to which HBV may be resistant. Although telbivudine resistance after 1 year of treatment was less common than lamivudine resistance,[75,76] by year 2, telbivudine resistance increased to 22% and 9% for HBeAg-positive and HBeAg-negative patients, respectively.[77] Resistant virus usually has the M2041 resistance pattern with or without the rtL80I/V mutant.[75]

Pharmacology/Pharmacokinetics

Telbivudine is rapidly absorbed orally, and C_{max} is reached 1.5 to 4 hours after administration.[73,74] In a steady state after multiple 600-mg doses of telbivudine, C_{max} was 3.7 μg/mL. Plasma concentrations declined in a biexponential manner with a terminal $T_{½elim}$ of 40 to 49 hours.[73]

Approximately 42% of the dose is recovered in the urine, and 50% is recovered in the feces.[73,78] Dosage adjustments for renal impairment are recommended for a CrCl less than 50 mL/min. Telbivudine absorption is not affected by food.[73]

Interactions

Telbivudine does not seem to be metabolized by the CYP450 isoenzymes, and the likelihood for interactions with drugs that use that pathway is low. Drugs that inhibit renal function may cause inhibition of excretion of telbivudine.

Toxicity

In general, telbivudine has a similar tolerability to lamivudine. Asymptomatic elevations of creatinine kinase (7× upper limits of normal) occurred in 13% of telbivudine recipients in phase III studies, compared with 4% of lamivudine recipients.[73] Fatigue and myalgias were also noted in those studies. FDA black box warnings for lactic acidosis and severe hepatomegaly with steatosis are included in the prescribing information as they are for other nucleoside analogues. Exacerbations of hepatitis B upon discontinuation of the drug are noted as they are for other anti-HBV drugs. Myopathy and peripheral neuropathy have been reported. Peripheral neuropathy with telbivudine may be exacerbated with coadministration of PEG IFN-α2a or other IFNs. Telbivudine is classified as pregnancy category B.

Clinical Studies

In large-scale trials telbivudine, at a dose of 600 mg/day for 52 weeks, reduced HBV DNA by a median of 6.4 $\log_{10}$ in HBeAg-positive and 5.2 $\log_{10}$ in HBeAg-negative patients.[76] HBV DNA was reduced to undetectable (<100 copies/mL) in 60% and 88% of HBeAg-positive and HBeAg-negative patients, respectively. ALT returned to normal in 74% to 77%, and histopathology improved in 65% to 67% of patients, respectively.[77] Despite its excellent activity, telbivudine has not been widely used as therapy for hepatitis B because of the frequency of resistance, as noted earlier; its similarity to lamivudine and inferiority to other available hepatitis B antiviral drugs; and reported creatine kinase elevations, myopathy, and peripheral neuropathy. Telbivudine is not recommended as a first-line antiviral agent for the treatment of patients with HBV infection[19,20]; its production and distribution were discontinued in December 2016.

Tenofovir Disoproxil Fumarate

(See also Chapters 117 and 128.)

Spectrum and Mechanism of Action

Tenofovir disoproxil fumarate (TDF, Viread) is a prodrug of tenofovir (see Fig. 47.2A) that has been approved for treatment of HIV-1 infection since 2001 and was approved for treatment of chronic HBV infection in 2008. The prodrug is hydrolyzed to tenofovir, which is an acyclic nucleotide analogue of adenosine 5′-monophosphate. It is phosphorylated by cellular enzymes to form tenofovir diphosphate, which competitively inhibits HIV-1 and HBV polymerases, and, after incorporation into DNA, acts as a chain terminator. The EC_{50} values for tenofovir against HBV in a hepatoma cell line ranged from 0.14 to 1.5 μM.[79] Activity of tenofovir against HIV-1 is discussed in Chapter 128 and activity against HBV in Chapter 117.

Resistance

Tenofovir is active against lamivudine-resistant HBV and generally active against viruses with entecavir-resistant mutations. Development of resistance to tenofovir has not been observed in HBV-infected patients who were HIV negative and were treated for up to 5 years.[80–82] HBV resistance to tenofovir has been noted in patients coinfected with HIV and HBV and who had an rtA194T mutation, but this was not a consistent finding.[83,84] Tenofovir would be the drug of choice for treatment of entecavir-resistant HBV infection, if encountered. When adefovir was used to treat lamivudine resistance, the recommendation was to *add* adefovir to lamivudine to prevent ALT elevations and preempt the emergence of adefovir resistance; however, switching to tenofovir monotherapy, which has not been associated with the emergence of tenofovir resistance, is now recommended for patients with L-nucleoside resistance.[85–87]

Pharmacology/Pharmacokinetics

Oral administration of TDF provides a 25% bioavailability of tenofovir. C_{max} is achieved in 1 ± 0.4 hours at a level of 0.30 ± 0.09 μg/mL. The terminal $T_{½}$ of TDF is 17 hours, and 70% to 80% of the drug is recovered in the urine. Tenofovir's pharmacokinetics and drug interactions are discussed in more detail in Chapter 128.

Toxicity

The general safety profile of TDF is similar to that of adefovir, but renal dysfunction has not been a major problem with TDF at the doses given in registration studies or in clinical practice; nephrotoxicity has been observed in no more than 1% of patients treated for hepatitis B.[82] Renal dysfunction, a proximal tubular injury, is a recognized side effect of TDF,[88] however, and in an observational study, TDF was associated with a greater decline in renal function than that seen with other nucleoside reverse-transcriptase inhibitors.[89] Additional studies with longer-term follow-up continue to support the safety of TDF and the rarity of nephrotoxicity.[81,82] TDF has also been associated, rarely, with reduced bone density (likely related to proximal tubular dysfunction and phosphate wasting), but, in patients treated for hepatitis B, this side effect is uncommon; in a 5-year study of 585 patients, only 3 had evidence of reduced bone density.[82] Still, because kidney and bone toxicity occur occasionally with TDF, patients now have the option of switching to tenofovir alafenamide (TAF) (see later). Tenofovir is classified as pregnancy category B.

Clinical Studies in Hepatitis B Virus Infection

(See also Chapter 117.)

In studies in immunocompetent and immunocompromised patients, treatment with TDF in naïve or lamivudine-resistant patients reduced HBV viral level by greater than 6 $\log_{10}$; achieved DNA suppression rapidly and consistently, with little development of resistance; and was clearly superior to adefovir.[90–94] Given its superiority to adefovir and its high barrier to resistance, TDF supplanted adefovir for the treatment of chronic hepatitis B, and TDF is now recommended as a first-line antiviral agent for hepatitis B.[19,20]

In a large phase III trial[94] 300 mg daily of TDF was compared with, and shown to be superior to, 10 mg daily adefovir for 48 weeks in both HBeAg-positive and HBeAg-negative patients. In HBeAg-positive chronic hepatitis B, tenofovir achieved the following: HBeAg seroconversion in 21%, mean HBV DNA reduction of 6.2 $\log_{10}$, undetectable HBV DNA in 76%, normalization of ALT in 68%, and histologic improvement in 74%. In HBeAg-negative chronic hepatitis B, tenofovir achieved the following: mean HBV DNA reduction of 4.6 $\log_{10}$, undetectable HBV DNA in 93%, normalization of ALT in 76%, and histologic improvement in 72%. In HBeAg-positive patients, HBeAg seroconversion increased from 21% at the end of 1 year to 40% at the end of 5 years, and HBsAg loss occurred in 3% at 1 year, 6% at 2 years, and 8% at 3 and 5 years[81,82,94] in the absence of resistance.[81,82] The long-term benefit of TDF has been demonstrated even in challenging patients with very high levels of HBV DNA—greater than or equal to 10^9 IU/mL.[95] Long-term (5-year) therapy in 348 patients has also been associated with progressive histologic improvement in 87%, regression in fibrosis score in 51%, and, among 96 patients with cirrhosis at baseline, reversal of cirrhosis in 71%.[82] TDF has also been used effectively as salvage therapy in patients with prior adefovir treatment failure (i.e., inadequate suppression of HBV DNA but not adefovir resistance) or nucleoside analogue (lamivudine, entecavir) resistance.[96,97]

Tenofovir Alafenamide

(See also Chapters 117 and 128.)

Spectrum and Mechanism of Action

TAF (Vemlidy) (see Fig. 47.2B) is a prodrug of tenofovir (an inhibitor of HBV and HIV reverse transcriptase) that must be activated to tenofovir in cells (e.g., hepatocytes, peripheral blood mononuclear cells), allowing for higher targeted delivery of the drug to the liver and a 90% reduction

in systemic exposure,[98] reducing significantly the risk of proximal renal injury and loss of bone density (phosphate wasting as a result of proximal tubular injury). TAF is converted by hydrolization within cells to an alaninyl-tenofovir intermediate, then to tenofovir, an acyclic nucleotide analogue of adenosine 5′-monophosphate. Finally, tenofovir is phosphorylated by host nucleotide kinases to the pharmacologically active metabolite tenofovir diphosphate, which is incorporated by HBV reverse transcriptase into HBV DNA. This process results in HBV DNA chain termination.[99–101] At an oral dose of 25 mg daily, TAF is as effective and well tolerated as 300 mg daily of TDF with a comparably high barrier to resistance.

TAF is now one of the first-line antiviral drugs for chronic hepatitis B recommended for patients with impaired renal function (CrCls < 50 mL/min), reduced bone density, anyone at risk for renal injury, and for patients older than 60 years, who are more prone to the potential nephrotoxicity of TDF.[20] Dosage adjustments of TAF are not required for patients with renal impairment; however, TAF is not recommended in patients with CrCls less than 15 mL/min. No dose adjustments are required for patients with mild hepatic impairment; however, TAF is not recommended for patients with severe hepatic impairment (Child-Pugh class B and C).[102]

Resistance

The resistance pattern of TAF is similar to that of TDF (see earlier). Tenofovir has a high barrier to resistance; as noted earlier, no resistance to TDF has been encountered clinically, even after 5 or more years of use, and no resistance to TAF was encountered in phase III clinical trials of TAF (see later).[103,104]

Pharmacology/Pharmacokinetics

After oral administration of TAF, >80% of the dose is metabolized; <1% of the drug is recovered in urine, and 31.7% is recovered in feces. C_{max} for TAF is 0.27 ± 63.3 μg/mL. The terminal $T_{½}$ of TAF is 0.51 hours.[102] Pharmacokinetics and drug interactions are discussed in more detail in Chapter 128.

Drug Interactions

TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters; therefore drugs that influence the activity of P-gp and BCRP may affect TAF absorption. CYP3A metabolism is minimal.

Toxicity

In clinical trials of TAF, low frequencies of mild side effects (headache, abdominal pain, fatigue, cough, nausea, back pain) occurred in 5% to 9% of patients, indistinguishable from frequencies in patients taking TDF. Similarly, nonrenal, nonbone laboratory abnormalities tended to be similar to those recorded for TDF recipients. Patients treated with TAF have a reduced renal and bone toxicity compared with patients treated with TDF (see clinical trial data later).[103,104] Although proximal tubular injury has been reported in patients taking TDF, no such reports have appeared in patients taking TAF. Changes in serum lipids among TAF recipients are similar to those recorded in TDF recipients. Reductions in high-density lipoprotein cholesterol have been noted in TAF recipients. Like all nucleoside analogs for hepatitis B, TAF has a black box warning about the risk of severe acute exacerbations of hepatitis B if the drug is stopped, the importance of close monitoring after discontinuation, and the option to resume therapy should reactivation occur.[102] Like TDF, TAF is classified as pregnancy category B.

Clinical Studies

(See also Chapter 117)

Randomized, double-blind, phase III, 48-week noninferiority trials of TAF versus TDF were conducted in HBeAg-reactive and HBeAg-negative patients.[103,104] In HBeAg-reactive patients for TAF versus TDF, HBV DNA was undetectable by polymerase chain reaction (<29 IU/mL) in 64% versus 67%, ALT was normal (in central laboratory) in 72% versus 67%, HBeAg loss/seroconversion was 14%/10% versus 12%/8%, and HBsAg loss was 4 of 576 (1%) versus 1 of 288 (0.3%). Mean reductions in bone density were lower for TAF (e.g., hip, 0.10%) versus TDF (hip, 1.72%), mean increases in serum creatinine were smaller for TAF (0.01 mg/dL) versus TDF (0.03 mg/dL), and median reductions in CrCl (estimated glomerular filtration rates) were lower for TAF (–0.6 mL/min) versus TDF (–5.4 mL/min).[103] In HBeAg-negative patients for TAF versus TDF, HBV DNA was undetectable in 94% versus 93%, ALT was normal in 83% versus 75%, and no one in either group lost HBsAg. Mean reductions in bone density were lower for TAF (e.g., hip, 0.29%) versus TDF (hip, 2.16%); mean increases in serum creatinine were comparably small for TAF (0.01 mg/dL) and TDF (0.02 mg/dL), but median reductions in CrCl were lower for TAF (–1.8 mL/min) versus TDF (–4.8 mL/min).[104] These findings were similar at week 96, and the more substantial ALT reduction with TAF was sustained over 96 weeks. This sustained, enhanced biochemical advantage of TAF over TDF remains unexplained. Between weeks 96 and 120, when initial TDF recipients were switched to TAF, earlier differences between TDF and TAF in ALT normalization, renal function, and bone density all resolved. No resistance to either TAF or TDF was encountered through 120 weeks of observation.

Other Agents of Potential Interest

Emtricitabine

Emtricitabine ([–]FTC) is a 5′-fluorinated derivative of lamivudine approved for treatment of HIV infection (see Fig. 47.2D; see also Chapter 128), but it is not currently approved for treatment of HBV infection. The potency and selectivity of emtricitabine for HBV are comparable to those of lamivudine in cell culture. It is not inhibitory for lamivudine-resistant HBV variants, and its resistance patterns are similar to those of lamivudine.[22] Emtricitabine is phosphorylated by cellular enzymes to the triphosphate that inhibits HBV DNA polymerase.

Emtricitabine is rapidly absorbed and has a plasma $T_{½elim}$ of about 6 to 9 hours.[105] Once-daily dosing (25–300 mg for 8 weeks) is associated with nearly dose-proportional steady-state plasma concentrations (peak 1.7 μg/mL with 100-mg doses) and rapid antiviral effects with approximate 3 $\log_{10}$ reductions in HBV DNA levels.[105] Resistance mutations develop in 19% of patients within 2 years of treatment.[63] Emtricitabine is generally well tolerated, and its safety profile is similar to that of lamivudine. Clinical studies have shown good activity against HBV in monotherapy[106] and in combination therapy.[107] Although not formally approved as therapy for hepatitis B, emtricitabine (200 mg) is available in combination with TDF (300 mg) or TAF (25 mg) for the treatment of HIV infection.

Clevudine

Clevudine (L-FMAU) is a fluorinated L-arabinofuranosyl nucleoside analogue (see Fig. 47.2E) that is inhibitory for hepadnaviruses and Epstein-Barr virus. Clevudine is about 10-fold more potent than lamivudine against HBV in cell culture, although it is not inhibitory for most lamivudine-resistant variants.[22] Once-daily oral administration reduces woodchuck hepatitis virus replication profoundly, including hepatocyte ccc DNA levels.[108]

In patients with chronic HBV infection, clevudine (10–200 mg once daily for 4 weeks) reduces HBV DNA levels by 2.5 to 3 $\log_{10}$ copies/mL and is associated with sustained biochemical and antiviral effects at 6 months after dosing, that is, delayed HBV DNA rebound after therapy.[109] Administration for 24 weeks resulted in a 4.25 $\log_{10}$ decrease in HBV DNA.[110] Despite these promising early findings, clinical trials demonstrated no advantage in potency or resistance profile over approved drugs, and, in 2009 the discovery that prolonged clevudine administration was associated with severe myopathy resulted in the discontinuation of its development.

The Future

To date, no other nucleoside inhibitors are being developed that are competitive with the leading hepatitis B drugs entecavir or tenofovir (TDF and TAF), and these drugs are so potent and resistance-free that they can be used effectively as monotherapy; tenofovir monotherapy is effective even in patients with lamivudine resistance, without the need to continue lamivudine.[85–87] In general, the current antivirals convert chronic hepatitis into an inactive carrier state with suppressed viral replication as well as biochemical, histologic, and clinical quiescence

and marked reductions in the late, dire consequences of chronic HBV infection (e.g., hepatic decompensation, all-cause mortality, HCC).[111] Still, because almost all patients treated with the current oral agents require long-term, indefinite therapy, a substantial research effort is being devoted both to immunologic interventions and to interference with other components of the HBV replicative life-cycle besides the viral polymerase targeted by nucleoside inhibitors. Immunomodulatory approaches being pursued include reconstitution of innate and adaptive immune responsiveness, Toll-like receptor agonists, T-cell vaccines, checkpoint inhibitors, IFN gene agonists, and retinoic acid–inducible gene-I activation. Viral targeting strategies being studied include inhibitors of viral entry, HBV core assembly, cccDNA, and HBV secretion; RNA interference and gene editing with CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) are novel genetic technologies being pursued. Whether immunomodulatory therapy or novel approaches to direct viral inhibition can overcome host tolerance to HBV infection and lead to recovery from chronic infection, which is now the exception to the rule during antiviral therapy, remains to be seen. So far, none of these imaginative approaches has been successful in "curing" HBV infection and eliminating the need for continued antiviral therapy.[112]

HEPATITIS C

Overview

Extensive advances have been made recently in recommended treatments for hepatitis C, with the approval of the DAAs ledipasvir/sofosbuvir (SOF) in October 2014, ombitasvir/paritaprevir/ritonavir plus dasabuvir in December 2014, daclatasvir in July 2015, elbasvir/grazoprevir in January 2016, SOF/velpatasvir (VEL) in June 2016, SOF/VEL/voxilaprevir (VOX) in July 2017, and glecaprevir (GLE)/pibrentasvir (PIB) in August 2017. These newly approved drugs are discussed subsequently, as well as in Chapters 117 and 154.

Historically, as was true for hepatitis B, IFN-α was the first agent applied to and approved for the treatment of hepatitis C (see Chapters 117 and 145). Approved originally as a 24-week course of therapy, IFN suppressed HCV RNA to undetectable levels during therapy and for greater than or equal to 24 weeks after therapy (sustained virologic response [SVR]) in fewer than 10% of patients. The frequency of SVR doubled when the duration of IFN therapy was extended to 48 weeks and increased again when ribavirin (RBV) was added to IFN (SVR ≈ 40%) and when longer-acting PEG IFNs were introduced (SVR ≈ 55%; lower in genotype 1, ≈45%; higher in genotypes 2 and 3, ≈80%). The addition of RBV added a new dimension of efficacy but also of intolerability, especially hemolytic anemia, to the profile of IFN adverse effects (see earlier under "Hepatitis B"), aggravating the challenge of navigating therapy for both patients and their clinicians. The combination of PEG IFN and RBV remained the standard of care for a decade. In 2011 the first oral protease inhibitors were approved for the treatment of chronic hepatitis C in patients with HCV genotype 1 but were highly prone to resistance when used as monotherapy. When these agents were evaluated in clinical trials and approved, they had to be taken together with the former standard of care, PEG IFN and RBV. For patients with chronic hepatitis C and genotypes 2 and 3, the old standard remained the only option, although the duration of therapy was shorter and its intensity lower (reduced RBV doses) (see Table 47.1).

The first-generation protease inhibitors ushered in a new era of antiviral therapy and catapulted the response rate for genotype 1 from approximately 45% with the old standard of care to greater than or equal to 75%. Moreover, the duration of therapy could be shortened in half to two-thirds of patients. Unfortunately, first-generation protease inhibitor regimens added new and challenging side effects, a high pill burden and thrice-daily dosing along with meals, cumbersome drug-drug interactions, and complicated response-guided therapy (RGT) milestones and stopping rules. Now, however, that novel oral agents, such as later-generation protease inhibitors and drugs that interfere with other targets in the HCV life cycle (polymerase inhibitors, NS5A inhibitors), have become available, as noted earlier, many of the limitations of first-generation protease inhibitors have been overcome. These new agents include pangenotypic drugs with improved pharmacokinetics (once-daily dosing), excellent resistance profiles, very high potency, excellent tolerability, and fewer drug-drug interactions. In addition, the most current of the first-line all-oral drug-combination regimens, which do not require IFN injections and need to be taken for only 8 to 12 weeks, have become the new standard of care as of September 2016 (www.hcvguidelines.org).[113]

As is true for hepatitis B, effective antiviral therapy for chronic hepatitis C has been shown to result in not only virologic improvement but also in biochemical, histologic, and clinical benefit, including a reduction in progression to cirrhosis, hepatic decompensation/liver death, and HCC.

Interferons

The classification, mechanism of action, and pharmacokinetic properties of IFNs are reviewed in Chapter 48. Clinical studies of IFNs in hepatitis C are discussed later and in Chapters 117 and 154.

In acute hepatitis C infection, high-dose IFN monotherapy (IFN-α2b, 5 MU daily for 4 weeks, then three times per week for 20 weeks) markedly reduced the risk for chronicity[114]; lower-dose regimens were less effective.[115] Before the DAA era, PEG IFN plus RBV at conventional doses (see later) for 24 weeks were used to treat patients with acute hepatitis C.[116–118] Efficacy was improved by treating patients as early as possible. In chronic HCV infection, the combination of a PEG IFN and oral RBV is superior to IFN/RBV.[119] Although IFN-α monotherapy (3 MU three times a week for 6–12 months) was associated with serum aminotransferase normalization[120,121] and loss of detectable serum HCV RNA in about 40% to 60% of patients,[122] greater than 50% of responding patients relapsed 1 to 2 months after treatment was stopped, and less than 20% had an SVR predictive of long-term biochemical and histologic improvement.[123–126]

In chronic hepatitis C, combining IFN with oral RBV (1000–1200 mg daily in divided doses) increased the likelihood of SVR to 35% to 45% and was superior to IFN monotherapy in initial treatment and retreatment after IFN failure or relapse, especially in patients with high HCV RNA levels or genotype 1 infections.[127,128] Combined IFN and RBV treatment helped HCV-related systemic vasculitis, cryoglobulinemia, and glomerulonephritis.[129,130] RBV, as discussed later in the chapter, is an oral guanosine that has minimal activity against HCV in vitro and is ineffective against HCV when used alone.[131] Although the mechanism of its effect in treatment of chronic HCV infection is not understood, RBV has been postulated to exert a subtle antiviral effect or an immunomodulatory effect, facilitating a Th2 response.[132] Combined IFN and RBV, but not IFN alone, reduced the risk for recurrent HCV infection after liver transplantation, but treatment resulted in an SVR in only 21% and was not well tolerated.[133] Such antiviral therapy was shown to slow disease progression after liver transplantation.[134]

Two PEG IFNs were approved for treatment of hepatitis C: PEG IFN-α2b, which is 12 kilodaltons (kDa) in size, linear, and partially renally excreted, and PEG IFN-α2a, which is 40 kDa in size, branched, and nonrenally excreted. The 40-kDa molecule has a longer $T_{1/2}$ and a more restricted volume of distribution (8 L), which permits a common dose to be used over a wide range of patient weights. The 12-kDa molecule has a much larger volume of distribution (20 L) and is administered based on weight. PEG IFN monotherapy doubled the frequency of SVR (30%–39%) relative to monotherapy of its nonpegylated counterpart,[123,124] and addition of RBV to PEG IFN increased the frequency of SVR to 55%.[135–137] PEG IFN monotherapy was a treatment option in patients unable to take RBV. Combined therapy with PEG IFN-α2a (180 μg once weekly for 48 weeks) and RBV (1000 or 1200 mg daily in divided doses) yielded an overall SVR of 56%, compared with 44% for IFN and RBV, and was more effective in genotype 1 infections (46% vs. 36%) in previously untreated patients.[138] Similarly, combined PEG IFN-α2b (1.5 μg/kg once weekly for 48 weeks) and RBV (800 mg daily) yielded an overall SVR of 54%, compared with 47% for IFN/RBV.[139]

Higher, weight-adjusted doses of RBV were more effective, particularly in genotype 1 infections. A shorter duration of therapy (24 weeks) and lower RBV dose (800 mg daily) were effective in genotype 2 and 3 infections (84% SVR), but prolonged therapy was needed for genotypes 1 and 4.[140] Failure to achieve an early viral response (undetectable HCV RNA or reduction of ≥2 $\log_{10}$ at 12 weeks) was highly predictive of lack of SVR after further therapy and was relied upon as a stopping point

for futility.[141] Treatment was associated with reductions in steatosis and fibrosis progression, and histologic improvement was shown to occur even in patients who did not achieve SVRs. In patients with compensated cirrhosis, treatment appeared to reverse cirrhotic changes and to reduce the risk for HCC.[142–144] Retreatment for 48 weeks was shown to clear infection in patients relapsing after an initial course.[145] Only 15% to 20% of nonresponders to combined IFN/RBV achieved SVR with PEG IFN/RBV therapy, however.[119]

Age (<40 years), genotype other than 1, host *IL28B* genotype C/C, body weight (<75 kg), disease duration (<5 years), absence of cirrhosis, serum levels of HCV RNA (<2×10^6 copies/mL), and RBV dosage (>10.6 mg/kg) were predictors of response to IFNs.[138,139] Differences in genotype and, for genotype 1, mutations within an IFN sensitivity-determining region of the *NS5A* gene affected virologic responses.[146,147] Individuals coinfected with HIV also seemed to respond better to combined PEG IFN/RBV therapy and could achieve SVRs.[119,145]

As noted earlier, the use of IFNs to treat hepatitis C was supplanted by the recent availability, since 2014, of all-oral DAAs, as discussed later.

Ribavirin

The mechanism of action and pharmacokinetic properties of RBV are presented in Chapter 45. Clinical studies of RBV in hepatitis C are discussed later and in Chapters 117 and 154. RBV played an important role during the IFN era, was still required during the time of the first-generation protease inhibitors, and maintained a niche even during the early IFN-free DAA era before the availability of pangenotypic combinations in 2017. With the advent of these contemporary, high-potency, pangenotypic *first-line* DAAs, the need for RBV in combination with DAAs was reduced substantially, as recommended in the September 2017 guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) (www.hcvguidelines.org; see Chapter 117) and is now reserved for (1) DAA-naïve compensated cirrhotic patients with genotype 3 being treated with ledipasvir/SOF in the setting of baseline ledipasvir resistance-associated substitution (RAS) Y93H and (2) DAA-experienced cirrhotic patients with genotype 3 who had failed a prior NS5A inhibitor and are being treated with SOF/VEL/VOX. RBV also has a role in several of the alternative DAA regimens (e.g., elbasvir/grazoprevir for genotype 1a in patients with baseline NS5A elbasvir mutations) and in first-line regimens in patients with decompensated liver disease and after liver or kidney transplantation (www.hcvguidelines.org).

RBV is an oral guanosine whose mechanism of action in treatment of hepatitis C is not well understood. Its direct antiviral activity, if present, appears to be relatively weak inhibition of the *NS5B* gene–encoded RNA-dependant RNA polymerase[148]; RBV may promote mutational errors in RNA viruses,[149] and it may inhibit cellular inosine monophosphate dehydrogenase and influence intracellular nucleoside pools. RBV may also stimulate IFN-response genes and modulate Th1/Th2 balance, which may contribute to its clinical effect.[148–151] When administered alone, RBV reduced aminotransferase levels in 21% of patients but had little impact on HCV RNA levels.[152–154]

In adults with chronic hepatitis C, long-term oral RBV therapy reversibly reduced not only serum aminotransferase elevations but also hepatic inflammation and fatigue without, as noted earlier, affecting serum HCV RNA concentrations significantly.[154–156] In earlier studies, for patients with HCV genotype 1, RBV was administered in split (twice-daily) doses of 1000 to 1200 mg for PEG IFN-α2a and doses of 600 to 1400 mg for PEG IFN-α2b. In earlier studies, for patients with genotypes 2 and 3, a daily RBV dose of 800 mg sufficed. The combination of oral RBV and conventional IFNs or PEG IFNs significantly increased the frequency of sustained biochemical and virologic responses compared with IFN monotherapy.[127,157] Increases in sustained responses also occurred in patients nonresponsive to, or relapsing after, previous IFN monotherapy.[128,145,157]

Orally administered RBV causes a dose-related extravascular hemolytic anemia. Dosages greater than 800 mg/day often resulted in decreases in hemoglobin of 2 to 4 g/dL in most patients. When used in combination with IFN, hemoglobin levels less than 11 g/dL developed in 25% to 35% of patients.[158] Renal failure increases the risk for hemolysis. Severe anemia requires dosage reduction or cessation, but erythropoietin treatment can be used.[158] Other reported RBV side effects include pruritus, rash, myalgia, nervousness, depression, and cough. Weight-adjusted dosages of RBV improved tolerability and overall results.

Boceprevir

Boceprevir is no longer recommended for therapy of hepatitis C in guidelines issued by the AASLD and IDSA and by the European Association for the Study of the Liver (EASL) because of the availability of new, better therapies.[113,159]

Spectrum and Mechanism of Action

Boceprevir (Victrelis) is an orally administered ketoamide peptidomimetic inhibitor of the NS3 protease of HCV (Fig. 47.3A).[160] Monotherapy at a dose of 400 mg three times daily resulted in a reduction of HCV RNA of 1.61 ± 0.21 $\log_{10}$ after 1 week.[161] Boceprevir activity was demonstrated

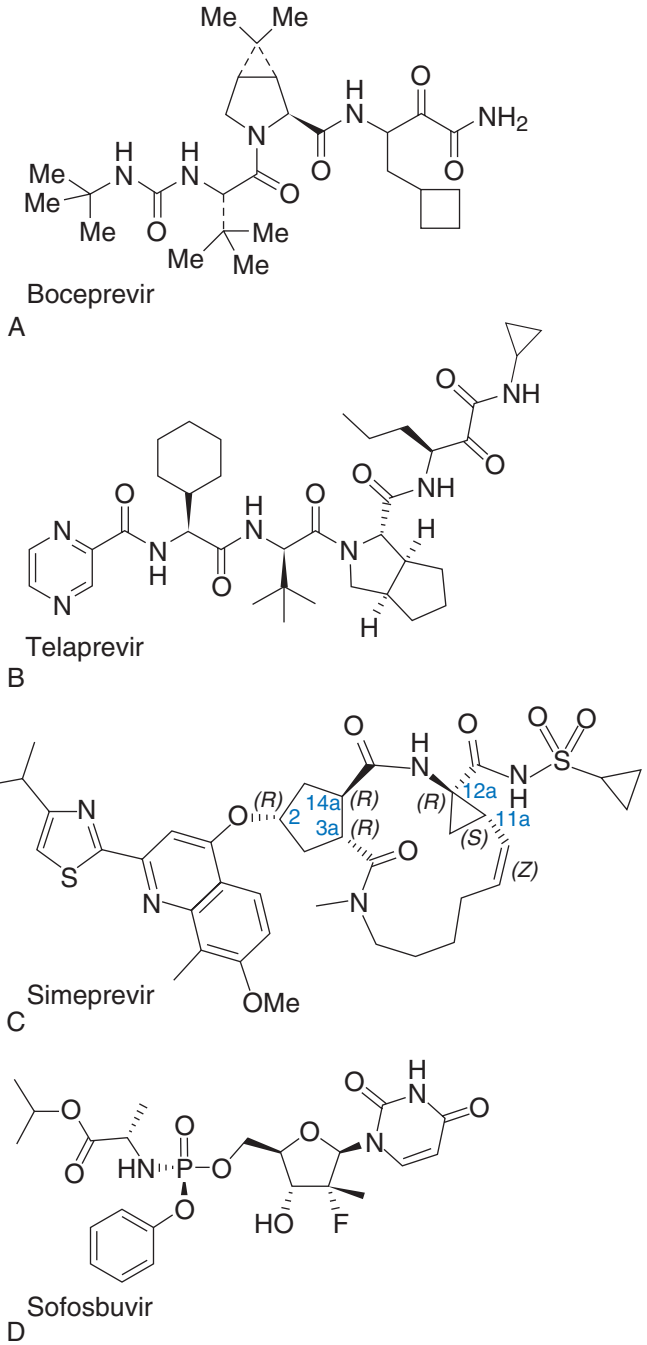

FIG. 47.3 Chemical structures of boceprevir (A), telaprevir (B), simeprevir (C), and sofosbuvir (D).

against HCV genotype 1 (genotype 1b > 1a) and was approved for its treatment; its activity against genotypes 2 and 3 was limited, and boceprevir was not approved for these genotypes. In preliminary trials among patients with genotype 1 chronic HCV infection, when boceprevir was administered at a dose of 800 mg three times daily in combination therapy with weekly PEG IFN and twice-daily weight-based RBV, at week 12 HCV RNA was undetectable in 80% of patients, and after 48 weeks of triple-drug therapy, SVR was as high as 66%.

Mechanism of Action

Boceprevir inhibits the HCV NS3/4A protease by forming a reversible covalent bond with the NS3 serine active site, preventing proteolytic cleavage by NS3 of the HCV polyprotein into NS4A, NS4B, NS5A, and NS5B proteins.[160,162] In an HCV genotype 1b replicon, boceprevir has an EC_{50} of 200 nM; its activity against genotype 1a, relative to genotype 1b, is reduced by approximately twofold; its activity against genotypes 2 and 3 is reduced even more substantially; and its activity is additive—not synergistic—with IFN.[160]

Resistance

In most patients who failed to achieve an SVR after boceprevir treatment, HCV RASs emerged, the most common of which were V36M, T54S, and R155K for genotype 1a and T54A/S, V55A, A156S, and I/V170A for genotype 1b. For the R155K RAS, compared with genotype 1a, which requires only a single amino-acid substitution, genotype 1b has a higher barrier to resistance, requiring two amino-acid substitutions. These RASs were not archived, and reversion to wild-type HCV occurred within 18 to 24 months in almost all cases. Very low-level RASs were present before therapy in almost all patients,[163] but their presence did not predict the emergence of resistance during boceprevir therapy; therefore pretreatment resistance testing was not indicated. Because RASs emerged efficiently and rapidly during boceprevir monotherapy, boceprevir had to be used in combination with other antivirals, and boceprevir antiviral therapy was developed as a triple-drug combination with PEG IFN and RBV.

Pharmacology/Pharmacokinetics

Boceprevir is metabolized primarily by aldoketoreductase to ketone-reduced metabolites but also by oxidative metabolism via CYP3A4, and its pharmacokinetic disposition is the same in normal subjects and in patients with HCV infection. At an oral dose of 800 mg (four 200-mg tablets) three times daily, boceprevir has a C_{max} of 1723 ng/mL, C_{min} of 88 ng/mL, area under the time-concentration curve $(AUC)_{(T)}$ of 5408 ng × h/mL, median absorption T_{max} of 2 hours, plasma $T_{½}$ of approximately 3.4 hours, and mean volume of distribution of approximately 772 L. Boceprevir is metabolized by the liver predominantly; approximately 79% is eliminated in stool and approximately 9% in urine.[160] Because food (independent of fat content) increases boceprevir exposure by as much as 65%, boceprevir is taken with food (fatty meal is not necessary). No dose adjustments were necessary in patients with renal or hepatic impairment.

Interactions

Medications that are CYP3A4 inducers lower boceprevir plasma levels and efficacy, and boceprevir competition for CYP3A4 metabolism can raise plasma levels of multiple medications, leading to toxicity. Thus boceprevir has multiple interactions with commonly prescribed drugs, including statins, benzodiazepines, calcineurin inhibitors, antiretroviral agents, antifungals, and opioid antagonists, to name a few. Before prescribing boceprevir, clinicians were encouraged to consult the boceprevir product insert and/or the website www.hep-druginteractions.org.[164]

Toxicity

The major adverse effects encountered in patients receiving boceprevir-based triple-drug therapy, including PEG IFN and RBV, were anemia (Hgb <10 g/dL) in approximately half of patients and dysgeusia (altered sense of taste) in approximately a third. In the triple-drug combination, all three drugs had an effect on red blood cells: RBV through hemolysis, PEG IFN through mild marrow suppression, and boceprevir through more severe marrow suppression. Patients treated with the triple-drug, boceprevir-based combination also experienced the following side effects that appeared to be more frequent than in patients treated with PEG IFN and RBV (without boceprevir): neutropenia (25%) and vomiting (20%). Boceprevir was not associated with rash and did not have cardiac toxicity (no effect on QT interval).[160] Because of the need to use boceprevir with PEG IFN and RBV, triple-drug boceprevir-based therapy was contraindicated in pregnancy.

Clinical Studies

A detailed review of boceprevir clinical trials appears in Chapter 117. As noted earlier, boceprevir has been supplanted by newly available therapies for hepatitis C.[113,159]

In clinical trials of boceprevir-based triple-drug therapy (in combination with PEG IFN-α2b, 1.5 μg/kg subcutaneously and weight-based RBV, 600–1400 mg/day orally) in treatment-naïve or treatment-experienced patients with genotype 1 chronic hepatitis C, a 4-week PEG IFN/RBV lead-in period preceded the introduction of boceprevir, 800 mg three times daily orally.

In *treatment-naïve* subjects, patients were randomized to 48 weeks of PEG IFN/RBV versus PEG IFN/RBV/boceprevir triple therapy ("SPRINT 2").[164] One group of triple-drug recipients received a full, fixed 48-week course (triple-drug therapy for 44 weeks after the 4-week lead-in period), and another group received RGT after the 4-week lead-in phase, that is, triple-drug therapy for 24 weeks if HCV RNA was undetectable at weeks 8 and 24 or a full 44 weeks of triple therapy if HCV RNA remained detectable at week 8 (as long as it was undetectable at week 24). SVRs occurred in 63% of RGT recipients (44% meeting criteria for shortened, 28-week therapy) and in an indistinguishable 66% of full 48-week boceprevir-based therapy but in only 38% of PEG IFN/RBV recipients, and SVR was achieved in 67% to 69% of non-Black subjects but only 42% to 53% of Black subjects. Among subjects in the RGT arm who did not meet criteria for shortened therapy, SVRs occurred in only 36%, no better than the PEG IFN/RBV control arm.[165]

In *treatment-experienced* patients, prior relapsers and partial responders (≥2 log_{10} reduction but not complete suppression in HCV RNA during previous IFN-based therapy) were randomized to RGT (4 weeks of PEG IFN/RBV lead-in plus 32 [instead of 24 in treatment-naïve subjects] weeks of triple therapy, that is, potential for shortened, 36-week treatment), full 48-week boceprevir-based therapy, or 48 weeks of PEG IFN/RBV ("RESPOND-2").[166] In the RGT group, if HCV RNA was undetectable at weeks 8 through 36, therapy was discontinued at week 36; if this criterion was not met (as long as HCV RNA was undetectable at week 24 and thereafter), subjects received an additional 12 weeks (to week 48) of PEG IFN/RBV. In this trial, 59% in the RGT arm, a statistically indistinguishable 66% in the full 48-week arm, and 21% in the control PEG IFN/RBV arm achieved an SVR. In the RGT arm, among the 46% who met criteria for short-duration therapy, 86% had an SVR, whereas among the 95.4% who did not meet criteria for shortened therapy, 35% had an SVR. Efficacy was substantially higher in prior relapsers (up to 75%) than in prior partial responders (up to 52%)[166]; null responders (<2 log_{10} HCV RNA reduction during prior IFN-based therapy) were not included in this trial, but in a small ($n = 46$) subsequent, open-label trial of a full 48-week regimen (4 weeks of PEG IFN/RBV lead-in, followed by 44 weeks of boceprevir-based triple therapy), an SVR was observed in 38% of prior null responders.

Based on these trials and on additional analyses conducted by the FDA,[167] RGT (28 weeks total if truncation criteria are met vs. an additional 8 weeks of triple therapy and then 12 weeks of PEG IFN/RBV) was approved for noncirrhotic treatment-naïve patients. For noncirrhotic prior relapsers and partial responders, RGT (36 weeks total if truncation criteria are met vs. an additional 12 weeks of PEG IFN/RBV) was approved. For cirrhotic patients who failed to achieve a 1-log_{10} HCV RNA reduction during the 4-week lead-in period and for prior null responders, a full 48 weeks (4 weeks of PEG IFN lead-in, followed by 44 weeks of triple-drug therapy) was the recommended option.[160,168,169] Therapy was stopped if HCV RNA equaled or exceeded 100 IU/mL at week 12 or remained detectable at week 24; in such instances, additional therapy was shown to be futile. Thus, although boceprevir-based triple therapy improved efficacy compared with PEG IFN/RBV therapy, the complexity of the treatment regimen and drug-drug interactions, as

well as the need to follow complicated response-guided and futility milestones, limited the drug's appeal and adoption. Because of the superiority, improved tolerability, and simplicity of use of currently available treatments (see later), boceprevir is no longer recommended in the treatment of chronic hepatitis C.[113,159]

Telaprevir

Telaprevir is no longer recommended for therapy of hepatitis C in guidelines issued by the AASLD, IDSA, and EASL because of the availability of new, better therapies.[113,159]

Spectrum and Mechanism of Action

Telaprevir (Incivek; see Fig. 47.3B)[170] is an orally administered peptidomimetic inhibitor of the HCV NS3/NS4A protease; the ketoamide moiety of telaprevir binds to the active enzymatic site. As monotherapy, it induced a 4 $\log_{10}$ decrease in HCV RNA within 2 weeks, but it was followed by the frequent emergence of resistance.[171,172] Telaprevir is active against HCV genotype 1 (genotype 1b > 1a), much less so for genotype 2, and even less so for genotype 3; it was approved for use in genotype 1. In studies of a combination of PEG IFN and RBV along with telaprevir administered three times daily at a dose of 750 mg (total daily dose 2250 mg), HCV RNA was reduced rapidly (within 4 weeks) in 80% of subjects. Telaprevir could also be administered, with comparable efficacy, at a dose of 1125 mg twice daily (three 375-mg tablets) for the same total daily dose of 2250 mg. In early-phase trials, 12 weeks of triple-drug therapy, followed by 12 weeks of PEG IFN plus RBV, resulted in SVRs in 61% to 68% of patients.[172,173] In these early studies patients who had either relapsed or been nonresponders to PEG IFN or standard IFN had SVRs of 41% to 72%. Responsiveness to combination telaprevir with PEG IFN alone was less than that to the combination with PEG IFN plus RBV; therefore, RBV was an important ingredient of this combination therapy. A severe maculopapular rash was observed in 3% to 6% of patients, and gastrointestinal discomfort and anemia were also seen. See additional details as follows.

Mechanism of Action

Telaprevir inhibits the HCV NS3/4A protease by forming a reversible covalent bond with the NS3 serine active site, preventing proteolytic cleavage by NS3 of the HCV polyprotein into NS4A, NS4B, NS5A, and NS5B proteins.[170] The 50% inhibitory concentration (IC_{50}) in a biochemical assay of HCV NS3 proteolytic activity is 10 nM. In an HCV genotype 1b replicon telaprevir has an EC_{50} of 354 nM; in a genotype 1a replicon it has an EC_{50} of 280 nM. The median IC_{50} of telaprevir in biochemical enzymatic assays is 20 nM for genotypes 1a and 1b, 16 nM against genotype 2, 40 nM against genotype 3a, and 130 nM against genotype 4a. The activity of telaprevir does not interfere with the activity of IFN, and the activity of the two together is additive—not synergistic.[170]

Resistance

Please see the discussion of resistance to boceprevir, which applies as well to telaprevir. Resistance-associated substitutions appeared to account for clinical nonresponse to telaprevir-based therapy. The telaprevir HCV RASs that emerged most commonly during clinical trials were V36M/A/L, T54A/S, R155K, and A156S/T (V36M, R155K, or the combination of V36M and R155K for genotype 1a and V36A, T54A/S, and A156S/T for genotype 1b).[170] Telaprevir RASs are not archived, and reversion to wild-type HCV occurred within 24 to 36 months in almost all cases. Very-low-level RASs were present before therapy in almost all patients,[170] but their presence did not predict the emergence of resistance during telaprevir therapy; therefore pretreatment resistance testing was not indicated. Because RASs emerged efficiently and rapidly during telaprevir monotherapy, telaprevir had to be used in combination with other antivirals, namely PEG IFN and RBV.

Pharmacology/Pharmacokinetics

Telaprevir is metabolized predominantly by ketoamide reduction but also by oxidative metabolism via CYP3A4 and by hydrolysis. At an oral dose of 750 mg (two 375-mg tablets) three times daily, telaprevir has a mean ± SD C_{max} of 3510 ± 1280 ng/mL, C_{min} of 2030 ± 930 ng/mL, AUC_{8h} of 22,300 ± 8650 ng × h/mL, median absorption T_{max} of 4 to 5 hours, plasma $T_{1/2}$ of 4.0 to 4.7 hours after a single dose and at steady state approximately 9 to 11 hours, and mean volume of distribution of 252 L. Telaprevir is metabolized by the liver. Metabolites appear in stool (median, 82%), urine (1%), and expired air (9%).[170] Food, and especially a fatty meal, increases telaprevir exposure by as much as 237% (low-fat meal by 117%, high-fat meal by 330%)[170]; therefore telaprevir was taken with a fatty (≈20 g fat) meal. No dose adjustments were necessary in patients with renal impairment. Because moderate hepatic impairment (Child class B) reduces telaprevir steady-state exposure by 46%, telaprevir was not recommended in moderate-to-severe hepatic impairment; however, mild hepatic impairment, which has a minimal effect on telaprevir exposure, did not necessitate any telaprevir dose adjustment, and no dose adjustment was necessary in patients with compensated cirrhosis.[170]

Interactions

As is the case for boceprevir (see earlier), telaprevir is metabolized via the P450 (CYP3A4) system, accounting for multiple drug-drug interactions. Careful review of coadministered medications was important before initiation of treatment. For example, statins had to be stopped for the duration of telaprevir therapy. Medications that are CYP3A4 inducers lower telaprevir plasma levels and efficacy, and telaprevir competition for CYP3A4 metabolism can raise plasma levels of multiple medications, leading to toxicity. Thus telaprevir had multiple interactions with commonly prescribed drugs, including statins, calcium channel blockers, benzodiazepines, calcineurin inhibitors, antiretroviral agents, antifungals, and opioid antagonists, to name a few.[170] Before prescribing telaprevir, clinicians were encouraged to consult the product insert and/or www.hep-druginteractions.org.[164]

Toxicity

Telaprevir can amplify the anemia associated with PEG IFN/RBV therapy (Hgb ≤ 10 in a third of patients), mandating close laboratory monitoring and occasionally requiring red blood cell transfusions, especially in prior null responders with cirrhosis. Rectal burning and other anorectal discomfort occurred in approximately a third and dysgeusia (altered sense of taste) in approximately 10% of patients. Rash occurred in approximately half, but a severe, confluent, maculopapular, pruritic rash of the trunk and extremities occurred in 3% to 6% of patients at a median of 8 weeks. In clinical trials such severe rash led to withdrawal from treatment and, in some cases, necessitated systemic corticosteroid therapy. If patients were monitored closely, such rashes could be identified when they were sufficiently early and mild, to stop therapy, thus preventing them from becoming severe. Telaprevir had a "boxed warning" regarding serious skin reactions and rashes, including toxic epidermal necrolysis and erythema multiforme, which were reported in postmarketing surveillance.[170] Also more common than in patients treated with PEG IFN/RBV alone were pruritus (≈50%), nausea (≈49%), and diarrhea (≈25%). Telaprevir was not associated with renal, hepatic, or cardiac toxicity (no effect on QT interval). Because of the need to use telaprevir with PEG IFN/RBV, telaprevir triple-drug therapy was contraindicated in pregnancy.

Clinical Studies

As noted earlier, telaprevir has been supplanted by newly available therapies for hepatitis C.[113,159] A detailed review of telaprevir clinical trials appears in Chapter 117.

In registration clinical trials of telaprevir-based triple-drug therapy (in combination with PEG IFN-α2a, 180 μg subcutaneously, and weight-based RBV, 1000– 1200 mg/day orally) in treatment-naïve or treatment-experienced patients with genotype 1 chronic hepatitis C, telaprevir was administered at a dose of 750 mg three times daily orally. Because phase II trials showed no advantage of continuing telaprevir beyond 12 weeks, in phase III trials triple-drug therapy lasted only 12 weeks, and subsequent extension of therapy involved PEG IFN/RBV. Unlike boceprevir trials, telaprevir trials in treatment-naïve subjects did not include a 4-week PEG IFN/RBV lead-in period,[174,175] although a lead-in arm was included in the registration trial among prior nonresponders, and outcomes were indistinguishable between the arms with and without a lead-in period.[176]

In *treatment-naïve* subjects patients were randomized to 48 weeks of PEG IFN/RBV versus response-guided PEG IFN/RBV/telaprevir triple therapy for 8 or 12 weeks, followed by PEG IFN/RBV for up to another 40 or 36 weeks, respectively. Trial subjects with undetectable HCV RNA at week 4 and 12 extended PEG IFN/RBV therapy for only an additional 16 (for the 8-week triple-drug arm) to 12 weeks (for the 12-week triple-drug arm), for a total duration of 24 weeks; trial patients who did not meet the early stopping milestone but who cleared HCV RNA by week 24 continued PEG IFN/RBV therapy for 24 more weeks ("ADVANCE").[174] In the RGT groups an SVR occurred in 75% of the 12-week triple-therapy recipients and 69% of the 8-week triple-therapy recipients but in only 46% of PEG IFN/RBV recipients. Criteria for early stopping at week 24 were met by 58%, among whom the likelihood of an SVR was 83% (8-week telaprevir arm) to 89% (12-week telaprevir arm); those failing to meet early stopping criteria, but in whom HCV RNA was undetectable by week 24, achieved SVR in 50% to 54%, respectively, more frequently than in the PEG IFN/RBV arm, 39%. In a subsequent treatment-naïve follow-up study of RGT ("ILLUMINATE"), of the 65% who met criteria for early discontinuation of therapy (undetectable HCV RNA at weeks 4 and 12), 92% achieved an SVR.[175]

In *treatment-experienced* patients, the registration trial of telaprevir ("REALIZE")[176] contained 12-week, but not 8-week, triple-drug treatment arms in which triple therapy was followed by PEG IFN/RBV for the rest of 48 weeks and involved prior relapsers, partial responders, and null responders; the trial did not have an RGT arm (all trial patients were treated for 48 weeks) but did include a lead-in arm. In the triple-drug, telaprevir-based treatment arms, SVRs occurred in 64% with lead-in therapy and in 66% without a lead-in, compared with 17% in the 48-week PEG IFN/RBV control group. Relapsers had the best response: SVR in 86%, then partial responders (57%), and null responders with the poorest response (31%).[176] In another trial patients who failed PEG IFN/RBV therapy during phase II telaprevir trials were re-treated with telaprevir-based triple-drug therapy: (1) RGT—12 weeks of triple therapy, followed by 12 to 36 weeks of PEG IFN/RBV therapy (based on meeting early stopping criteria) for relapsers and partial responders or (2) a fixed 48-week regimen—12 weeks of three drugs, followed by 36 weeks of PEG IFN/RBV for null responders. SVRs occurred in 97% of relapsers, 55% of partial responders, and 37% of null responders.[177]

Based on these trials and on additional analyses conducted by the FDA,[178] RGT—12 weeks of triple therapy plus 12 weeks of PEG IFN/RBV (total of 24 weeks) if truncation criteria are met versus an additional 24 weeks of PEG IFN/RBV if truncation criteria are not met (total of 48 weeks)—was formerly recommended for noncirrhotic treatment-naïve patients and relapsers. For partial and null responders, a full 48-week course of therapy was recommended (12 weeks of triple therapy, followed by 36 weeks of PEG IFN/RBV) without RGT. For cirrhotic treatment-naïve patients, even if they met RGT criteria for shortened therapy, a full 48-week course was advised.[168–170,178] Therapy was stopped for futility if HCV RNA exceeded 1000 IU/mL at week 4 or 12 or if HCV RNA remained detectable at week 24. After its initial approval at a three-times-daily dose of 750 mg, telaprevir was shown to be equally effective at a twice-daily dose of 1125 mg. Although telaprevir-based triple therapy improved efficacy compared with PEG IFN/RBV therapy, the complexity of the treatment regimen, the high frequency of drug-drug interactions, the need to follow complicated response-guided and futility milestones, and the greater-than-anticipated drug toxicities and morbidity encountered once the drug was approved (especially in cirrhotic prior nonresponders) limited the drug's appeal and adoption. Because of the superiority, improved tolerability, and simplicity of use of newly available therapies (see later), telaprevir is no longer recommended in the treatment of chronic hepatitis C.[113,159]

Simeprevir

Spectrum and Mechanism of Action

Simeprevir (Olysio; see Fig. 47.3C), a second-generation NS3/4A protease inhibitor (approved November 2013) with antiviral activity against HCV genotype 1 (1b > 1a), has improved pharmacokinetic properties compared with those of first-generation protease inhibitors and therefore can be taken once a day; simeprevir must be taken with food. Initial approval of simeprevir was based on trials in combination with PEG IFN and RBV in genotype 1 HCV infections. Based on current recommendations, however, simeprevir has a very limited role and is not part of *first-line* DAA combinations. As an alternative regimen, simeprevir can be used in combination with SOF in genotype 1a and 1b infections in treatment-naïve and PEG IFN/RBV treatment-experienced patients if no cirrhosis is present (www.hcvguidelines.org).[113] Approximately a third of patients with HCV genotype 1a harbor an NS3 polymorphism, Q80K, which renders them refractory to the antiviral activity of simeprevir; if simeprevir therapy is being considered, Q80K testing is advisable, and, if positive, should discourage the use of simeprevir. In early phase III clinical trials, 150 mg of simeprevir along with PEG IFN and RBV was associated with an SVR in 80% of treatment-naïve subjects as well as treatment-experienced subjects who had relapsed after a prior course of PEG IFN and RBV. For treatment-naïve patients and prior relapsers, 150 mg by mouth of simeprevir daily was administered for an initial 12 weeks of triple therapy, followed by another 12 weeks of PEG IFN and RBV dual therapy (total course, 24 weeks); for prior nonresponders, based on data extrapolated from phase II trials, the initial 12 weeks of triple therapy were followed by 36 weeks of dual therapy (total course 48 weeks). These treatment approaches in clinical trials applied to patients with any stage of fibrosis, including those with cirrhosis. If an HCV RNA suppression milestone of ≤25 IU/mL was not met by week 4, further treatment was futile, and therapy was be stopped; if HCV RNA was not suppressed to ≤25 IU/mL at week 12 or 24 (by which time simeprevir had been completed), PEG IFN and RBV were stopped for futility. In Black patients simeprevir therapy was approximately 10% less effective in achieving an SVR than in white patients.[179] (See "Clinical Studies" later for more recent studies.)

Simeprevir inhibits the HCV NS3/A protease directly with an EC_{50} in a genotype 1b replicon of 9.4 nM, which is increased by up to 11-fold in isolates with a Q80K polymorphism. The activity of the drug in vitro is not reduced by IFN, RBV, or polymerase inhibitors (nucleoside or nonnucleoside). The simeprevir plasma concentration is reduced by two-thirds when administered with darunavir/ritonavir. Like first-generation protease inhibitors that needed to be taken with PEG IFN and RBV, simeprevir-based triple-drug therapy was most effective in patients with the IFN-γ–associated *IL28B* C/C haplotype and reduced in patients with non-C/C haplotypes C/T and T/T.[179]

Resistance

The most common treatment-emergent RASs observed during clinical trials of simeprevir among study subjects who failed to achieve an SVR were NS3 substitutions Q80R, S122A/G/I/T/R, R155K, and/or D168E/V/X. For genotype 1a the most common RAS was R155K (alone or along with Q80 S122, and/or D168 substitutions); for genotype 1b, D168V was the most common RAS. For study subjects with genotype 1a and a baseline Q80K substitution (prevalent in 30%–35% of persons with genotype 1a), the most common emerging RAS was R155K. Cross-resistance was demonstrated between simeprevir and the first-generation protease inhibitors boceprevir and telaprevir (e.g., boceprevir- or telaprevir-induced R155K or A156T/V—less so V36A/G and I170A/T—would be expected to reduce simeprevir responsiveness).[179]

Pharmacology/Pharmacokinetics

Simeprevir, formulated as a 150-mg capsule, is metabolized by hepatic cytochrome P450 3A (CYP3A) and excreted by biliary excretion. The $T_{½elim}$ for simeprevir is 10 to 13 hours in healthy subjects and 41 hours in persons with HCV infection. The AUC for plasma reaches steady state after 7 days. In patients with hepatitis C the mean steady-state predose AUC was 1936 ng/mL, and the AUC_{24} was 57,469 ng·h/mL; C_{max} occurs 4 to 6 hours after oral administration, and oral bioavailability is increased by taking the drug with food. Almost all of the drug is plasma protein bound. Because the drug is not renally excreted, no dose modifications are necessary in patients with renal impairment, but, because of its hepatic metabolism, simeprevir should not be used in patients with decompensated liver disease.[179]

Interactions

Simeprevir is metabolized in the liver by CYP3A; therefore concomitant administration of simeprevir along with CYP3A inducers or inhibitors

can amplify or reduce simeprevir exposure; although simeprevir does not induce hepatic CYP3A activity, coadministration of simeprevir with drugs metabolized by CYP3A can increase plasma concentrations of these drugs. Similarly, concomitant administration of simeprevir with drugs that are substrates for hepatic organic anion-transporting polypeptide 1B1 or 1B3 (OATP1B1/3) or P-gp transporters can elevate plasma concentrations of these drugs. Because of these substantial drug-drug interactions, prescribing information and/or the website www.hep-druginteractions.org should be consulted before simeprevir is prescribed.[179]

Toxicity

Potential toxicity encountered during clinical trials included photosensitivity, rash (in 28%; mild-to-moderate in almost all, severe [grade 3] in 1%), and reversible mild elevation of bilirubin (both unconjugated and conjugated; mild-to-moderate in 45% of treated subjects; grade 3 in 4%). Although most other adverse events during simeprevir therapy are attributable to PEG IFN and RBV, the following were slightly more common in the simeprevir group than in the placebo group: pruritus, nausea, myalgias, and dyspnea. Simeprevir has no effect on the QT interval on electrocardiography. Simeprevir could not be used in pregnant women when it was combined with PEG IFN and RBV, which are contraindicated during pregnancy. Simeprevir is unlikely to be used during pregnancy and is classified as pregnancy category C.[179]

Clinical Studies

In phase III clinical trials among treatment-naïve subjects with chronic hepatitis C, simeprevir 150 mg daily plus PEG IFN and RBV for 12 weeks, followed by another 12 weeks of PEG IFN and RBV, an SVR was achieved in 80% (compared with 50% of control subjects treated with PEG IFN and RBV). In subjects with genotype 1a and a Q80K variant, simeprevir triple-drug therapy was no more effective than PEG IFN/RBV, and the efficacy of simeprevir-based triple-drug therapy was reduced to 58% in subjects with cirrhosis. Phase III trials included RGT: If HCV RNA < 25 IU/mL at week 4 and undetectable at week 12, the treatment course could end at week 24; if these milestones were not met, but stopping rules not violated, treatment was extended to 48 weeks; however, in the 8% of study subjects who failed to meet RGT milestones for shortened therapy, only 25% experienced an SVR. Therefore RGT is not recommended for simeprevir. The efficacy of simeprevir-based triple-drug therapy is similar in prior relapsers to IFN-based therapy, achieving an SVR in 79%, compared with 37% in a PEG IFN/RBV-treated control group. Phase III trials did not include treatment-experienced nonresponders, but, based on phase II trials, simeprevir-based triple-drug therapy was approved for partial responders and null responders, for all of whom a full 48 weeks of therapy (12 weeks of simeprevir with PEG IFN and RBV, followed by 36 weeks of PEG IFN and RBV) is indicated; in these phase II trials, an SVR was achieved in 70% of partial responders and 45% of null responders. In more recently conducted studies, the combination of simeprevir and SOF for 12 weeks resulted in SVR_{12}s of 97% in treatment-naïve and treatment-experienced patients without cirrhosis.[180] In patients with compensated cirrhosis, the overall rate of SVR_{12} was 83%. Based on this trial, addition of RBV and expansion of therapy for 24 weeks was recommended in treatment-naïve and treatment-experienced cirrhotic patients,[181] before subsequent revision of treatment guidelines (see later).[113]

The combination of SOF and simeprevir was also found to be very effective in patients with genotype 1 (well tolerated; SVR_{12} after 12 to 24 weeks of therapy, with or without RBV, in 92%–94% of 167 treatment-naïve ["METAVIR F3–F4"] and IFN-experienced prior nonresponders ["METAVIR F0–F2"]),[182] including those with decompensated cirrhosis (well tolerated; 74% SVR_{12}, with or without RBV, in 42 patients with Child-Pugh class B and C)[183] and was a recommended first-line combination regimen until superseded by later-generation DAAs (see later).[113] Currently, all protease inhibitor regimens, including those containing simeprevir, are not recommended in patients with decompensated cirrhosis because of reports of liver deterioration, including liver failure and death.[113] Overall, as noted earlier, based on current recommendations, simeprevir has a very limited role and is not part of *first-line* DAA combinations. As an alternative regimen, simeprevir can be used in combination with SOF in genotype 1a and 1b infections in treatment-naïve and PEG IFN/RBV treatment-experienced patients if no cirrhosis is present (www.hcvguidelines.org).[113]

Sofosbuvir

Spectrum and Mechanism of Action

The first nonprotease inhibitor direct antiviral to be approved (in December 2013) was SOF (Sovaldi; see Fig. 47.3D), a uridine nucleoside polymerase inhibitor with one of the best profiles among the all-oral DAA agents available (and part of three of the five first-line recommended regimens). SOF is very potent, has a high barrier to resistance and pangenotypic activity, is very well tolerated with few adverse events, requires only once-daily oral administration with or without food, and appears to be relatively free from major drug-drug interactions.[184–186] In clinical trials SOF at a daily dose of 400 mg has been studied in all genotypes (1–6); in treatment-naïve subjects and prior null responders to PEG IFN–based therapy; in prior telaprevir and boceprevir nonresponders, with PEG IFN/RBV or in IFN-free regimens; in combination with RBV or with NS5A inhibitors (SOF/ledipasvir, SOF/VEL, see later) and in combination with both an NS5A inhibitor and a protease inhibitor (SOF/VEL/VOX, see later); and for treatment periods as brief as 8 to 12 weeks to as long as 24 weeks.[187,188] Currently, SOF-containing DAA combinations are recommended as *first-line* therapy of both treatment-naïve and treatment-experienced patients, both noncirrhotic and cirrhotic patients (compensated and decompensated) with genotypes 1 to 6 (see Tables 47.1 and 117.9); as noted earlier, SOF plus simeprevir is recommended as an alternative DAA regimen in noncirrhotic patients with genotypes 1a and 1b (www.hcvguidelines.org).[113]

SOF is a prodrug nucleoside inhibitor of HCV RNA NS5B polymerase that is metabolized to the active uridine nucleoside triphosphate, resulting in chain termination. SOF is active against all HCV genotypes and has an EC_{50} of 0.7 to 2.6 μM against recombinant NS5B and of 0.014 to 0.11 μM in NS5B-containing replicons.[186]

Resistance

Susceptibility to SOF is reduced by an S282T substitution in NS5B, but clinically apparent, treatment-emergent resistance with this RAS or others (M289L, L159F, V321A, C316N, S282R) is very rare in patients receiving SOF.[186]

Pharmacology/Pharmacokinetics

In the liver, SOF is metabolized to the active triphosphate nucleoside analog by sequential hydrolysis, phosphoramidate cleavage, and phosphorylation. After oral administration of SOF, peak plasma concentrations of SOF and its active metabolite occur at 0.5 to 2 hours and 2 to 4 hours, respectively; the AUC_{0-24} in normal subjects was 828 ng·h/mL and 6790 ng·h/mL, respectively; and the AUC_{50} in persons with HCV infection was 39% higher and 39% lower, respectively. Food has no effect on SOF metabolism. Approximately 61% to 65% of SOF is bound to plasma proteins, but plasma protein binding of its active metabolite is negligible. Most of SOF and its active metabolite are eliminated by renal clearance; the $T_{1/2}$ for SOF is 0.4 hours and of its metabolite is 27 hours.[186]

Interactions

Clinically relevant drug-drug interactions are rare for SOF. P-gp inducers, which can reduce plasma SOF concentrations, should not be used with SOF; however, P-gp inhibitors do not affect the concentration of the active metabolite of SOF and can be given with SOF, and SOF does not increase exposure of drugs that are a substrate for P-gp. Drugs that can reduce concentrations of SOF and its active metabolite—and that should not be administered with SOF—include carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin, rifapentine, St. John's wort, and tipranavir/ritonavir. Proton pump inhibitors (PPIs) such as omeprazole raise gastric pH, which reduces SOF solubility; if a PPI is to be used, both the PPI (equivalent to ≤20 mg of omeprazole) and SOF should be taken together under fasted conditions.[186]

Toxicity

In initial clinical trials, the most commonly reported side effects (in ≥20% of participants) associated with SOF appeared to be attributable to concomitant PEG IFN and RBV (headache, fatigue, nausea, insomnia)

or concomitant RBV (headache and fatigue). SOF appears to have no effect on hematologic markers that are not attributable to PEG IFN and RBV. SOF does not prolong the QT interval on electrocardiography. SOF is contraindicated in pregnancy when used with RBV (category X); however, when used without RBV, SOF, which has no effect in animals on fetal development, is classified as pregnancy category B.[186] SOF has been associated with severe bradycardia when taken with amiodarone, especially in patients also taking β-blockers; therefore SOF, either alone or in combination with other DAAs, should not be used in patients taking amiodarone. Although no dose reductions are necessary in either decompensated liver disease or mild-moderate chronic kidney disease (stages 1–3), insufficient data are available for, and the DAA combinations containing SOF are not recommended in, patients with severe chronic kidney disease who have a CrCl <30 mL/min (stages 4 and 5).[186]

Clinical Studies

In a phase III IFN-free trial of SOF plus RBV—in patients with genotypes 2 and 3 who were IFN intolerant, ineligible, or unwilling—78% achieved SVR (93% genotype 2, 61% genotype 3).[189] Similarly, among prior PEG IFN/RBV nonresponders with genotypes 2 and 3 treated with open-label SOF/RBV (IFN-free) for 12 or 16 weeks, 50% (86% genotype 2, 30% genotype 3) and 73% (94% genotype 2, 62% genotype 3), respectively, experienced SVRs.[189] In phase III trials, among patients with genotypes 1 and 4 to 6, open-label SOF plus PEG IFN/RBV for 12 weeks yielded SVRs of 90% (compared with 60% in historical control subjects), 89% in genotype 1, and 97% in genotypes 4 to 6.[188] In treatment-naïve subjects with genotypes 2 and 3, SVRs occurred in 67% of patients treated with either SOF and RBV for 12 weeks or PEG IFN/RBV for 24 weeks; again, SVR was more frequent in SOF/RBV recipients with genotype 2 (97%) than in those with genotype 3 (56%).[188] Exploratory trials of IFN-free combinations of SOF plus NS5A inhibitors yielded near-100% SVRs in both treatment-naïve subjects and prior null responders with genotypes 1, 2, and 3 after treatment durations as brief as 12 weeks (ledipasvir) and 24 weeks (daclatasvir). A fixed-dose combination tablet containing SOF and the NS5A inhibitor ledipasvir was approved in October of 2014 (see later).[190] Fixed-dose combinations of SOF were approved as well with another NS5A inhibitor, VEL (approved June 2016) and with both NS5A inhibitor VEL and the protease inhibitor VOX (approved July 2017). The two-pill combination of SOF with the protease inhibitor simeprevir occupies a small niche in DAA guideline (see earlier), as does the two-pill combination of SOF with the NS5A inhibitor daclatasvir approved in July 2015 (see later) (www.hcvguidelines.org).[113] These DAAs and the clinical trials demonstrating their efficacy are described later.

Ledipasvir/Sofosbuvir (Harvoni)

Spectrum and Mechanism of Action

Ledipasvir/SOF is a fixed-dose combination tablet containing 90 mg of ledipasvir and 400 mg of SOF, approved by the FDA in October 2014. Ledipasvir is an NS5A inhibitor, and SOF is an NS5B polymerase inhibitor, reviewed earlier. The EC_{50} of ledipasvir against full-length replicons from genotypes 1a and 1b is 0.031 nM and 0.004 nM, respectively. It has somewhat less activity against genotypes 4, 5, and 6 and substantially lower activity against genotypes 2 and 3.[191]

Resistance

Reduced susceptibility to ledipasvir was seen with NS5A amino-acid substitution at Y93H/N, Q30E, and L31M in genotype 1a, and at Y93H in genotype 1b. Approximately 20% of genotype 1 viruses have polymorphisms associated with decreased susceptibility to ledipasvir; however, these variants do not appear to reduce the efficacy in treatment-naïve patients but may do so in treatment-experienced patients.[191] Ledipasvir is active against SOF-resistant viruses with NS5B substitutions, but resistance to ledipasvir may confer resistance to other NS5A inhibitors. In patients who had failed prior DAA treatment, including those with ledipasvir RASs, clinical trials demonstrated that increasing the duration of ledipasvir/SOF (e.g., from 8–12 weeks to 24 weeks) and/or adding RBV was highly effective in achieving an SVR_{12}. Such addition of RBV and the extension of treatment to 24 weeks are rarely needed now that an even more potent NS5A inhibitor, VEL, has been combined with SOF (see later).

Pharmacology/Pharmacokinetics

The combination of ledipasvir and SOF is administered once daily with or without food. The median terminal half-life of ledipasvir is 47 hours. Ledipasvir is greater than 99.8% bound to human plasma proteins, and biliary excretion is the major route of elimination. No adjustment of dose is needed for mild or moderate renal impairment, but SOF and its metabolite can accumulate in severe renal impairment, and SOF-containing DAA combinations are not recommended for patients with CrCl of <30 mL/min. No dose reduction is needed for moderate (Child-Pugh class B) or severe (Child-Pugh class C) liver dysfunction.[191]

Drug Interaction

Compared with protease inhibitors, ledipasvir and SOF have few clinically important drug-drug interactions. Ledipasvir and SOF are both substrates for P-gp; therefore P-gp inducers can reduce ledipasvir and SOF plasma concentrations. These drugs include rifampin, St. John's wort, phenytoin, and phenobarbital. Neither ledipasvir nor SOF is a substrate for hepatic or renal transporters. Ledipasvir is also an inhibitor of P-gp, may increase levels of tenofovir, and should not be used with the combination of elvitegravir, cobicistat, and emtricitabine.

Toxicity

Ledipasvir/SOF is generally well tolerated, with discontinuation of medication of 0%, less than 1%, and 1% for subjects receiving the combination for 8, 12, and 24 weeks, respectively. The most frequent adverse effects were fatigue, headache, nausea, diarrhea, and insomnia and were mostly of grade 1 severity.[191] As with all SOF-containing DAAs, ledipasvir/SOF should not be administered to patients taking amiodarone, in whom SOF has been associated with severe bradycardia. PPIs such as omeprazole raise gastric pH, which reduces SOF solubility; if a PPI is to be used, both the PPI (equivalent to ≤20 mg of omeprazole) and SOF should be taken together under fasted conditions.[186]

Clinical Studies

Clinical trials of ledipasvir/SOF have resulted in high SVR_{12} rates (91%–100%) in both treatment-naïve ("ION-2" and "ION-3") and treatment-experienced ("ION-2") patients with HCV genotype 1.[190,192–194] The duration of therapy is 12 weeks for treatment-naïve patients and for treatment-experienced patients without cirrhosis; 8 weeks of therapy may be sufficient for treatment-naïve non-Black patients without cirrhosis (and without HIV coinfection) who have HCV RNA levels of $<6 \times 10^6$ IU/mL. For treatment-experienced patients with cirrhosis who were treated with ledipasvir/SOF, clinical trials showed that 24 weeks of therapy was required; however, ledipasvir/SOF has been supplanted by other SOF-containing DAA combinations (SOF/VEL and SOF/VEL/VOX), as well as combinations of SOF-free DAAs (see later) that require only 12 weeks in these patients (treatment-experienced cirrhotic patients). Studies with and without RBV indicate that addition of RBV did not improve efficacy of ledipasvir/SOF. Moreover, in patients with genotypes 1 and 4 this combination DAA has been shown to be effective and is now indicated for patients with decompensated cirrhosis. In one such study in the United States ("SOLAR-1"), 337 patients received 12 to 14 weeks (which turned out to be indistinguishable) of ledipasvir/SOF plus RBV. In the cohort of patients who had not undergone liver transplantation, SVR_{12} was achieved in 86% to 89% in decompensated cirrhotic patients. In the cohort of patients who had undergone liver transplantation, SVR_{12} was achieved in 96% to 98% without cirrhosis or with compensated cirrhosis, in 85% to 88% with Child-Pugh class B, in 60% to 75% with Child-Pugh class C, and in six out of six with fibrosing cholestatic hepatitis.[195] Additional discussion of clinical studies can be found in Chapter 117.[113,159]

Paritaprevir/Ritonavir/Ombitasvir Plus Dasabuvir (Viekira Pak)

Spectrum and Mechanism of Action

Paritaprevir is an inhibitor of the HCV NS3/4A protease, with EC_{50} activities against genotypes 1a and 1b of 1.0 nM and 0.21 nM, respectively. Good EC_{50} activities were also noted against genotypes 4a and 6a (0.09 nM and 0.68 nM, respectively).[196] Paritaprevir was less active against genotype 2A (EC_{50} 5.3 nM) and 3a (EC_{50} 19 nM). Ritonavir is an HIV-1 protease

inhibitor and a CYP3A inhibitor that boosts levels of paritaprevir pharmacokinetically but has no direct activity against HCV. (See Chapter 128 for further discussion of ritonavir.)

Ombitasvir is an inhibitor of HCV NS5A and has EC_{50} activities against replicons of genotypes 1a and 1b of 0.68 pM and 0.94 pM, respectively. EC_{50}s were 1.7 to 19 pM against genotypes 2a, 2b, 3a, 4a, and 5a. The EC_{50} against genotype 6a was 366 pM.[196]

Dasabuvir, a nonnucleoside inhibitor of NS5B RNA-dependent RNA polymerase, targets the palm domain of NS5B and acts as an allosteric inhibitor. The EC_{50} values of dasabuvir against replicons of genotypes 1a and 1b are 0.6 nM and 0.3 nM, respectively. Dasabuvir has reduced activity in biochemical assays against NS5B polymerase from genotypes 2a, 2b, 3a, and 4a (IC_{50} values range from 900 nM– >20 μM).[196]

Because later-generation DAAs consist of fewer individual drugs, have broader genotype specificity, and require once-daily RBV-free dosing, this combination DAA is no longer recommended as a *first-line* treatment for hepatitis C; however, ritonavir/paritaprevir-ombitasvir-dasabuvir remains included among the recommended *alternative* regimens (www.hcvguidelines.org).[113] Still, by and large, the current use of this DAA combination is very limited.

Resistance

Resistance can be generated by exposure of genotype1a and 1b replicons to paritaprevir, ombitasvir, or dasabuvir. In clinical trials of HCV 1a resistance emerged with amino-acid substitutions in NS3 (D168V/any), NS5A (M28A/T/V and Q30E/K/R), and NS5B (S556G/R). Few virologic failures were noted in genotype 1b infections. Resistance-associated substitutions were slightly more frequent among patients who did not achieve SVR, but the presence of such polymorphisms was not anticipated to have a clinically significant effect on treatment responses.[196]

Pharmacology/Pharmacokinetics

Paritaprevir/ritonavir/ombitasvir are formulated as a fixed-combination tablet consisting of 75/50/12.5 mg of each component, respectively. Two tablets are given once daily in the morning (daily dose of 150, 100, and 25 mg, respectively). Dasabuvir tablets (250 mg) are given twice daily (morning and evening) for a total daily dose of 500 mg. In July 2016 an extended-release version (Viekira XR) was approved, consisting of three individual tablets (ritonavir [33.33 mg]-boosted paritaprevir [50 mg], ombitasvir [8.33 mg], and long-acting dasabuvir [200 mg])—three tablets of each taken once daily (daily doses ritonavir 100 mg, paritaprevir 150 mg, ombitasvir 25 mg, dasabuvir 600 mg), with or without twice-daily RBV. Except for noncirrhotic patients with genotype 1b, all others must take RBV in divided doses (twice daily) along with paritaprevir/ritonavir/ombitasvir plus dasabuvir. The regimen is given with meals.

The components of the regimen are highly plasma protein bound. Paritaprevir is metabolized predominantly by CYP3A4 and to a lesser extent by CYP3A5; ritonavir is metabolized predominantly by CYP3A and to a lesser extent by CYP2D6; ombitasvir is metabolized predominantly by amide hydrolysis, followed by oxidative metabolism; and dasabuvir is metabolized predominantly by CYP2C8 and to a lesser extent by CYP3A. The mean plasma half-lives of paritaprevir, ritonavir, and dasabuvir are 5.5, 4, and 5.5 to 6 hours, respectively. The ombitasvir mean elimination half-life was 21 to 25 hours. Nonrenal mechanisms account for the elimination of greater than 85% of the administered drugs. Therefore renal insufficiency does not affect levels of this regimen significantly. If RBV is needed, this DAA cannot be used in renal insufficiency; if RBV is not needed (e.g., treatment-naïve noncirrhotic patients with genotype 1b), this DAA combination can be administered in patients with mild, moderate, or severe renal insufficiency. Dose adjustment is not required for mild hepatic impairment (Child-Pugh class A), but use of this combination therapy is not recommended in moderate hepatic impairment (Child-Pugh class B) and contraindicated in severe (Child-Pugh class C) hepatic impairment.[196]

Interactions

As noted earlier, the components of this treatment regimen are substrates and inhibitors of important metabolic enzymes; therefore the potential for drug-drug interactions is considerable. Individual drugs that may increase levels of the treatment regimen or, alternatively, drugs whose levels may be affected by the treatment regimen are tabulated in the most recent product brochures, to which the reader is referred. Such drugs include rifampin, St. John's wort, anticonvulsants, estradiol-containing products, and salmeterol. Potential elevation of immunosuppressants (cyclosporine, tacrolimus), antiarrhythmics, and statins may occur.[197]

Toxicity

The above regimen has been generally well tolerated. Mild adverse events were common but led infrequently to discontinuation of therapy (generally <1%). Nausea, pruritus, insomnia, and asthenia were most common. In trials in which the treatment regimen included RBV, some of the side effects may have been related to RBV. Hyperbilirubinemia (primarily unconjugated) and elevations of aminotransferases were seen in approximately 1% of subjects. These usually occurred early and resolved shortly thereafter while patients remained on therapy. Mean decreases in hemoglobin of 2.4g/dL, which were noted in the phase III studies when RBV was added to the regimens, generally returned to pretreatment levels after treatment had ended.[196]

In October 2015, the FDA issued a warning to be added to prescribing information for Viekira Pak—that hepatic decompensation and failure have been reported with this medication.[198] Patients who received the medication should be monitored closely for hepatic decompensation, and, if noted, administration of Viekira Pak should be stopped. Like other DAA combinations including a protease inhibitor, Viekira Pak should not be used in patients with decompensated cirrhosis (Child-Pugh class B or C).

Clinical Studies

Clinical trials demonstrated that the regimen is highly effective in treatment-naïve patients, both with and without cirrhosis as well as in those who have failed therapy with PEG IFN and RBV.[197,199–202] High rates of SVRs have been noted in clinical studies, ranging from 93% to 100%, with the highest efficacy seen in noncirrhotic subjects with genotype 1b infections. When approved, the regimen was recommended for treatment of genotypes 1a, 1b, and 4. For genotype 1a, this drug combination was given with weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis). For genotype 1b, this treatment was given for 12 weeks, without RBV (no cirrhosis) or with RBV (cirrhosis). For genotype 4, the regimen was given for 12 weeks with RBV but without dasabuvir. Clinical studies are discussed further in Chapter 117.

Paritaprevir/Ritonavir/Ombitasvir (Technivie)

Technivie is an oral fixed-dose medication that consists of three of the four components of Viekira Pak. It does not include dasabuvir, which does not have activity against genotype 4. The regimen is two tablets taken daily with or without food, for total daily doses of paritaprevir 150 mg/ritonavir 100 mg and ombitasvir 25 mg. In July 2015 Technivie plus RBV received FDA approval for treatment of HCV genotype 4 in patients without cirrhosis but was also recommended at the time in AASLD/IDSA guidelines for patients with compensated cirrhosis (Child-Pugh class A) (see Table 47.1). In October 2015, the FDA issued the same warning letter that had been issued for Viekira Pak,[198] namely, that hepatic decompensation and failure have been reported with Technivie. Patients receiving the medication should be followed closely for hepatic decompensation, and, if noted, the drug should be stopped. Technivie should not be used in patients with decompensated cirrhosis (Child-Pugh class B or C).

As with Viekira Pak, administration of Technivie has been generally well tolerated, and the most common side effects consist of fatigue, weakness, insomnia, and pruritus, most often in the RBV-containing regimen.[203] Discussion of resistance, pharmacology, and drug interactions is presented in the section on Viekira Pak, earlier.

Technivie administered for 12 weeks with or without RBV was shown to be highly effective against HCV genotype 4. In a clinical trial involving 135 patients without cirrhosis,[204,205] SVR_{12} was achieved in 91% (40/44) of treatment-naïve patients without RBV and in 100% (42/42) with RBV. In treatment-experienced patients, SVR_{12} occurred in 100% (49/49) treated with the RBV-containing regimen. As noted

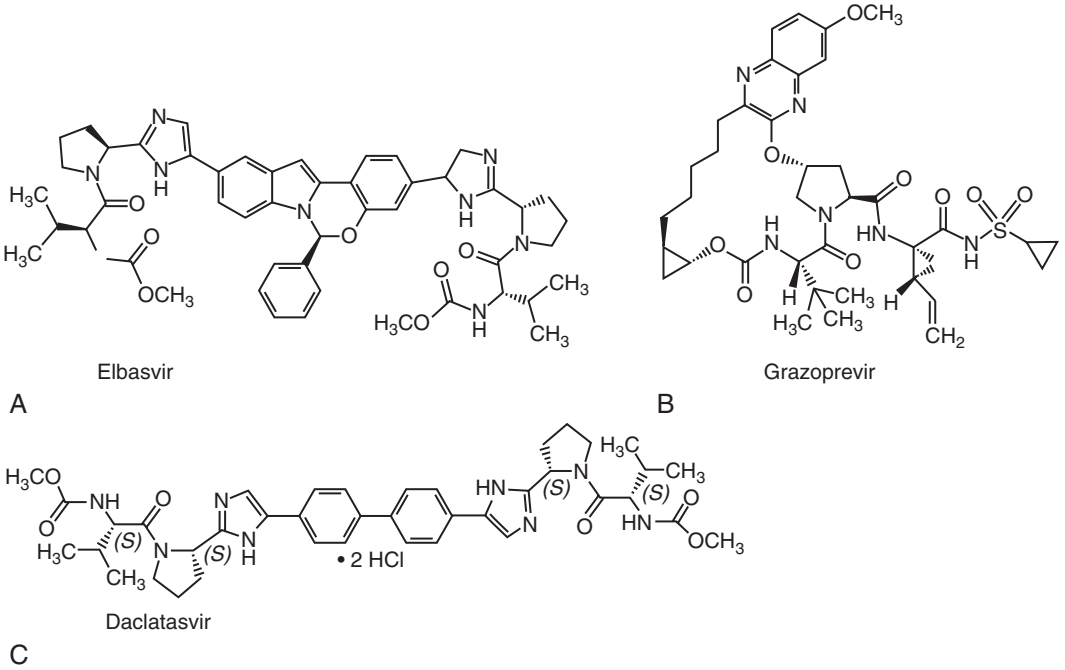

FIG. 47.4 **Chemical structures of elbasvir (A), grazoprevir (B), and daclatasvir (C).**

earlier for Viekira Pak, although retained as an alternative regimen, Technivie is no longer included in AASLD/IDSA guidelines as *first-line* therapy (www.hcvguidelines.org).[113]

Elbasvir/Grazoprevir (Zepatier)

Spectrum and Mechanism of Action

Elbasvir (50 mg)/grazoprevir (100 mg) is an oral fixed-dose combination that was approved in January 2016 for treatment of HCV infections in patients with genotypes 1a, 1b, and 4 (see Table 47.1). Compared with earlier-generation DAAs, it is highly potent and active against some of the major resistance-associated substitutions of earlier DAAs. The standard dosage regimen is one tablet once daily with or without food for 12 weeks. Because of the availability of later-generation DAAs, in patients with genotype 1a infection who have baseline NS5A RASs for elbasvir, elbasvir/grazoprevir is not recommended.

Elbasvir is a DAA inhibitor of the HCV NS5A replication complex (Fig. 47.4A). In HCV full-length replicon assays, it has activity against genotypes 1a, 1b, and 4, with EC_{50} values of 4 pM, 3 pM, and 0.3 pM, respectively.[206]

Grazoprevir is a DAA inhibitor of HCV protease NS3/4A (see Fig. 47.4B). In HCV full-length replicon assays, grazoprevir has EC_{50} values against genotypes 1a, 1b, and 4 of 0.4 mM, 0.5 mM, and 0.3 mM, respectively.[206]

Thus elbasvir and grazoprevir target different mechanisms of action of viral replication. Combined effects of elbasvir and grazoprevir did not show antagonism either by themselves or with the addition of RBV.

Resistance

Resistant polymorphisms against NS5A are present at positions M28, Q30, L31, and Y93 and result in reduced efficacies of 12-week courses of treatment.[207] Before therapy with this DAA, patients with HCV genotype 1a infection should undergo RNA NS5A resistance testing to determine if such polymorphisms are present. If so, an alternative DAA regimen should be selected.

Resistant NS3 polymorphisms in genotypes 1, 1a, and 4, are most commonly at positions A156T and D168A.

Pharmacology/Pharmacokinetics

After oral administration, peak concentrations occur at 3 hours for elbasvir and at 2 hours for grazoprevir.[206] Both elbasvir and grazoprevir are extensively bound to plasma proteins (≥99%). The half-lives are 24 hours for elbasvir and 31 hours for grazoprevir. Excretion is primarily through feces (>90%), and less than 1% is recovered in urine. No dosage adjustment is required for patients with renal insufficiency or for patients with mild hepatic impairment (Child-Pugh class A). Like other DAAs that include a protease inhibitor, elbasvir/grazoprevir should not be used in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) because of potential ALT elevations and increased grazoprevir plasma concentrations; however, this DAA is a preferred regimen for patients with advanced renal insufficiency (CrCl <30 mL/min); no dosage adjustment is necessary for patients with any level of chronic kidney disease, including those undergoing hemodialysis.[206]

Drug Interactions

Elbasvir and grazoprevir are substrates of CYP3A and P-gp, although the role of intestinal P-gp in absorption of elbasvir and grazoprevir appears to be minimal.[206] Coadministration of moderate and strong CYP3A inducers, which may reduce the plasma concentration of elbasvir and grazoprevir, is not recommended. Coadministration of CYP3A inhibitors, which may increase the plasma concentrations of elbasvir and grazoprevir, is also not recommended.

Grazoprevir is a substrate of OATP1B1 and B3, and coadministration of drugs that inhibit these transporters may increase grazoprevir plasma concentrations. Consult the full prescribing information for elbasvir/grazoprevir for further discussion of drug-drug interactions.[206]

Toxicity

Elbasvir/grazoprevir is generally well tolerated. In pooled data from phase II and III clinical trials, the most common adverse events were fatigue (11%), headache (10%), and nausea (5%), similar to rates in placebo recipients.[206–208] Increased ALT levels occurred in 1% of subjects, usually at or after 8 weeks of therapy, and mostly resolved at or after completion of therapy. Anemia has been observed when RBV was included in therapy.

Clinical Studies

(Also see Chapter 117.)

Elbasvir/grazoprevir has been shown to be highly effective in treatment of genotypes 1a, 1b, 4, and 6 infection in both treatment-naïve and treatment-experienced patients with or without cirrhosis. A regimen of one tablet taken daily resulted in SVR_{12} in 92% to 100% of treatment-naïve patients treated for 12 weeks ("C-EDGE-TN" [treatment-naïve])[209] and in 92% to 98% of treatment-experienced patients who received elbasvir/grazoprevir for 12 to 16 weeks with or without RBV ("C-EDGE-TE"

[treatment-experienced]).[210] Patients coinfected with HIV and HCV also had high SVR_{12} responses, 96% ("C-EDGE COINFECTION"),[211] as did patients with renal impairment ("C-SURFER").[212]

Daclatasvir (Daklinza)

Spectrum and Mechanism of Action

Daclatasvir (see Fig. 47.4C) is an orally administered inhibitor of HCV NS5A that is used at a daily dose of 60 mg in combination with 400 mg of SOF. It was approved in July 2015 for treatment of genotype 3 infection, and its approval was expanded in February 2016 to include treatment of genotype 1 infection. The AASLD/IDSA September 2017 guidelines no longer include daclatasvir/SOF as a *first-line* DAA, with rare exceptions (12-week course, except as noted): for (1) patients with decompensated cirrhosis, genotypes 1 to 4, with or without RBV (for 24 or 12 weeks, respectively), and (2) after liver transplantation along with RBV in treatment-naïve or treatment-experienced patients with genotypes 2 and 3, with or without cirrhosis, including decompensated cirrhosis. The September 2017 guidelines do retain daclatasvir/SOF as an *alternative* regimen in (1) treatment-naïve noncirrhotic patients with genotypes 1a and 1b, genotype 2 without or with compensated cirrhosis, and genotype 3 without or with (+RBV) cirrhosis; (2) PEG IFN/RBV-experienced noncirrhotic patients with genotypes 1a, 1b, and 3, as well as in both noncirrhotic and cirrhotic (extended to 16–24 weeks) patients with genotype 2; (3) after liver transplantation in treatment-naïve or treatment-experienced patients with genotypes 1, 4, 5, and 6 (along with RBV) with or without cirrhosis; and (4) after renal transplantation in treatment-naïve or treatment-experienced patients with genotypes 2, 3, 5, and 6 (along with RBV). In general, however, other highly effective DAA regimens are available for all these indications, relegating daclatasvir/SOF to a marginal role in the treatment of hepatitis C (www.hcvguidelines.org).

Daclatasvir inhibits the HCV phosphoprotein NS5A by binding to the N-terminus of domain 1 of the protein, therefore inhibiting both viral RNA replication and virion assembly.[213,214] In hybrid replicons containing NS5A sequences from genotypes 1a, 1b, and 3, median EC_{50} values of 0.008 mM, 0.002 mM, and 0.02 mM, respectively, were found.

Resistance

In genotype 1a–infected subjects with cirrhosis, the presence of an NS5A amino-acid polymorphism at positions M28, Q30, L31, or Y93 was associated with reduced efficacy.[213] Polymorphisms in NS5A were also noted in genotype 1b infections, but SVR_{12} was achieved in all treated with daclatasvir and SOF, with or without RBV. In genotype 3 infections, NS5A polymorphisms appeared to be associated with reduced efficacy of treatment.

Pharmacology/Pharmacokinetics

After one administration of daclatasvir, peak plasma concentration occurs within 2 hours. Administration of food does not have a major effect on absorption.[213] Protein binding of daclatasvir is high (99%) and independent of dose. Elimination of daclatasvir is mostly fecal (88%), and 6.6% is detected in urine. Dosage does not need to be adjusted for renal impairment, and, because of the high plasma protein binding, daclatasvir is unlikely to be removed by hemodialysis. Daclatasvir is recommended only when combined with SOF, however. Thus, because SOF has not been shown to be effective in patients with CrCl <30 mL/min (chronic kidney disease stages 4 and 5), the combination of daclatasvir and SOF is not indicated for patients with advanced renal insufficiency. No dose adjustment is recommended for patients with hepatic impairment; SOF with daclatasvir is one of the recommended first-line DAA regimens for patients with decompensated cirrhosis and genotypes 1 to 4 (www.hcvguidelines.org).

Drug Interactions

Daclatasvir is a substrate of CYP3A, and levels will be reduced when administered with moderate inhibitors of CYP3A. In that situation the dosage of daclatasvir should be increased to 90 mg/day. The use of daclatasvir with strong inducers of CYP3A should be avoided. If a strong inhibitor of CYP3A is given, the dose of daclatasvir should be reduced to 30 mg/day. Daclatasvir is a moderate inhibitor of OATP1B1, OATPB3, and BCRP and thus has the possibility to increase levels of drugs that are substrates for those transporters.

Toxicity

Daclatasvir has been generally well tolerated in reported studies. When administered along with SOF, the most commonly reported adverse events were fatigue (14%), headache (14%), nausea (8%), and diarrhea (5%). Dacalatasvir plus SOF, like any drug combination that includes SOF, may cause serious bradycardia when administered with amiodarone, particularly if a β-blocker is being administered.[215] Therefore concomitant administration of those drugs should be avoided. Because SOF has not been shown to be effective in patients with CrCl <30 mL/min (chronic kidney disease stages 4and 5), the combination of daclatasvir and SOF is not indicated for patients with advanced renal insufficiency. PPIs such as omeprazole raise gastric pH, which reduces SOF solubility; if a PPI is to be used, both the PPI (equivalent to ≤20 mg of omeprazole) and SOF should be taken together under fasted conditions.[186]

Clinical Studies

In a phase II study, among 211 treatment-naïve or treatment-experienced (with first-generation protease inhibitors plus PEG IFN/RBV) noncirrhotic patients treated with SOF plus daclatasvir with or without RBV for 12 to 24 weeks, the SVR_{12} was 98% for genotype 1; 92% for genotype 2; and 89% for genotype 3.[216] Three open-label phase III clinical trials of daclatasvir plus SOF ("ALLY-1," "ALLY-2," and "ALLY-3") showed high rates of SVR_{12} in patients with genotypes 1a, 1b, 2, 3, and 4 HCV infections treated for 12 weeks. In 101 treatment-naïve and 51 treatment-experienced patients with genotype 3 treated with the combination for 12 weeks, SVR_{12} occurred in 90% and 86%, respectively. In these patients with genotype 3, noncirrhotic patients responded substantially more frequently to this regimen than did cirrhotic patients (SVR_{12}, 96% vs. 63%) (ALLY-3).[217]

In patients with cirrhosis with Child-Pugh class A (compensated), B (moderately decompensated), or C (severely decompensated), treatment with daclatasvir plus SOF and RBV for 12 weeks resulted in an SVR_{12} ranging from a high of 93% in Child-Pugh class A and B, down to 56% in Child-Pugh class C (ALLY-1).[218] In this study, rates of SVR_{12} in cirrhotic patients were 82% in genotype 1, 80% in genotype 2, 83% in genotype 3, and 100% in genotype 4. Patients coinfected with HCV and HIV also responded well to daclatasvir and SOF for 12 weeks; across genotypes 1 to 4 the SVR_{12} was 97% in treatment-naïve and 98% in previously treated patients (ALLY-2).[219]

Velpatasvir/Sofosbuvir (Epclusa)

Spectrum and Mechanism of Action

The combination of the pangenotypic, high-barrier-to-resistance, picomolar-EC_{50} NS5A inhibitor VEL (Fig. 47.5A) with the NS5B polymerase inhibitor SOF was shown in clinical trials to be highly effective in patients with genotypes 1 to 6, including in difficult-to-treat patients with genotype 3 (e.g., prior null responders with cirrhosis) and patients who have genotypes 1 to 4 and 6 with decompensated (Childs-Pugh class B) cirrhosis.[220–222] VEL/SOF, a fixed-dose combination tablet containing 100 mg of VEL and 400 mg of SOF taken daily for 12 weeks, was approved in June 2016 for patients infected with HCV genotypes 1 to 6 and in August 2017 for patients with HIV-HCV coinfection. SOF is reviewed earlier.

The mean EC_{50} of VEL against full-length replicons from genotypes 1a and 1b is 0.014 nM and 0.016 nM, respectively. For most other genotypes, the EC_{50} of VEL is lower, accounting for its highly effective, broad pangenotypic activity: genotype 2, 0.002 to 0.016 nM; genotype 3, 0.004 nM; genotype 4, 0.004 to 0.009 nM; genotype 5, 0.021 to 0.054 nM; and genotype 6a, 0.006 to 0.009 nM.[223] The IC_{50} of VEL in biochemical assays ranges from 0.36 to 3.3 μM.[223]

Resistance

Reduced susceptibility to VEL in clinical trials was rare but was seen with NS5A amino-acid substitution at Y93H/N, K24M/T, Q30E, and L31I/V in genotype 1 and Y93H, L314F/I/P in genotype 3 (none in genotype 2).[223] In clinical trials baseline RASs for genotypes 1 to 6 ranged from a low of 9% in genotype 5 to a high of 83% in genotype

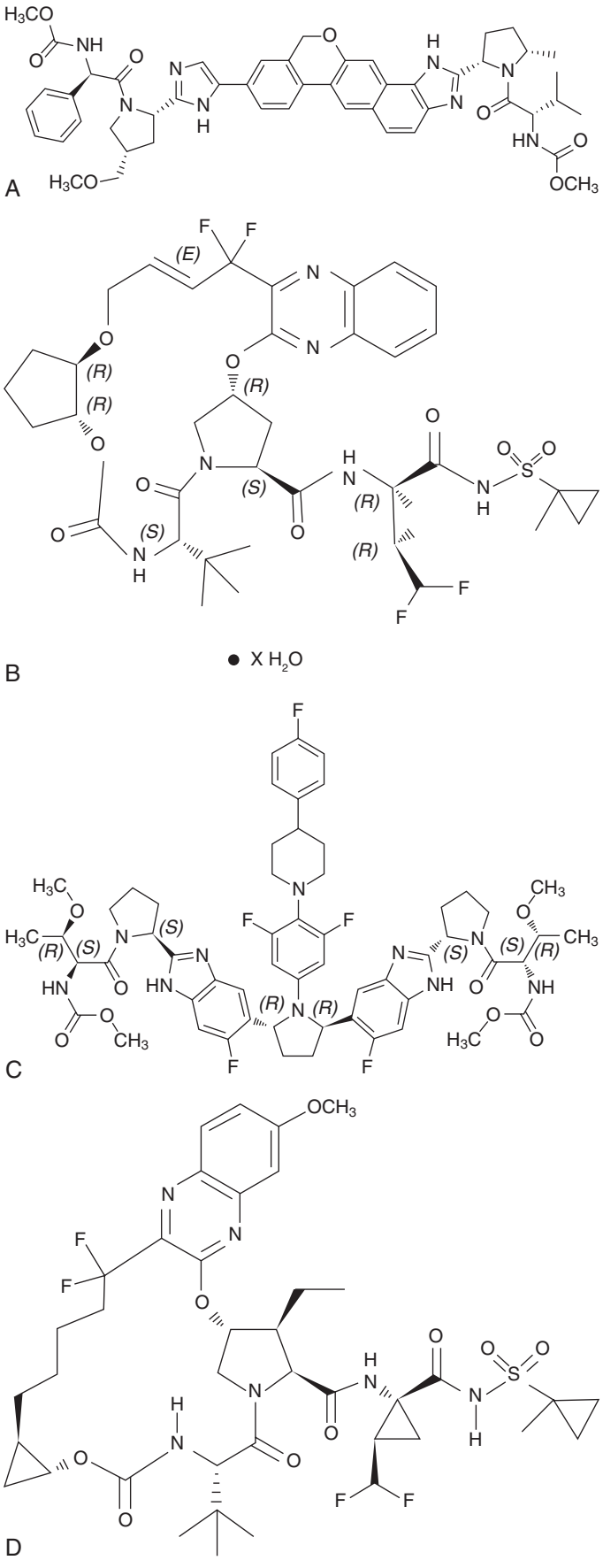

FIG. 47.5 **Chemical structures of velpatasvir (A), glecaprevir (B), pibrentasvir (C), and voxilaprevir (D).**

6 (18%–32% genotype 1, 64% genotype 2, 20% genotype 3). In trials of subjects with or without cirrhosis, relapses occurred in 1 of 75 with genotype 1 and baseline RASs, 4 of 56 with genotype 3 and baseline RASs (20% of 15 with baseline Y93H), but none with genotypes 2 and 4 to 6 with baseline RASs.[223]

Pharmacology/Pharmacokinetics

The combination of VEL and SOF is administered once daily with or without food. The median $T_{1/2}$ of VEL is 15 hours. Mean C_{max} is 259 ng/mL. VEL is greater than 99.5% bound to human plasma proteins, and biliary excretion is the major route of elimination. Because VEL is excreted via the biliary route, severe renal impairment has no impact on VEL pharmacokinetics; however, VEL is administered with SOF, which is renally excreted. No adjustment of the VEL/SOF dose is needed for mild or moderate renal impairment, but SOF and its metabolite can accumulate in severe renal impairment, and SOF-containing DAA combinations are not recommended for patients with CrCl of <30 mL/min. No dose reduction is needed for moderate (Child-Pugh class B) or severe (Child-Pugh class C) liver dysfunction. VEL does not prolong the QTc interval.[223]

Drug Interactions

Compared with protease inhibitors, VEL and SOF have few clinically important drug-drug interactions. VEL is an inhibitor of drug transporter P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1; if VEL is taken with drugs that are substrates for these transporters, drug levels of these other drugs can be increased.[223] The effect of VEL may also be reduced by moderate to potent CYP inducers.[223] VEL drug-drug interactions occur with rifampin, St. John's wort, phenytoin, and phenobarbital, among others. Neither VEL nor SOF is a substrate for hepatic or renal transporters. Because VEL is an inhibitor of P-gp, coadministration of the two drugs together may increase levels of tenofovir; VEL should not be used with efavirenz. For all DAA treatment, before initiating therapy, checking for drug-drug interactions is advisable.[223]

Toxicity

In clinical trials VEL/SOF was well tolerated; the most common adverse events were headache, fatigue, nausea, asthenia, and insomnia—all but asthenia occurring in a comparable proportion of placebo recipients, and only headache and fatigue occurred in >10% ("ASTRAL-1").[220] The frequency of these adverse events was higher in patients with decompensated cirrhosis ("ASTRAL-4").[222] As with all SOF-containing DAAs, VEL/SOF should not be administered to patients taking amiodarone, in whom SOF has been associated with severe bradycardia, especially in patients also taking β-blockers (see earlier). PPIs such as omeprazole raise gastric pH, which reduces SOF solubility; if a PPI is to be used, both the PPI (equivalent to ≤20 mg of omeprazole) and SOF should be taken together under fasted conditions.[186] Like other SOF-containing DAA combinations, SOF/VEL is not recommended in patients with CrCls <30 mL/min.[186,223] Data on safety of VEL during pregnancy are not available.

Clinical Studies

(See also Chapter 117.)

Efficacy of this pangenotypic combination was demonstrated in a series of trials: ASTRAL 1 to ASTRAL 4[220–222] and ASTRAL-5.[224] In 626 patients (including treatment-naïve, treatment-experienced, noncirrhotic patients and compensated cirrhotic patients) with genotypes 1, 2, 4, 5, and 6, treatment with SOF/VEL achieved SVR_{12} in 97% to 100% (ASTRAL-1). In ASTRAL-1, among patients receiving SOF/VEL, treatment was well tolerated; adverse events occurred in indistinguishable percentages of SOF/VEL recipients (78%) and 116 placebo recipients (77%).[220] In 134 patients with genotypes 2 (ASTRAL-2) and 277 patients with genotype 3 (ASTRAL-3), 26% to 29% of whom had failed prior antiviral treatment, 29% to 30% of whom had compensated cirrhosis, SOF/VEL for 12 weeks achieved SVR_{12} rates of 99% and 95%, respectively, superior to outcomes in control groups receiving the previous standard-of-care, SOF with weight-based RBV for 12 weeks in genotype 2 (n = 132, SVR_{12} 94%) and 24 weeks in genotype 3 (n = 275, SVR_{12} 80%).[221] Moreover, SOF/VEL was highly effective and superior to SOF/RBV in

the most refractory patient subsets, those with genotype 3 who had cirrhosis and/or had failed prior IFN-based therapy. Among treatment-naïve subjects, the rate of SVR_{12} for SOF/VEL versus SOF/RBV was 98% versus 90% in noncirrhotic patients and 93% versus 74% in compensated cirrhotic patients. The differences were even more pronounced in treatment-experienced subjects: 91% versus 71% in noncirrhotic patients and 89% versus 58% in compensated cirrhotic patients.[221]

In 267 patients with Child-Pugh class B decompensated cirrhosis (78% genotype 1, 4% genotype 2, 15% genotype 3, 3% genotype 4, <1% genotype 6; 55% treatment-experienced [44% with PEG IFN/RBV, 11% with a protease inhibitor regimen], 75%–83% with ascites), SOF/VEL achieved SVR_{12} in 83% treated for 12 weeks and in 86% treated for 24 weeks; a third group treated with SOF/VEL/RBV for 12 weeks had a slightly higher SVR_{12} of 94%. Efficacy was comparable across genotypes, except for patients with genotype 3, in whom the SVR_{12} rate for the 12-week and 24-week SOF/VEL regimens were both only 50% but 85% in the 12-week SOF/VEL/RBV regimen.[222] Baseline NS5A RASs did not affect responsiveness, except in cirrhotic patients with baseline Y93H, who had a slightly reduced SVR_{12} of 84% and in whom the addition of RBV has been recommended. In a study of SOF/VEL in 106 patients with HIV-HCV coinfection and genotypes 1 to 4, an SVR_{12} was reported in 95%—i.e., 95% in genotype 1, 100% (11/11) in genotype 2, 92% in genotype 3, and 100% (4/4) with genotype 4.[224]

Based on these data, SOF/VEL for 12 weeks is recommended as initial treatment for all genotypes, for noncirrhotic patients and compensated cirrhotic patients, and for re-treatment in subgroups of treatment-experienced patients with genotype 1 and 2; for re-treatment of patients with genotypes 3 to 6, the more effective triple combination of SOF/VEL/VOX (see later) is recommended (see Table 117.9) (www.hcvguidelines.org).

Glecaprevir/Pibrentasvir (Mavyret)

Spectrum and Mechanism of Action

The single-pill combination of two pangenotypic, high-potency, high-barrier-to-resistance DAAs, the protease inhibitor glecaprevir (GLE, 300 mg, see Fig. 47.5B) and the NS5A inhibitor pibrentasvir (PIB, 120 mg, see Fig. 47.5C), is highly effective across all genotypes. Each pill contains a third of the daily dose of both drugs; therefore daily treatment consists of three pills, which should be taken with food. In treatment-naïve noncirrhotic patients an 8-week course suffices, whereas for treatment-naïve cirrhotic patients and all treatment-experienced patients (noncirrhotic or cirrhotic) a 12-week course is required (www.hcvguidelines.org). This combination DAA was approved for adults 18 years or older in August 2017 and for children ages 12 to 17 in April 2019.[225] This DAA is a *first-line* treatment for hepatitis C in treatment-naïve, treatment-experienced, noncirrhotic, and cirrhotic patients, including patients with severe renal impairment (chronic kidney disease, stages 4 and 5, CrCl <30 mL/min) (www.hcvguidelines.org).[225]

The median EC_{50} of GLE against replicons from genotypes 1 to 6 is 0.08 to 4.6 nM; the median EC_{50} of PIB against replicons from genotypes 1 to 0.5 to 4.3 nM.[225] The IC_{50} of GLE in biochemical assays ranges from 3.5 to 11.3 μM (the IC_{50} of PIB is not provided by the manufacturer).[225]

Resistance

Reduced susceptibility to GLE/PIB and treatment failure in clinical trials were rare across all HCV genotypes. In clinical trials patients with virologic failure who were treatment-naïve or PEG IFN/RBV-experienced and/or SOF-experienced, treatment-emergent NS3 RASs included A156V, and treatment-emergent NS5A RASs included Q30R, L31M, and H58D in two patients with genotype 1a; no RASs in two patients with genotype 2; and NS3 RASs Y56H/N, Q80K/R, A156G, or Q168L/R and NS5A RASs M28G, A30G/K, L31F, P58T, or Y93H in 18 patients with genotype 3.[225] In prior nonresponders to protease (NS3/4A) inhibitors and/or NS5A inhibitors, treatment-emergent RASs in 11 GLE-/PIB-treated clinical trial subjects who failed this DAA therapy included NS3 RASs V36A/M, Y56H, R155K/T, A156G/T/V, or D168A/T and NS5A RASs M28A/G (or L28M for genotype 1b), P29Q/R, Q30K/R, H58D or Y93H/N.[225]

In clinical trials, baseline NS3 RASs were found in 1% of subjects with genotypes 1, 2, and 4; 2% with genotype 3; and 42% with genotype 3. Baseline NS5A RASs were found, in ascending order, in 13% of subjects with genotype 5, 22% with genotype 3, 27% with genotype 1, 50% with genotype 4, 54% with genotype 6, and 80% with genotype 2.[225] For patients with genotypes other than 3, baseline RASs had no influence on treatment efficacy; however, for treatment-naïve, noncirrhotic patients with genotype 3, the NS5A RAS A30K, present in 10%, was associated with a reduced SVR_{12} of 78%. In contrast, SVR_{12} occurred in all patients with genotype 3 harboring baseline Y93H RASs.[225]

Pharmacology/Pharmacokinetics

The combination of GLE and PIB is administered once daily with food. The median $T_{½}$ of GLE is 6 hours and of PIB is 13 hours. The geometric mean C_{max} is 597 ng/mL for GLE and 110 ng/mL for PIB. Percent bound to human plasma protein is 97.5% for GLE and >99.9% for PIB; biliary-fecal excretion is the major route of elimination for both DAA components. Because GLE/PIB is excreted via the biliary route, severe renal impairment has no impact on pharmacokinetics of this DAA. No adjustment of the GLE/PIB dose is needed for mild, moderate, or severe renal impairment, including patients with a CrCl of <30 mL/min. This protease inhibitor–containing DAA is not recommended in patients with moderately decompensated cirrhosis (Child-Pugh class B) and is contraindicated in patients with severely decompensated cirrhosis (Child-Pugh class C). GLE/PIB does not prolong the QTc interval.[225]

Drug Interactions

Compared with first-generation protease inhibitors, GLE/PIB has relatively few clinically important drug-drug interactions. Both GLE and PIB are inhibitors of drug transporter P-gp, BCRP, OATP1B1, and OATP1B3; if GLE/PIB is taken with drugs that are substrates for these transporters, plasma concentrations of these other drugs can be increased, as can plasma concentrations of GLE/PIB. Plasma concentrations of GLE/PIB are reduced when the DAA is taken together with P-gp of CYP3A inducers.[225] GLE and PIB are weak CYP3A, CYP1A2, and UGT1A1 inhibitors.[225] GLE and PIB drug-drug interactions occur with rifampin, carbamazepine, efavirenz, atazanavir, and St. John's wort, among others. Neither drug in the DAA combination is a substrate for hepatic or renal transporters. For all DAA treatment, before initiating therapy, checking for drug-drug interactions is advisable.[225]

Toxicity

In clinical trials GLE/PIB was well tolerated; the most common adverse effects (mild in >80% of instances), encountered in >50% of treated subjects, were headache, fatigue, diarrhea, and nausea. Like other DAAs for hepatitis C, GLE/PIB has a black box warning about reactivation of HBV infection (some cases resulting in fulminant hepatitis, hepatic failure, and death) in patients with HBV and HCV coinfection in the absence of antiviral therapy for hepatitis B.[225] Like other DAAs that contain a protease inhibitor, which can cause elevations of ALT activity and that have been complicated by liver decompensation in patients with advanced disease, GLE/PIB should not be used in patients with decompensated cirrhosis.[225] Data on safety of GLE/PIB during pregnancy are not available.[225]

Clinical Studies

(See also Chapter 117.)

In phase II and phase III trials of >2300 treatment-naïve and treatment-experienced noncirrhotic patients, this DAA achieved SVR_{12} in 99.0% to 99.7% of patients with genotypes 1, 2, and 4 to 6 and 95% with genotype 3; across all genotypes in noncirrhotic patients, 8 weeks of therapy was equivalent in efficacy to 12 weeks (phase III trials "ENDURANCE"-1–4 and phase II trial "SURVEYOR-1" and "SURVEYOR-2").[226–229] In patients with compensated cirrhosis, both treatment-naïve and treatment-experienced (IFN/RBV-based or SOF/RBV ± PEG IFN), 12 weeks of GLE/PIB achieved SVR_{12} in 99% across genotypes 1, 2, and 4 to 6 (phase III "EXPEDITION-1") and in up to 98% of patients with treatment-naïve genotype 3 (phase II SURVEYOR-2). In DAA-treatment–experienced patients (approximately a third each with protease inhibitor experience only, NS5A inhibitor only, and both protease inhibitor and NS5A experience) with genotypes 1 and 4, with or without compensated cirrhosis, GLE/PIB achieved SVR_{12}

just as frequently after 12 weeks of treatment (89%) as after 16 weeks of treatment (91%) (phase II "MAGELLAN-1").[230] In this trial both the number of previous DAA treatments and the number of baseline RASs were associated with degradation of GLE/PIB treatment. For example, in the cohort treated for 12 weeks, the GLE/PIB-associated SVR_{12} fell from 100% for prior protease inhibitor only, to 88% for prior NS5A inhibitor only, to 79% for prior protease inhibitor and NS5A inhibitor; SVR_{12} rates were 100% for patients with no baseline RASs and baseline RASs limited to NS3 (protease inhibitor) only but 83% for patients with NS5A baseline RASs.[230]

In a phase III trial among 104 patients with stage 4 or 5 renal disease (CrCl of <30 mL/min), with or without cirrhosis, whether treatment-naïve or treatment-experienced, the SVR_{12} rate across all genotypes was 98%.[226]

Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi)

Spectrum and Mechanism of Action

First-line DAA regimens for chronic hepatitis C are so effective that "cure" rates approach 100%; however, a small subset of patients fail to achieve SVR_{12}—for instance, up to 6% for genotype 1 and up to 12% for genotype 3. This efficacy gap is addressed by one of the latest generation combination DAAs, approved in July 2017, a combination of three pangenotypic, high-potency, high-barrier-to-resistance DAAs—SOF/VEL/VOX, that is, with the NS5B polymerase inhibitor SOF (400 mg), the NS5A inhibitor VEL (100 mg), and the NS3/4A protease inhibitor VOX (100 mg; see Fig. 47.5D). The single-pill DAA combination is highly effective across all genotypes.[231,232] Treatment consists of one daily triple-drug–containing pill, which should be taken with food. A 12-week course of SOF/VEL/VOX is recommended in noncirrhotic and compensated cirrhotic patients with all HCV genotypes but not in patients with decompensated cirrhosis (Child-Pugh class B and C) or in patients with severe renal impairment (chronic kidney disease, stages 4 and 5, CrCl <30 mL/min) (www.hcvguidelines.org). In noncirrhotic and compensated cirrhotic patients with hepatitis C, SOF/VEL/VOX is a *first-line* treatment for (1) treatment-experienced patients with genotypes 1 to 6 and (2) DAA-treatment-naïve (not PEG IFN/RBV-naïve) patients with genotype 3 (www.hcvguidelines.org).[177] Among treatment-experienced patients, SOF/VEL/VOX is recommended for patients with failed prior protease inhibitor/PEG IFN/RBV treatment who have genotypes 3 to 6; for patients who failed prior SOF but not an NS5A and who have genotypes 1 and 3 to 6; and for patients who failed prior NS5A treatment and who have genotypes 1 to 6. In the latter treatment-experienced category (prior NS5A treatment), patients with *cirrhosis* should have RBV added to SOF/VEL/VOX (see Table 117.9) (www.hcvguidelines.org).[233]

The EC_{50} values for SOF and VEL are listed earlier; the median EC_{50} of VOX against full-length replicons from genotypes 1 to 6 is 0.2 to 6.6 nM.[233] The IC_{50} of VOX in biochemical assays ranges from 0.36 to 3.3 μM.[233]

Resistance

In the "POLARIS"-1 clinical trial,[231] SOF/VEL/VOX treatment failure occurred in 7 of 263 (3%) patients (all with cirrhosis) who had failed prior NS5A-containing/SOF-containing treatment. All 7 had treatment-emergent NS5A RASs when they failed SOF/VEL/VOX—L31M, Y93H, K24R; the 1 patient with NS5A RAS K24R also had NS3 RAS V36A RAS at the time of failure.[233] In the POLARIS-4 clinical trial,[231] among patients who had failed a non–NS5A-containing DAA regimen, only 1 patient relapsed and had a treatment-emergent NS5A RAS M28T but no NS3/4A or NS5B RASs. In these clinical trials (described later), neither the presence of baseline NS5A RASs nor the presence of baseline NS3 RASs influenced efficacy (SVR_{12} in 98% to 99% without and in 97% to 100% with baseline RASs).[231] Similarly, in these trials the number of baseline RASs (of any kind, NS3, and/or NS5A) had no influence on SVR_{12}, 97% with one RAS, 98% with two, and 100% with three or greater than four.[231]

Pharmacology/Pharmacokinetics

The combination of SOF, VEL, and VOX is administered once daily with food. Pharmacokinetic profiles of SOF and VEL appear above. The median $T_{1/2}$ of VOX is 33 hours. Mean C_{max} is 192 ng/mL. VOX is >99% bound to human plasma proteins, and biliary excretion is the major route of elimination. Because VOX is excreted via the biliary route, severe renal impairment has no impact on VOX pharmacokinetics; however, VOX is administered with SOF, which is renally excreted. No adjustment of the SOF/VEL/VOX dose is needed for mild or moderate renal impairment, but SOF and its metabolite can accumulate in severe renal impairment, and SOF-containing DAA combinations like SOF/VEL/VOX are not recommended for patients with CrCl of <30 mL/min. Like other DAA combinations that include a protease inhibitor, SOF/VEL/VOX is not recommended for patients with moderate hepatic impairment (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C).[233] VOX does not prolong the QTc interval.[233] Data on safety of VEL during pregnancy are not available.[233]

Drug Interactions

Compared with first-generation protease inhibitors, SOF, VEL, and VOX have few clinically important drug-drug interactions. VOX is a substrate of drug transporters P-gp, BCRP, OATP1B1, and OATP1B3; if VOX is taken with drugs that are substrates for these transporters, drug levels of these other drugs can be increased.[233] VOX is metabolized primarily by CYP3A4 and to a lesser extent CYP1A2 and CYP2C8. The effect of VOX may be reduced by moderate-to-potent CYP inducers.[233] SOF/VEL/VOX administration is not recommended along with P-gp inducers and/or moderate-to-potent CYP inducers.[233] VOX drug-drug interactions occur with rifampin, St. John's wort, and carbamazepine, among others. SOF/VEL/VOX should not be administered with BCRP substrates (including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan).[233] Neither SOF, VEL, nor VOX is a substrate for hepatic or renal transporters. VOX has no effect on the metabolism of TDF or TAF or their combinations with emtricitabine and rilpivirine (TAF) or with emtricitabine and raltegravir (TDF). Administration of VOX together with efavirenz is not recommended.[233] For all DAA treatment, drug-drug interactions should be considered before initiating therapy (www.hcvguidelines.org).[233]

Toxicity

In clinical trials ("POLARIS"),[231] side effects in the SOF/VOL/VOX group were mild and uncommon; the four most common (in 12%–27%) were headache, fatigue, nausea, and diarrhea; the SOF/VEL/VOX side-effect profile was similar to that in placebo recipients and SOF/VEL recipients, for instance, for these four adverse events, 8% to 20% and 5% to 28%, respectively.

Like all DAAs that include a PI, SOF/VEL/VOX should not be used in decompensated cirrhotic patients. Similarly, like all DAAs that include SOF, this combination is effective and recommended for patients with mild-to-moderate renal impairment but not with severe renal impairment (CrCl <30 mL/min). Like other DAAs for hepatitis C, SOF/VEL/VOX has a black box warning about reactivation of HBV infection (some cases resulting in fulminant hepatitis, hepatic failure, and death) in patients with HBV and HCV coinfection in the absence of antiviral therapy for hepatitis B.[233] As with all SOF-containing DAAs, SOF/VEL/VOX should not be administered to patients taking amiodarone, in whom SOF has been associated with severe bradycardia, especially in patients also taking β-blockers (see earlier). PPIs such as omeprazole raise gastric pH, which reduces SOF solubility.[186] SOF/VEL/VOX can be taken with 20 mg of omeprazole, but the safety of other PPIs has not been evaluated.[233]

Clinical Studies

(See also Chapter 117.)

In a randomized, double-blind, placebo-controlled, phase III trial involving 263 patients with genotype 1 who had failed a course of an NS5A-containing DAA treatment (114 patients with other genotypes were included as well but were all assigned to the triple-combination group), 96% of SOF/VEL/VOX-treated subjects (12-week course of daily treatment) versus 0% of placebo recipients achieved SVR_{12} (POLARIS-1).[231] The SVR_{12} ranged from 91% for genotype 4, 95% for genotype 3, 97% for genotype 1 (1a and 1b indistinguishable), and 100% for the small numbers with genotypes 5 and 6. Noncirrhotic patients had higher SVR_{12} than compensated cirrhotic patients (99% vs. 93%), but the

presence of baseline NS5A RASs did not influence efficacy (SVR_{12} in 98% without and in 97% with baseline RASs). In a complementary randomized, double-blind, positive-controlled trial among prior nonresponders to DAA regimens that did not contain an NS5A inhibitor (POLARIS-4), patients with genotypes 1 to 3 were randomized to receive 12 weeks of SOF/VEL/VOX ($n = 163$) versus SOF/VEL ($n = 151$); 19 additional patients with genotype 4 were treated with SOF/VEL/VOX without randomization, for a total SOF/VEL/VOX cohort of 182. SVR_{12} occurred in 98% of the triple combination group versus in 90% of the double-combination group.[231] SVR_{12} rates were higher for SOF/VEL/VOX than for SOF/VEL for all genotypes except for 1b (and, in genotype 4, none received SOF/VEL): genotype 1a, 98% versus 89%; genotype 1b, 96% versus 95%; genotype 2, 100% versus 97%; genotype 3, 94% versus 85%; genotype 4 100%. SOF/VEL/VOX responsiveness was indistinguishable between noncirrhotic patients (98%) and compensated cirrhotic patients (96%), whereas, as described earlier for SOF/VEL, responsiveness to SOF/VEL in this trial was reduced in compensated cirrhotic patients (86%) compared with noncirrhotic patients (94%). The presence of baseline NS5A or NS3 RASs did not influence efficacy (SVR_{12} in 99% without and in 100% with baseline RASs) in SOF/VEL/VOX recipients; similarly, in the SOF/VEL arm of POLARIS-4,[231] SVR_{12} rates were the same in those with and without baseline NS5A or NS3 RASs (90% vs. 89%), consistent with the roughly 10% inferiority of SOF/VEL to SOF/VEL/VOX. Between POLARIS-1 and POLARIS-4, the number of baseline RASs (of any kind, NS3, and/or NS5A) had no influence on SVR_{12}—97% with one RAS, 98% with two, and 100% with three or greater than four. In these trials side effects in the SOF/VOL/VOX group were mild and uncommon (see earlier).

The potential for an 8-week course of SOF/VEL/VOX was pursued in treatment-naïve patients. Two SOF/VEL/VOX phase III trials, in which an 8-week versus a 12-week course was compared, showed that 8 weeks was inferior, yielding SVR_{12} rates of 95% versus 98% for all genotypes and for both compensated cirrhotic patients and cirrhotic patients (with the exclusion of cirrhotic patients with genotype 3), primarily because of the lower 8-week course response in genotype 1a (92%) (POLARIS-2). Eight versus 12 weeks of SOF/VEL/VOX was evaluated separately in patients with genotype 3 and cirrhosis; 96% in both duration groups achieved SVR_{12} (POLARIS-3).[232]

These trials established the basis for treatment recommendations. As noted earlier, SOF/VEL/VOX is recommended as a *first-line* DAA combination for patients with genotype 1 who have failed a prior non-NS5A, SOF-containing regimen or an NS5A-containing regimen and for patients with genotypes 3 to 6 who have failed any DAA regimen. For cirrhotic patients with genotype 3 who had failed a prior NS5A regimen, SOF/VEL/VOX efficacy was slightly lower, leading to the recommendation that RBV be added. This triple-drug DAA combination is not recommended for treatment-naïve patients, except for cirrhotic patients with genotype 3 (www.hcvguidelines.org; see Table 117.9).

State of the Art

First-generation protease inhibitors improved antiviral efficacy substantially over that of the previous standard of care (PEG IFN/RBV) but were plagued by the complexity of their regimens, suboptimal resistance profiles, limited genotype specificity, intolerability, and frequent drug-drug interactions. As noted earlier, improved HCV DAAs are available, and gone are the complexities of RGT and futility rules—not to mention the need for PEG IFN injections and the side effects of PEG IFN/RBV that beleaguered first-generation protease inhibitor–based DAA regimens. IFN-based therapy and first-generation protease inhibitors have been supplanted by combinations of simple-regimen, once-daily, orally administered, well-tolerated, pangenotypic, high-barrier-to-resistance DAAs with treatment courses as brief as 8 to 12 weeks and near-100% efficacy (almost always without RBV), the best of which are now recommended as *first-line* treatment (www.hcvguidelines.org). Because the current first-line combinations have been so successful, the impetus for and momentum behind development of new DAAs have been blunted substantially, leading to the abandonment of several DAA candidates that were not competitive with current first-line agents. Thus, the pace of new DAA development for hepatitis C has slowed dramatically, and, because current DAAs are so effective, pursuit of alternative treatment approaches (e.g., RNA interference, gene editing, immunologic manipulation) is no longer competitive. The initial costs of several of the new DAA combinations approved beginning in late 2013 were exorbitant, resulting in restrictions on approval of these therapies by insurers (including state Medicaid) and pharmacy benefits management organizations; however, as competing DAAs were approved, prices came down, and restrictions were relaxed. Still, the goal of universal therapy for patients with hepatitis C remains elusive, because, despite screening recommendations, most persons with HCV infection go undetected, and, even among those with known hepatitis C, many are lost to a porous "cascade of care" and do not find their way to initiating or completing therapy.[234,235]

Finally, worth reiterating are important considerations in selecting a DAA regimen for individual patients: (1) SOF-containing DAA combinations are not recommended for patients with severe renal impairment (CrCls <30 mL/min); the first-line regimens approved for severe renal impairment are grazoprevir/elbasvir and GLE/PIB. (2) Protease inhibitor–containing DAA combinations are not recommended for patients with moderately to severely decompensated cirrhosis (Child-Pugh B and C); for such patients, the recommended first-line DAA combinations are SOF/ledipasvir, SOF/VEL, and SOF plus daclatasvir. (3) SOF-containing DAA combinations should not be taken along with amiodarone, especially in patients taking β-blockers. (4) All DAAs for HCV infection can lead to reactivation of HBV infection (some cases resulting in fulminant hepatitis, hepatic failure, and death) in patients with HBV and HCV coinfection in the absence of antiviral therapy for hepatitis B.

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48 Miscellaneous Antiviral Agents (Interferons, Tecovirimat, Imiquimod, Pocapavir, Pleconaril)

Raphael Dolin and Stephen R. Walsh

SHORT VIEW SUMMARY

INTERFERONS

- Interferons are potent cytokines that stimulate antiviral, immunomodulating, and antiproliferative effects.
- They are classified as type I (α, β), II (γ), or III (λ) (see Table 48.1) and administered subcutaneously or intramuscularly, but pharmacokinetic properties are not well linked to physiologic effects.
- Attachment to polyethylene glycol (pegylation) prolongs half-life and possibly decreases immunogenicity and results in more convenient dosing, but toxicities persist including anemia and other cytopenias, depression, thyroid dysfunction, and fatigue.
- Major clinical use is in treatment of hepatitis B, but their use in treatment of hepatitis C has been largely supplanted by direct-acting antivirals (see Chapter 47).
- They are also approved for treatment of anogenital warts.

TECOVIRIMAT

- Tecovirimat is a low-molecular-weight compound active against smallpox virus and other orthopoxviruses.
- It inhibits formation and egress of enveloped virus through inhibition of p37 protein.
- It is effective against monkeypox virus infection in nonhuman primates and rabbitpox virus infection in rabbits.
- A phase 1 clinical safety study showed tecovirimat to be well tolerated in healthy volunteers.
- It was approved by the US Food and Drug Administration (FDA) in July 2018 under the Animal Rule, which allows use if clinical efficacy studies cannot be conducted.

IMIQUIMOD AND RESIQUIMOD

- These agents are topically applied Toll-like receptor (TLR) 7 (imiquimod) and TLR7/TLR8 (resiquimod) agonists.
- Imiquimod is approved for treatment of anogenital warts and results in clearance of these lesions in 37% to 52% of cases.
- Local skin toxicity is common, consisting of erythema, burning, and tenderness.
- Resiquimod is an investigational compound with somewhat greater potency than imiquimod.
- Resiquimod has been studied in genital herpes simplex virus infection, with early suggestion of decreases in rates of recurrences, but a phase III study failed to support an effect on recurrences.

PLECONARIL

- Pleconaril is an antipicornavirus drug that inhibits viral replication by binding to a hydrophobic pocket on the viral capsid.
- In vitro activity is against almost all commonly isolated enteroviruses and 90% of rhinovirus clinical isolates.
- Orally administered and generally well tolerated, pleconaril induces CYP3A isoenzymes and therefore has multiple drug interactions.
- Its use has been studied in enteroviral meningitis, but effects on headache and illness duration were inconsistent.
- Pleconaril has reduced the duration of rhinovirus infection by 1 day but is not approved by the FDA for this indication.
- Pleconaril is no longer under clinical development.

POCAPAVIR

- Pocapavir is an orally available antiviral active against polioviruses 1, 2, and 3 and many enteroviruses.
- Antiviral activity is through binding on specific sites on viral capsid proteins.
- In a clinical trial in healthy volunteers who were challenged with oral poliovirus 1 vaccine, pocapavir reduced duration of shedding of virus in stool, but it was associated with frequent emergence of resistant virus.
- Pocapavir is being considered for future studies in immunodeficient persons at risk for shedding of virulent polioviruses.

Antiviral agents discussed in this chapter have activity against a variety of viral infections in addition to the infections addressed in Chapters 44 to 47. The major current clinical use of interferons is in treatment of hepatitis B, which is discussed in Chapter 47.

INTERFERONS

Classification

Since their discovery in 1957 as mediators of the phenomenon of viral interference (i.e., inhibition of growth of one virus by another), interferons (IFNs) have become recognized as potent cytokines that are associated with complex antiviral, immunomodulating, and antiproliferative actions.[1–4] IFNs are proteins that are synthesized by eukaryotic cells in response to various inducers and that cause biochemical changes leading to a nonselective antiviral state in exposed cells of the same species. Three subfamilies of IFNs are recognized. Type I IFNs are the largest subfamily and include the IFN-αs (13 subtypes in humans) and the IFN-βs. The type II subfamily has only one member, IFN-γ. Type III is a more recently identified subfamily and includes IFN-λ,[5] of which there are three subtypes (λ1, λ2, λ3), also known as interleukin (IL)-28, IL-29, and IL-28R.[6,7] A fourth interferon λ subtype (λ4) has been identified as well.[8] Type I IFNs are clustered on the short arm of chromosome 9 in humans,[9] type II IFN is on chromosome 12, and type III IFNs are encoded on chromosome 19.[10] Formerly designated on the basis of the cell types from which they were derived, the IFN-αs, IFN-β, and IFN-γ are the IFNs currently in clinical use (Table 48.1). Each type is immunologically distinct and has different producer cells, inducers, and biologic effects and unique physicochemical characteristics.[2,5,11]

The IFN-αs and IFN-βs are produced by almost all cells in response to viral infection and various other stimuli including double-stranded RNA (dsRNA); bacteria; protozoa; mycoplasmas; polyanions; several low-molecular-weight organic compounds; and certain cytokines and growth factors such as IL-1, IL-2, and tumor necrosis factor. IFN-γ production is restricted to T lymphocytes ($CD4^+$ T helper cells and $CD8^+$ cytotoxic cells)[12] and natural killer cells responding to antigenic stimuli, mitogens, and certain cytokines such as IL-2. The IFN-λs also appear to be produced by multiple cell types.[13] The principal antiviral IFNs, IFN-αs and IFN-βs, are approximately 30% homologous at the amino-acid level. The human IFN-αs share a high degree of amino-acid sequence homology (>70%) but have differing in vitro antiviral and biologic effects on human cells.[14] Compared with the IFN-αs and IFN-βs, IFN-γ has less antiviral activity but more potent immunoregulatory effects, particularly with respect to macrophage activation, expression

TABLE 48.1 Nomenclature and Classification of Human Interferons

SUBFAMILY	TYPE I	TYPE I	TYPE II	TYPE III
Class[a]	α	β	γ	λ
No. subtypes	13	1	1	4
Receptor	IFNAR1/2	IFNAR1/2	IFNGR1/2	IL10R2, IFNLR1
Human chromosome	9	9	12	19
Commercial formulations	rIFN-α2b (Intron A) IFN-α2a (Roferon-A) Le-IFN-αn3 (Alferon N) Ly-IFN-αn1 (Wellferon) rIFNalfacon-1 (Infergen) Peg-IFN-α2a (Pegasys) Peg-IFN-α2b (PEG-Intron)	rIFN-β1b (Betaseron) rIFN-β1a (Avonex, Rebif)	rIFN-γ1b (Actimmune) rIFN-γ (Immuneron)	Peg-IFNλ1

[a]Type I classes in humans also include IFNε and IFNώ.

of class II major histocompatibility complex (MHC) antigens, and mediation of local inflammatory responses. Most IFNs in clinical use are produced by recombinant DNA techniques (see Table 48.1).

Recombinant interferons are available as interferon alfa-2a and interferon alfa-2b, which differ by a single amino acid. Interferon alfa-n3 is a mixture of subtypes of IFN-α purified from human leukocytes. Interferon alfacon-1 is a bioengineered form of IFN-α based on a consensus amino-acid sequence derived from naturally occurring forms of IFN-α. IFN-β is available as recombinant interferon beta-1a and interferon beta-1b.

Mechanisms of Action

A wide range of animal viruses are sensitive to the antiviral actions of IFNs, although many DNA viruses are relatively insensitive, and considerable differences in potency exist among viruses and assay systems. IFN activity is usually measured in terms of antiviral effects in cell culture. Typically one unit of IFN activity is the amount present in a sample dilution that causes a 50% reduction in virus replication or expression in certain cell lines; this is generally expressed as international units (IU) relative to National Institutes of Health or World Health Organization reference standards.

IFNs are not directly antiviral but cause elaboration of effector proteins in exposed cells, which contribute to a state of viral resistance.[1,15,16] The initial step involves IFN binding to specific cell surface receptors. For the type I IFNs (IFN-αs and IFN-β), the cognate receptor is IFNAR1/2. Type II IFNs (IFN-γ) use the homodimeric receptor, IFNGR1/2. Type III IFNs (IFN-λ) signal through a receptor complex consisting of IL10R2 and IFNLR1.[7,17–19] IFN receptors are linked to the Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathways, which, through a multistep process, activate transcription factors that bind selectively to and upregulate approximately 100 IFN-regulated genes.[20–22] The distinct pattern of STAT proteins activated by different IFNs is one mechanism for eliciting different cellular responses. For IFN-α and IFN-β, a three-protein complex known as IFN-stimulated gene factor 3 localizes to the nucleus and binds to a *cis*-acting DNA element (designated IRSE) that activates transcription of the target genes.[1,4]

A family of IFN regulatory factors exists, and other pathways may contribute to regulation of the IFN response. Microarray analysis shows that many genes are upregulated by IFN-β, but not by IFN-α or IFN-γ, in vitro.[20] The onset of IFN-induced antiviral action is rapid, and IFN exposure can induce production of more than 300 cellular proteins.[20] For many viruses, the primary antiviral effect of IFN in vitro is mediated by inhibition of viral protein synthesis. Depending on the virus and cell type, the antiviral actions of IFNs may also include inhibition of viral penetration or uncoating, synthesis or methylation of messenger RNA (mRNA), or viral assembly and release.

Among the better characterized IFN-induced proteins are unique 2′-5′-oligoadenylate (2-5[A]) synthetases and protein kinase R (PKR), either of which can inhibit protein synthesis in the presence of dsRNA.[1] The 2-5(A) synthetase produces adenylate oligomers that activate a latent cellular endoribonuclease (RNase L) to cleave cellular and viral single-stranded RNAs, leading to inhibition of protein synthesis. Activated PKR selectively phosphorylates and inactivates eukaryotic initiation factor-2 to impede translation. Activated PKR also phosphorylates the transcription factor inhibitor IκB and mediates dsRNA-induced activation of nuclear factor kappa B, which is required for IFN-β synthesis. IFNs may also block mRNA capping by inhibiting transmethylation reactions. IFNs also induce human guanylate binding protein-1, which mediates antiviral activity for several RNA viruses; the soluble form of the low-density lipoprotein receptor inhibitory for rhabdovirus assembly[23]; the MxA protein (a guanosine triphosphatase with activity against orthomyxoviruses and certain RNA viruses)[24]; and the RNA-specific adenosine deaminase ADR1, which modifies RNA transcripts after transcription.[1,4]

IFNs also inhibit hepatitis C virus (HCV) internal ribosome entry site–dependent RNA translation in vitro.[25] Induction of nitric oxide synthase seems to mediate a substantial antiviral effect of IFN-γ.[26] Increased levels of 2-5(A) synthetase activity and MxA protein or mRNA in peripheral leukocytes are also used as a marker for IFN exposure or endogenous release.[24]

Except possibly for the Mx proteins and influenza viruses and for 2-5(A) synthetase/RNase-L and picornaviruses, no consistent correlations exist between induction of a particular protein and resistance to a specific virus across a range of cell types.[16] A particular virus may be inhibited at several steps, and the principal inhibitory effect differs among virus families. Many viruses are able to counter IFN effects by blocking signaling and production or activity of selected IFN-inducible proteins.[1,16] The NS5A protein of HCV represses the function of the IFN-induced PKR,[27] and another HCV protein, E2, competitively inhibits PKR kinase activity. The *NS1* gene of influenza is an IFN antagonist that binds dsRNA to inhibit IFN production and dsRNA-activated pathways. IFN exposure may also reduce the expression of certain cellular genes including selected oncogenes and genes involved in collagen synthesis.

The viral and immune IFN systems are functionally nonredundant,[1,4,28] and complex interactions exist between IFNs and between IFNs and other parts of the immune system.[11,29] IFNs upregulate MHC class I expression and promote cytotoxic T-cell responses, regulate the expression of cytokines (IL-12, IL-15, IFN-γ) and chemokines that affect T-cell responses, alter expression of Toll-like receptors (TLRs), enhance natural killer cell cytotoxicity, and promote the differentiation of dendritic cells and Th1 lymphocytes.[15,29] IFN-α is produced by macrophages and can modify macrophage functions, increasing phagocytosis and cytolytic activity. Consequently, IFNs may ameliorate viral infections by exerting direct antiviral effects and by modifying the immune response to infection. IFN-induced expression of MHC antigens may contribute to the antiviral actions of IFN by enhancing antigen presentation and the lytic effects of cytotoxic T lymphocytes. The IFN-αs, the IFN-βs, and IFN-γ lead to increased expression of class I MHC molecules, but only IFN-γ efficiently induces class II MHC molecules.[1,4] Several viruses including cytomegalovirus (CMV) and varicella-zoster virus antagonize IFN-γ–induced MHC expression. In addition, proapoptotic and antiapoptotic genes are induced by IFNs,[20] and IFN-α and IFN-β are important mediators of apoptosis including induction of *TP53*.[1,30]

IFN titers generally appear at the sites of viral replication just after peak titers of virus and before humoral antibody responses. IFNs may

mediate some of the systemic symptoms associated with viral infections and contribute to immunologically mediated tissue damage in certain viral diseases. High IFN titers are usually followed by a reduction of virus titers, although persistently elevated IFN titers have been recognized in certain chronic and acute viral infections (e.g., hemorrhagic fevers).

Pharmacokinetics

The prolonged biologic effects of IFNs are not easily related to serum concentrations or other conventional pharmacokinetic parameters. After intramuscular (IM) or subcutaneous injection of IFN-α, absorption is greater than 80%.[31,32] Plasma levels are dose related, peaking at 4 to 10 hours and returning to baseline by 18 to 36 hours. Levels of 2-5(A) synthetase in peripheral blood mononuclear cells, which have been used as an index of biologic responsiveness to IFN, show increases beginning at 6 hours and lasting through 4 days after a single dose. An antiviral state in these cells is detectable at 1 hour, peaks at 24 hours, and slowly decreases to baseline by 6 days after injection. IM or subcutaneous injections of IFN-β result in negligible plasma levels, although increases in 2-5(A) synthetase may occur. Oral administration does not result in detectable serum IFN levels or increases in 2-5(A) synthetase activity in peripheral blood mononuclear cells.[33]

After systemic administration, low levels of IFNs are detected in respiratory secretions, cerebrospinal fluid, eye, and brain. After intravenous dosing, cerebrospinal fluid levels average less than 1% of serum concentrations.[34] The IFN-αs are stable in most body fluids, whereas the IFN-βs and IFN-γ seem to lose activity readily. It is unknown, however, whether measurable IFN levels at a particular site accurately reflect its antiviral or other biologic activities. The IFN-αs and the IFN-βs are cleared rapidly in a complex fashion. Leukocyte and recombinant IFN-α species have a plasma elimination half-life ($t_{½elim}$) of 3 to 8 hours. The clearance of IFN includes inactivation by various body fluids, cellular uptake, and metabolism by body organs, primarily the kidney, although negligible biologically active IFN is excreted in the urine. Clearance of IFN-α2 is reduced by 64% to 79% in patients on hemodialysis.[35]

The attachment of polyethylene glycol to IFN slows absorption, decreases clearance, increases $t_{½elim}$, and results in higher and more sustained serum concentrations, so that once-weekly dosing is effective. Two types of pegylated (peg) IFN-α are currently approved: peg-IFN-α2a has a 40-kDa branched polyethylene glycol moiety attached by a stable amide bond to lysine residues within the IFN protein, and peg-IFN-α2b has a 12-kDa linear moiety attached to histidine residues. peg-IFN-α2a is more stable and dispensed in solution, whereas peg-IFN-α2b requires reconstitution before use. peg-IFN-α2a is cleared primarily by the liver, whereas about 30% of peg-IFN-α2b is cleared renally.[35] For peg-IFN-α2a (multiple 180-μg doses), a peak serum concentration of 26 ng/mL occurs at about 45 hours after dosing, and $t_{½elim}$ is 80 to 90 hours. Steady-state serum levels are attained 5 to 8 weeks after initiation of weekly dosing. Moderate renal impairment and presence of cirrhosis do not affect pharmacokinetics, although clearance is reduced by 25% to 45% in patients with renal failure on hemodialysis. For peg-IFN-α2b, dose-related maximal plasma concentrations (1.4 ng/mL with multiple doses of 1.5 μg/kg) occur at 15 to 44 hours after dosing and decline with a $t_{½elim}$ of 30 to 40 hours, or about 10-fold longer than for IFN-α2b.[33] Some accumulation occurs with repetitive dosing. Dosage reductions in both peg-IFNs are indicated in end-stage renal disease.

Interactions

IFN and its inducers reduce the metabolism of various drugs by the hepatic cytochrome P-450 (CYP)–dependent mixed-function oxidase system and specifically decrease CYP1A2-mediated clearance of theophylline. IFNs may increase the neurotoxic, hematotoxic, or cardiotoxic effects of other drugs including increased risk for anemia with ribavirin.

Toxicity

Purified natural and recombinant IFNs are associated with dose-related immediate-onset and late-onset toxicities.[36] Adverse effects are generally mild and reversible at dosages of less than 5 million IU/day.[32] IM and subcutaneous injections of IFN doses of 1 to 2 million IU or more are usually associated with an acute influenza-like syndrome including fever, chills, headache, malaise, myalgia, arthralgia, nausea, vomiting, and diarrhea, especially during the first week of therapy. Symptoms begin several hours after administration and are most prominent 8 to 24 hours after dosing. Despite more prolonged blood levels, the duration of influenza-like symptoms after peg-IFN is similar to that after conventional IFNs.[35] Tolerance develops in most patients within several weeks. Febrile responses can be moderated by pretreatment with various antipyretics. Half of patients receiving intralesional therapy for genital warts experience the influenza-like illness. Intralesional IFN also causes discomfort at the injection site and leukopenia. Local reactions consisting of tenderness and erythema also occur after subcutaneous injection, and intranasal IFN causes local irritation.

Major toxicities that limit dosage and duration of IFN therapy are bone marrow suppression with granulocytopenia and thrombocytopenia; neuropsychiatric disturbance manifested by depression, anxiety, somnolence, confusion, behavioral disturbance, electroencephalographic changes, and, rarely, seizures; reversible neurasthenia with profound fatigue, anorexia, weight loss, and myalgia; thyroid dysfunction and autoimmune thyroiditis; and cardiotoxicity with hypotension, arrhythmias, and reversible cardiomyopathy. Psychiatric disturbance and depression are more common in patients with preexisting disorders but can also occur in otherwise healthy individuals. Elevations in hepatic enzymes and triglycerides and retinopathy are common.[37] IFN may lead to the development or exacerbation of various immunologically mediated disorders including sarcoidosis, systemic lupus erythematosus, psoriasis, vitiligo, lichen planus, and eczematoid skin lesions. Rare pulmonary manifestations include interstitial pneumonia, bronchiolitis obliterans, organizing pneumonia, asthma, and pleural effusion.[38] Alopecia, proteinuria, renal insufficiency, interstitial nephritis, autoantibody formation, bacterial infections, and hepatotoxicity occur.[39] Acute allergic reactions are rare. Patients with autoimmune chronic hepatitis, who may have false-positive enzyme immunoassay tests for anti-HCV antibodies, can experience worsening of their disease if treated with IFN.[40]

The adverse effects of peg-IFNs are similar to adverse effects with conventional IFNs, although dose-related neutropenia and thrombocytopenia and injection site reactions are more common with peg-IFNs. About 50% of patients with chronic hepatitis C treated with peg-IFN develop fatigue and systemic symptoms after injections; 20% to 30% experience depression or other psychiatric reactions; and approximately 10% to 16% discontinue treatment because of adverse events, most commonly psychiatric disorders.[41,42] peg-IFN-α2a may be associated with a lesser frequency of depression.[42]

The development of serum neutralizing antibodies to exogenous IFNs varies with the IFN type, dosage, and route of administration but may be more common with IFN-α2a.[43] Neutralizing antibodies may be associated infrequently with loss of clinical responsiveness.[32] Pegylation may reduce the immunogenicity of IFNs, and anti-PEG antibody seems to be rare.

IFNs may impair fertility and alter hormone levels in women. IFN is an abortifacient in monkeys at high dosages and has been used in small numbers of pregnant women, so safety during pregnancy is not established.[44] It is classified as pregnancy category C.

Clinical Studies

IFNs have undergone clinical studies in a broad variety of infections, malignancies, and other diseases. Depending on the IFN type, recombinant and natural IFN-α (see Table 48.1) are approved in the United States for treatment of condyloma acuminatum, chronic hepatitis C, chronic hepatitis B, Kaposi sarcoma in human immunodeficiency virus (HIV)–infected patients, and other malignancies. IFN-β is approved for management of multiple sclerosis. Recombinant IFN-γ is approved for treatment of chronic granulomatous disease. The major clinical uses for IFNs have been in treatments for hepatitis B and C, although they have been supplanted by the use of direct-acting antivirals for hepatitis C. The clinical studies of IFNs for those infections are discussed in detail in Chapters 47 and 117.

Herpesviruses

Although IFN is associated with antiviral effects against herpes simplex viruses (HSVs), no consistent reductions in symptoms or lesion duration have been observed with topical or systemic IFN treatment of genital

herpes.[45] Topical IFN seems to have some activity in combination with trifluridine in drug-resistant mucocutaneous HSV infections. In superficial HSV keratitis, combined administration of topical IFN-α with trifluridine or acyclovir seems to be more effective than single-agent therapy.

In localized herpes zoster in patients with cancer, early treatment with high-dose IFN-α (about 36 million IU/day for 5–7 days) reduces the risk for cutaneous or visceral dissemination, but systemic reactions are frequent, and more effective antiviral agents are available. IFN is ineffective in preventing CMV infection in bone marrow recipients or in treating CMV pneumonia.

Human Immunodeficiency Virus

HIV-infected patients frequently have detectable IFN levels, and plasma inhibitors of IFN activity are often present in patients with acquired immunodeficiency syndrome. High doses of IFN-α induce 10% to 40% response rates in patients with Kaposi sarcoma without benefiting concurrent herpesvirus infections or immune functions.[46] IFN treatment is associated not only with dose-related antiretroviral effects, particularly in early-stage infection, but also with adverse effects.[47] IFN seems to benefit HIV-related thrombocytopenia[48] and eosinophilic folliculitis.

Papillomavirus

Intralesional and systemic forms of administration of IFN produce some regression of anogenital warts,[49] although more cost-effective and better tolerated modalities are available (see Chapter 143).[50] Intralesional injection of various natural and recombinant IFNs is associated with complete clearance of injected warts in 42% to 62% of patients within 12 to 20 weeks.[51] Responders have low relapse rates (20%–30%). Responsiveness is poor in HIV-infected patients and patients with chronic lesions. Intralesional IFN does not reliably increase the response to other local therapies.[51] Mild-to-moderate systemic side effects (8%–10% dropout rate), pain and irritation at injection site, and leukopenia (≤30%) are common with intralesional IFN. Topical IFN gel provides inconsistent effects and does not seem to reduce the recurrence rate substantially after ablative therapies.[50]

Systemic IFN may provide adjunctive benefit in recurrent juvenile laryngeal papillomatosis. Most children have some initial decrease in lesions, but recurrence rates are high after cessation of therapy, and the long-term response to parenteral IFN-α is variable.[52] Laryngeal disease in older patients seems to be more responsive.

Respiratory Viruses

With the exception of adenoviruses, IFNs have broad-spectrum antiviral activity against respiratory viruses in vitro including severe acute respiratory syndrome (SARS) coronavirus.[53] In experimentally induced infections in humans, intranasal administration of leukocyte or recombinant IFN-α is protective against rhinovirus, coronavirus 229E, respiratory syncytial virus, and, to a lesser extent, influenza virus infections.[54] Under natural conditions, prophylactic intranasal IFN-α is protective only against rhinovirus colds, however, and long-term use is limited by the occurrence of nasal side effects. Intranasal IFN-α is ineffective in treating rhinovirus colds. IFN-αs, IFN-βs, and IFN-γ inhibit SARS coronavirus replication in vitro,[53] and the systemic IFN-αs have been used to treat SARS coronavirus illness, but the beneficial effect, if any, is unclear.[55,56]

Enteroviruses

Recombinant IFN-α (IFN-alfa-1b) was evaluated in a randomized, placebo-controlled study of an outbreak of hand-foot-and-mouth disease caused by enterovirus 71 (EV71) in China. The study included 312 children between 0.5 and 5 years of age. IFN-alfa-1b was administered daily for 5 days by ultrasonically nebulized inhalation or by IM injection. Both IM and aerosol IFN-alfa-1b were associated with modest, although statistically significant, reductions in duration of fever, time to healing of skin lesions, and virus load in stool.[57] Another study examined the effect of aerosol administration of IFN-alfa-2b in an outbreak of hand-foot-and-mouth disease in China caused by EV71 or coxsackievirus A16 in 372 children younger than 7 years of age. In the placebo-controlled trial, subjects received two aerosol administrations on day 1 and one administration on days 2 to 7. IFN-alfa-2b recipients had modest, although statistically significant, reductions in duration of fever, rashes, vesicles, or ulcers as well as in virus detection, along with an improvement in appetite.[58]

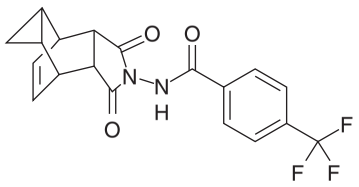

FIG. 48.1 Chemical structure of tecovirimat (ST-246, TPOXX).

TECOVIRIMAT

Tecovirimat (ST-246, TPOXX) is an antiviral that is active in vitro against smallpox virus (variola) and was approved by the FDA on July 13, 2018, for treatment of smallpox under Fast Track and Priority Review designations.[59] (See later discussion and Chapter 132.) Smallpox was declared eradicated in 1980, but the possibility remains that clandestine sources of variola exist or that virus may be recreated from published genomic sequences. Thus, the availability of effective antiviral chemotherapy is of considerable interest.

Tecovirimat is an orally bioavailable, low-molecular-weight compound (Fig. 48.1) that has activity against all known orthopoxviruses in vitro including variola,[60,61] but it does not have activity against other known viruses. It was identified after screening a chemically diverse library of more than 350,000 unique compounds.

The EC_{50} (50% effective concentration) of tecovirimat against variola is 0.010 to 0.068 μmol/L.[61] The mechanism of action of tecovirimat is through inhibition of p37, a highly conserved protein in all orthopoxviruses that mediates the formation and egress of enveloped virions.[62–66]

The efficacy of tecovirimat against orthopoxviruses was evaluated in pivotal studies in monkeypox infection in nonhuman primates and rabbitpox infection in rabbits.[60,67–75] Survival was the primary endpoint of the studies, and lesion formation (nonhuman primate model) and virus load were secondary endpoints. In nonhuman primates, treatment with tecovirimat increased survival rates to 95% compared with 5% in placebo recipients. The minimum effective dose was 3–10 mg/kg. The dose of 10 mg/kg had a greater effect on reduction of lesion count and virus load than lower doses tested. Tecovirimat was similarly efficacious in the rabbit model, with a minimum effective dose of 20–40 mg/kg.[60] A treatment-delay study in nonhuman primates showed that survival rate was improved if treatment was begun earlier after challenge (day 4 or 5) compared with later (day 6) after challenge.[75]

A phase 1 safety clinical study was conducted in 451 healthy volunteers who received either 600 mg of tecovirimat or placebo twice daily for 14 consecutive days. Tecovirimat was generally well tolerated, and overall adherence to treatment regimens was similar in tecovirimat and placebo recipients. No serious safety concerns were identified.[60] Pharmacokinetic studies revealed that half-lives of tecovirimat were approximately 23 hours, that steady-state levels were achieved by 6 days, and that elimination of drug was similar in fasting and fed groups.[60] Renal clearance is the major route of excretion. At a dose of 600 mg twice a day, maximum concentration and minimum concentration were 1591 mg/mL and 560 mg/mL at day 1 and 2209 mg/mL and 690 mg/mL at day 14, respectively.[60] This represents a ratio more than four times the minimum concentration associated with efficacy in the nonhuman primate model.[76]

The FDA approved tecovirimat based on the Animal Rule, which accepts evidence of "multiple effective exposures in animal models" when efficacy studies in humans are not possible,[77] along with evidence of safety in humans.

IMIQUIMOD AND RESIQUIMOD

Imiquimod (Aldara) is an imidazoquinoline compound (Fig. 48.2A) that is a TLR7 agonist; it acts as a topical immune response modifier lacking direct antiviral effects. Imiquimod exposure causes activation of immune cells (monocytes, macrophages, natural killer cells) to produce antiviral cytokines, particularly IFN-α and tumor necrosis factor-α and

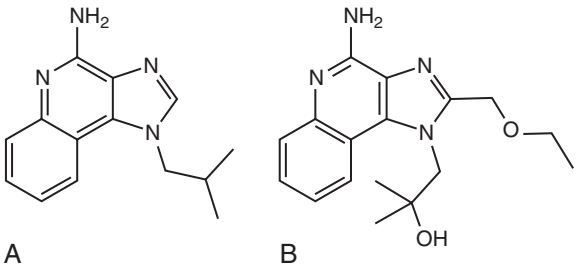

FIG. 48.2 Chemical structure of (A) imiquimod and (B) resiquimod.

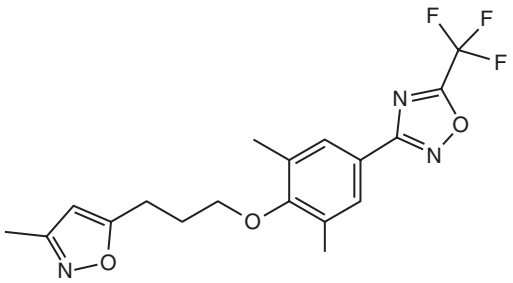

FIG. 48.3 Chemical structure of pleconaril.

IL-12, IL-10, IL-1, IL-6, and IL-8.[78,79] Imiquimod indirectly enhances acquired immune responses through activation of antigen-presenting dendritic cells including Langerhans cells and Th1 lymphocytes. IFN-γ production from T cells stimulates cytotoxic T lymphocytes, which is important in clearance of virally infected cells. Clinical responses in anogenital warts are associated with decreases in human papillomavirus (HPV) DNA copies and RNA transcripts in treated skin.[80] Resiquimod is a structurally related investigational compound (Fig. 48.2B) that is a TLR7/TLR8 agonist and is associated with greater stimulation of cytokines and with activation of dendritic cells.[81]

Topical imiquimod 5% cream is approved for patient-applied treatment of anogenital warts and has been used in other mucocutaneous infections and dermatologic conditions.[78] In immunocompetent patients, imiquimod (three overnight applications [for approximately 8 hours] weekly for up to 16 weeks) leads to complete wart clearance in 37% to 52%.[50,78,82] Clearance rates (39%–52%) are not different with 4, 8, 12, or 16 weeks of treatment.[83] Daily application increases local adverse effects without increasing clearance rates.[84] Imiquimod and podophyllin are similar in efficacy with 50% and 55% clearance rates, respectively.[85] Clearance rates are higher in women than in men and substantially lower (<15%) in HIV-infected individuals.[86–88] In one study in women, clinical outcome was related to HPV type: complete response rates were 76% for HPV-6, 67% for HPV-11, 35% for HPV-6 and HPV-11 coinfection, and 6% for other HPV types.[89] The time to clearance averages 8 to 10 weeks. Recurrences are less common (14%–19%) than after ablative therapies, and retreatment is frequently successful.[78] Imiquimod may be useful as an adjunct to laser or surgical ablative therapies.[78]

Imiquimod has been used for warts at nongenital sites[79] and in other types of HPV-related conditions. Both grade 2 and grade 3 intraepithelial neoplasia of the vulva respond to imiquimod therapy.[90] HPV anal infection in HIV-infected men may[91] or may not[92] respond. Imiquimod seems beneficial in refractory cutaneous leishmaniasis in combination with other drugs,[93,94] although other authors did not observe any benefit from combining standard intravenous antimony therapy with imiquimod.[95] Depending on the level of immunocompetence, imiquimod has been recommended as possibly beneficial for treatment of molluscum contagiosum.[78,79,96] A Cochrane Review concluded that no intervention had sufficient efficacy to be recommended for therapy in molluscum contagiosum in most patients.[97,98] A review of randomized clinical trial data in the product insert also concluded that imiquimod was not effective in treatment of molluscum contagiosum in children.[99] Imiquimod has been used successfully to treat chronic genital herpes resistant to acyclovir[100] and to foscarnet[101] in immunocompromised individuals with HIV and drug-induced immunosuppression.[102] No beneficial effects on lesions or recurrences are seen in immunocompetent adults with genital herpes.[103] Imiquimod 5% cream made recurrent herpes labialis lesions worse compared with the vehicle cream as control but increased the time to the next recurrence 80% from a median of 50 days to 91 days in the control and imiquimod-treated groups.[104] Other viral infections reported to respond to imiquimod include oral hairy leukoplakia,[105] orf,[106] and Kaposi sarcoma.[107] Tinea pedis resolved during imiquimod treatment of a contiguous basal cell carcinoma.[108]

Because of encouraging preliminary findings, topical resiquimod was investigated for treatment of recurrent genital herpes in an effort to reduce recurrences.[109] However, a controlled study did not show an effect of imiquimod on the rate of recurrences.[103] Resiquimod 0.01% gel applied to recurrent genital herpes lesions two times a week for 3 weeks reduced neither healing time nor shedding of HSV DNA by polymerase chain reaction assay compared with a control gel.[110] The same treatment regimen was associated in the subsequent 60 days with a reduction in lesional recurrence rate from 16% to 10% and with a trend toward reduced shedding from 17% to 10%. Seven months later, recurrence rates were reduced from 26% to 10% in control and resiquimod groups.[111] However, a phase III study of resiquimod did not show reduced rates of recurrence, and further development of the drug to treat anogenital herpes has been halted.[110,112]

Topical application of imiquimod 5% cream to affected skin can result in systemic absorption with serum levels of 0.1 to 3.5 ng/mL. Patients treated with imiquimod need to wash the affected area on awakening to remove residual drug. About two-thirds of treated patients experience local erythema. Application site reactions with erythema, irritation, pruritus, burning, tenderness, and scabbing (and less often with erosion or ulceration at the wart site and other exposed areas) are generally mild to moderate in intensity. These usually resolve within 2 weeks of cessation of the drug. The frequency of local reactions relates to frequency of application, and use in genital herpes may delay healing.[103] Severe local reactions including pain, erythema, or scarring are rare.[86] Unusual local reactions include erosive cheilitis[113] and aphthous ulcers,[114] angioedema and urticaria,[115] and worsening of psoriasis.[116] Systemic reactions to imiquimod such as fatigue and influenza-like symptoms have been reported infrequently.[117] Generalized psoriasis,[116] eczema,[118] exacerbations of myasthenia gravis,[119] and worsening of HLA-B27 spondyloarthropathy[120] have been reported during topical therapy with imiquimod.

Systemic reactions may be caused not by the drug itself, but rather by diffusion of cytokines from the skin into the systemic circulation. During repeated applications, small concentrations (<10 ng/mL of imiquimod) can be detected in the blood.[121] Safety during pregnancy has not been established (pregnancy category B), but there are case reports of its safe use in pregnant women.[122,123] Preclinical studies indicate that imiquimod is not genotoxic or teratogenic.

PLECONARIL

Pleconaril (3-[3,5-dimethyl-4([3-(3-methyl-5-isoxazoyl)propyl]oxy) phenyl]-5-[trifluoromethyl]-1,2,4-oxadiazole) is an orally active antipicornaviral agent (Fig. 48.3). Pleconaril inhibits picornavirus replication by binding to a specific hydrophobic pocket within the viral capsid and preventing viral attachment or uncoating of the genome. In cell culture, pleconaril inhibits replication of almost all commonly isolated enterovirus serotypes[124] and approximately 90% of rhinovirus clinical isolates.[125] Pleconaril is active in murine and human models of coxsackievirus infection.[124,126] Pleconaril has been reported to be active in vitro against enterovirus D68 (EV-D68).[127]

In adults, oral bioavailability is about 70% in the fed state, and peak plasma concentrations average 2.2 μg/mL after doses of 400 mg.[128] Pleconaril undergoes hepatic metabolism, and less than 1% is excreted unchanged in the urine. The initial plasma $t_{½elim}$ averages 2 to 3 hours, but there is a prolonged terminal $t_{½elim}$ of approximately 180 hours.[128] Single oral doses of 5 mg/kg in children provide maximal plasma concentrations of 1.3 μg/mL and approximately 40% lower overall drug exposure because of a larger volume of distribution and more rapid

clearance. Neonates seem to require higher dosages in part because of lower bioavailability.[129]

Pleconaril has been generally well tolerated, and the most common adverse events have been headache, nausea, diarrhea, and abdominal discomfort. Pleconaril induces CYP3A isoenzymes, however, and consequently has the potential for multiple drug interactions including with oral contraceptives.[130] In children or adults with enteroviral meningitis, pleconaril has inconsistent effects on headache and illness duration.[128] Pleconaril (400 mg three times a day for 5 days) reduces the duration of uncomplicated rhinovirus colds by about 1 day[130,131] but was not approved by the FDA for this indication. Pleconaril antiviral effects and clinical outcomes are related to in vitro susceptibility.[131] Pleconaril treatment (15 mg/kg/day [children] and 600–1200 mg/day [adults] in divided doses for 7–10 days) seems to be beneficial in some patients with severe or life-threatening enteroviral syndromes including chronic enteroviral meningoencephalitis in agammaglobulinemic patients and possibly neonatal enteroviral sepsis.[128,132–134] The drug was formerly available for compassionate use, but this is no longer the case.

Vapendavir, another capsid binder, has in vitro activity against EV71[135] and against EV-D68, although less so than pleconaril.[136]

POCAPAVIR

Pocapavir (V-073, SCH 48973) is an orally bioavailable antiviral that is an inhibitor of picornaviruses (Fig. 48.4). Its mechanism of action is through binding at a specific site on the viral capsid that inhibits uncoating of the virus and prevents subsequent release of viral RNA.[137,138] Pocapavir was originally developed to be a broad enterovirus inhibitor, but its major emphasis has been in potential management of poliovirus infections, particularly in the emergence of virulent poliovirus after live vaccine administration, particularly in immunodeficient persons (see Chapter 171).

Pocapavir is effective in vitro against all three poliovirus serotypes with EC_{50} of 0.003 to 0.126 μM[138] and showed effectiveness in a mouse model of poliovirus infection.[137] Pocapavir is also active against a broad variety of many, but not all, nonpolio enteroviruses with EC_{50} of 0.009 to 7.08 μM.[137]

The antiviral efficacy of pocapavir against orally administered live monovalent type 1 oral poliovirus vaccine (mOPV1) was examined in a trial in 144 healthy volunteers 18–50 years of age.[139,140] All subjects received one vaccine dose (10^7 $CCID_{50}$ [cell culture infectious dose 50%]) of mOPV1 and then pocapavir or placebo 1 or 3 days later, for a total of 14 days under a randomized, blinded allocation. The daily pocapavir dose was 1600 mg (8 capsules)/day, administered as either one or two doses per day, with or without a high-fat meal. The primary efficacy measure was duration of virus shedding in stool, and a secondary end point was quantity of virus shed. The median duration of virus shedding was 10 days for pocapavir recipients and 13 days for placebo recipients ($P = .0019$). Reduction of quantity of virus shed was significantly lower only in the cohort of pocapavir recipients who received the single daily dose beginning 72 hours after receiving oral polio vaccine ($P = .0138$).[139] The development of resistance to poliovirus was relatively common, occurring in 44% (41 of 93) of pocapavir recipients, but was also found in placebo recipients, indicating that cross-infection was common under the conditions of the study. Resistance of poliovirus to pocapavir in vitro has been previously described, with single amino-acid substitutions in capsid proteins VP1 or VP3.[141] In the current study, 70% of resistant viruses had an amino-acid substitution at VP1; 22%, at VP2; and 4%, at both sites.[139]

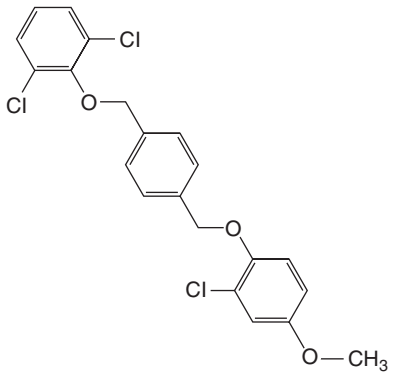

FIG. 48.4 Chemical structure of pocapavir (V-073, SCH 48973).

Administration of pocapavir appeared to be well tolerated, and the rates of adverse events were similar across treated and placebo groups. No significant safety laboratory or electrocardiogram findings were noted.

Interest in pocapavir remains as a part of therapeutic approaches to address the continuing problem of excretion of virulent poliovirus, particularly in immunodeficient persons, either singly or in combination with other antivirals. Discussions for potential studies in such settings are underway.[141]

Pocapavir is classified as an emergency investigational drug, and it has been used to treat serious cases of enteroviral sepsis[142] and enteroviral myocarditis.[143,144] The overall effect of such treatment is difficult to interpret.

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49 Immunomodulators

Andrea V. Page and W. Conrad Liles

SHORT VIEW SUMMARY

IMMUNOMODULATION FOR PROPHYLAXIS/ TREATMENT OF INFECTION

Colony-Stimulating Factors and Granulocyte Transfusions

- Colony-stimulating factors (CSFs) are glycoproteins that regulate the development and/or function of hematopoietic cells, in this case, of the myeloid series.
- Granulocyte colony-stimulating factor (G-CSF) may be used for primary prophylaxis in primary chronic neutropenic conditions, primary and secondary prophylaxis of chemotherapy-induced febrile neutropenia in selected patient populations, and treatment of febrile neutropenia only in highest risk populations.
- Granulocyte-macrophage colony-stimulating factor (GM-CSF) is approved for use in the United States as an alternative to G-CSF in selected patient populations.
- Granulocyte transfusions are recommended only for treatment of antimicrobial-refractory fungal infections in neutropenic patients, albeit with scant supporting evidence.

Interferons

- Type I interferons (IFN-α and IFN-β) have intrinsic antiviral properties. IFN-α has been used in the treatment of hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV) infections.
- Type II interferons (IFN-γ) activate macrophages and contribute to granuloma formation and the response to intracellular pathogens. IFN-γ may be used for prophylaxis of infection in patients with chronic granulomatous disease (CGD).

Interleukins

- Interleukin (IL)-2, IL-7, and IL-12 have been studied in viral diseases, including human immunodeficiency virus (HIV). IL-11 has been studied in sepsis and for the prevention of bacterial infection.
- No cytokine therapy is currently recommended for the treatment or prevention of infection.

Intravenous Immune Globulin

- Pooled, nonspecific intravenous immune globulin (IVIG) preparations have been used to replace naturally occurring immunoglobulins in primary immunodeficiencies.
- The use of IVIG is not currently recommended for the treatment of established sepsis in adults.
- Hyperimmune globulin preparations are available for the treatment and/or prophylaxis of cytomegalovirus (CMV), hepatitis B, varicella, rabies, botulism, anthrax, and tetanus.

Monoclonal Antibodies

- Palivizumab, a humanized mouse monoclonal antibody against respiratory syncytial virus (RSV), prevents viral fusion with respiratory epithelial cells and is administered monthly for up to five doses during RSV season to reduce the severity of infection and the need for hospitalization in selected high-risk infants.
- Bezlotoxumab was recently approved for the prevention of recurrent *Clostridioides difficile* (formerly *Clostridium difficile*) infection in high-risk adults already receiving anti–*C. difficile* therapy.
- Raxibacumab and obiltoxaximab are approved, based on animal studies, for use in the treatment of inhalational anthrax in combination with antibacterial therapy, and for prophylaxis of inhalational anthrax in the absence of other appropriate therapy.
- Ibalizumab-uiyk is approved for use in combination with an antiretroviral regimen in heavily treatment-experienced adults with multidrug resistant HIV-1 infection in whom current therapy is failing.

Glucocorticosteroids

- Glucocorticosteroids are used to suppress host immune responses that are contributing to the pathophysiology of an infection and have been shown to be of benefit in HIV-infected patients with moderate-to-severe hypoxia in the setting of *Pneumocystis jirovecii* pneumonia (PJP); paradoxical tuberculosis–immune reconstitution inflammatory syndrome (TB-IRIS) in patients with HIV infection but without Kaposi sarcoma; tuberculous meningitis and pericarditis when combined with antituberculous therapy; and bacterial meningitis, particularly pneumococcal meningitis, when administered with or just before the first dose of antimicrobial therapy in non–resource-constrained settings.
- Glucocorticosteroids have not been shown to be of benefit in HIV-associated cryptococcal meningitis, nor in community-acquired pneumonia.
- Their use in sepsis is currently recommended only for patients with persistent hemodynamic instability despite adequate fluid resuscitation and vasopressor support.

Synthetic Compounds With Immunomodulatory Activity

- The use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statins") has been studied, but they were not found to be of benefit in patients with sepsis, acute respiratory distress syndrome (ARDS), and community-acquired pneumonia.
- Imiquimod, a Toll-like receptor 7 (TLR7) agonist, is approved for the topical treatment of external genital and perianal condylomata acuminata in patients ≥12 years old.
- Thalidomide inhibits tumor necrosis factor (TNF) production by monocytes and macrophages and may be used for the treatment of erythema nodosum leprosum except in women of childbearing age.

Cell-Based Immunomodulatory Therapy

- Mesenchymal stromal or stem cells (MSCs) are immune-privileged pluripotent cells that influence immune cell development and function via cytokine and chemokine production.
- Although not currently used outside of clinical trials, MSCs have been studied in sepsis, ARDS, and HIV.

IMMUNOMODULATION AND RISK OF INFECTION

- Anti-TNF therapy affects the immune system's ability to eradicate intracellular pathogens and those that are sequestered in granulomas, and is therefore associated with risk for TB, bacterial sepsis, invasive fungal infections such as histoplasmosis, and other systemic infections.
- Screening for latent TB and hepatitis B should be undertaken before initiation of therapy.
- Rituximab is an anti-CD20 monoclonal antibody associated with risk of active HBV and progressive multifocal leukoencephalopathy (PML), both potentially fatal, and other bacterial, fungal, and viral infections.
- Immunomodulators targeting solid tumors include checkpoint inhibitors (such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies) which release immune cells from normal inhibition and may result in significant immune-mediated adverse reactions that are treated with conventional immunosuppressive medications.
- Immunomodulators targeting hematologic malignancies include chimeric antigen receptor

SHORT VIEW SUMMARY—cont'd

(CAR) T-cell therapies and bispecific T-cell engager (BiTE) monoclonal antibodies, both of which may result in cytokine release syndromes, and anti-CD30 antibody-drug conjugate therapy, which has been linked to PML and febrile neutropenia. Inhibition of certain PI3K isoforms has been associated with CMV disease and PJP, inhibition of Janus kinases (JAKs) with reactivation of TB and HBV, and inhibition of Bruton tyrosine kinase with invasive aspergillosis, particularly of the central nervous system.

- Immunomodulators are increasingly used to treat autoimmune and connective tissue diseases, inflammatory bowel diseases, multiple sclerosis, respiratory diseases, and other conditions. Specific infectious risks depend on the agent and its immune target (see Table 49.3). Those that target T cells or certain cytokines (IL-1, IL-6, IL-17, IL-23), their receptors (IL-2R, IL-6R), or their intracellular signaling pathways (JAKs) are associated with greater risk of TB reactivation, whereas those that target B cells or integrins are associated with increased risk of development of PML. Anti-T- and anti-B-cell agents and JAK inhibitors have been associated with HBV reactivation, and all agents have been associated with a variety of other serious infections. Monoclonal antibodies targeting IgE, IL-5, or IL-5R may be associated with risk of new or worsening helminthic infection. The anti-C5 antibody eculizumab has been associated with severe and potentially fatal meningococcal infections.

Antimicrobial agents and vaccines are the traditional strategies used for treatment and prevention of infectious diseases. Although both approaches have been remarkably successful, many infectious diseases continue to pose difficult clinical problems. Treatment may be hampered by defects of the immune system resulting from an underlying disease or immunosuppressive medications, and enhancement or reconstitution of the host immune response may be a prerequisite to long-term cure. In contrast, it is the aggressive host immune response that mediates inflammation and tissue damage in syndromes such as sepsis, and in this case downregulation of the host immune response, at least in the initial stages of the disease, may be beneficial.

An immunomodulator is a biologic or nonbiologic agent that alters the host immunoregulatory response. This response results from the actions and interactions of a complex network of cells and soluble mediators from both the innate and acquired arms of the immune system. As a result, immunomodulators can affect or influence a wide variety of targets. Immunomodulators currently in use for the treatment of infectious diseases can be divided into six main groups: (1) naturally occurring proteins or glycoproteins, many of which are reproduced by recombinant DNA technology, including the colony-stimulating factors (CSFs), interferons (IFNs), interleukins (ILs), and thymic hormones; (2) immunoglobulins, used either as replacement therapy in immunoglobulin-deficient individuals or as true immunomodulators to upregulate or downregulate the immune response; (3) monoclonal antibodies (MAbs) that block the action of proinflammatory cytokines, components of the complement cascade, or the pathogen itself; (4) glucocorticosteroids that exert pleiotropic effects on components of both the innate and acquired (adaptive) immune systems; (5) synthetic compounds with immunomodulatory activity, such as the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) pentoxifylline, imiquimod, and thalidomide; and (6) immunomodulatory cell-based therapies, including mesenchymal stromal or stem cells (MSCs).

This chapter focuses on (1) agents that are used in an effort to manipulate the immune system for the treatment or prevention of infection in humans, and (2) agents used to modulate the immune system for the treatment or control of noninfectious diseases that result in increased risk of infections. A number of potentially useful immunomodulators have been investigated in vitro or in preclinical experiments involving animal models of infection. However, because of the complexity of the host immune response, in vitro data may not correlate with in vivo results, and animal models have inherent limitations that compromise their applicability to human disease. Therefore this chapter is limited to immunomodulatory agents that have been investigated in clinical trials in humans. As knowledge of the molecular pathogenesis of inflammation, immunity, and infection evolves, novel immunomodulatory therapeutics and refinement of current immunomodulatory approaches are expected to emerge and change prevention, management, and outcomes of challenging infectious diseases.

COLONY-STIMULATING FACTORS

The CSFs are a group of naturally occurring glycoproteins that regulate the production, differentiation, survival, and activation of hematopoietic cells. Erythropoietin stimulates red blood cell production and is widely used clinically for the treatment of anemia. Thrombopoietin plays a key regulatory role in the growth and differentiation of megakaryocytes. Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF) act as growth factors for specific cell types in the myeloid series and have attracted considerable interest as immunomodulators.

Granulocyte Colony-Stimulating Factor

G-CSF is a glycoprotein that acts almost exclusively on neutrophils (polymorphonuclear leukocytes) and neutrophilic precursors to promote cell growth, differentiation, and function.[1] It is produced predominantly by monocytes-macrophages, fibroblasts, and endothelial cells and serves as a potent stimulus to both increase and accelerate neutrophil production.[1] The essential role of G-CSF in normal regulation of neutrophil development has been clearly demonstrated in studies of G-CSF knockout mice, which develop chronic neutropenia. These mice have a 50% reduction in the number of granulocyte precursor cells in the bone marrow, fail to develop sepsis-related neutrophilia, and demonstrate a diminished capacity to control experimental *Listeria monocytogenes* infection.[2] Endogenous G-CSF also influences the functional activity of developing and mature neutrophils, enhancing the inducible oxidative (respiratory) burst, phagocytosis, and chemotaxis, and delaying spontaneous apoptosis.[3–5]

Recombinant G-CSF is available for clinical use in three forms: filgrastim, a nonglycosylated polypeptide produced in *Escherichia coli*; pegfilgrastim and lipegfilgrastim, pegylated forms of filgrastim with long half-lives and single-dose administration; and lenograstim, a glycoprotein produced in Chinese hamster ovary cells, which bears the greatest resemblance to the naturally occurring molecule. Biosimilar forms of both filgrastim and pegfilgrastim have been reported to be comparable in efficacy to the original (reference or originator) forms of G-CSF when used for the prevention of febrile neutropenia in patients with breast cancer receiving myelotoxic chemotherapy.[6,7] Biosimilar forms of filgrastim are approved for use in both the United States and Europe, and a biosimilar of pegfilgrastim was recently approved for use in the United States.[8] Although concerns had been raised over long-term safety and efficacy of biosimilars, particularly when used in healthy stem cell donors, guidelines from the American Society of Clinical Oncology (ASCO) include biosimilar G-CSFs for use in the prophylaxis of chemotherapy-induced febrile neutropenia, which is usually brief.[9] For the purposes of this chapter, however, only the reference forms of G-CSF are discussed.

When administered in vivo, recombinant human G-CSF initially causes a transient decrease in the peripheral blood neutrophil count, followed by a sustained dose-dependent increase that persists while serum G-CSF concentrations remain elevated.[10] After a single subcutaneous dose of G-CSF, the highest neutrophil count is reached in approximately 12 hours (for filgrastim) or 48 hours (for pegfilgrastim), after which there is a slow decline over 2 to 3 days in patients receiving filgrastim or over 1 week or longer in those receiving pegfilgrastim.[11] The increase in neutrophil count results from an enhanced rate of

granulopoiesis combined with a shortened maturation time, culminating in increased release of immature neutrophil precursors from the bone marrow. In addition, recombinant G-CSF may also produce slight increases in monocyte and lymphocyte counts and relatively modest declines in platelet counts.[12]

Because of its potent ability to increase neutrophil counts, G-CSF has emerged as an important therapeutic option for a variety of primary chronic neutropenic conditions, including severe congenital neutropenia, cyclic neutropenia, and severe forms of idiopathic neutropenia, in which the absolute neutrophil count (ANC) may be cyclically or persistently less than $0.5 \times 10^3/mm^3$.[13] In this patient population, prophylactic administration of G-CSF significantly increases the ANC, accompanied by a concomitant reduction in infection, antibiotic use, and hospitalization.[14] It should be noted, however, that although G-CSF induces granulopoiesis in patients with congenital neutropenia via activation of the nicotinamide phosphoribosyl transferase (NAMPT)/sirtuin 1 signaling pathway, GM-CSF is unable to activate this pathway and therefore is not used in the treatment of this patient population.[15]

The most common use of G-CSF is for the prevention or treatment of neutropenia after cancer chemotherapy, in which the risk of infection is related to both the degree and duration of neutropenia. Opportunistic bacterial and fungal infections continue to be a major cause of morbidity and mortality, and each episode of febrile neutropenia has been shown to carry an in-hospital mortality rate of approximately 10%.[16] Therefore G-CSF has been used to both prevent and shorten febrile neutropenic episodes.[9]

G-CSF administration for primary prophylaxis of febrile neutropenia has been studied in multiple patient populations. However, because individual randomized controlled trials (RCTs) enrolling patients with specific malignancies may be underpowered to detect any potential effect on clinically relevant outcomes such as mortality, most of the recent data are derived from meta-analyses and systematic reviews. For instance, in a systematic review of patients who received chemotherapy for solid tumors, non-Hodgkin lymphoma, or acute lymphoblastic leukemia (ALL), administration of filgrastim was found to reduce the incidence of severe neutropenia and febrile neutropenia, and in a systematic review of patients undergoing chemotherapy for breast cancer, CSF support reduced febrile neutropenia and possibly all-cause, but not infection-related, mortality.[17,18] Although primary prophylactic G-CSF has been shown repeatedly to reduce the incidence of chemotherapy-induced neutropenia and febrile neutropenia, its detectable effects on mortality have been inconsistent. A systematic review and meta-analysis of 59 RCTs with a minimum follow-up duration of 2 years found that all-cause mortality was reduced in adult patients receiving primary prophylactic G-CSF during treatment for solid tumors or lymphomas.[19] Reductions in mortality were found in subgroups of older patients and individuals in whom chemotherapy was noncurative in intent. However, mortality reductions were most evident in individuals receiving dose-dense chemotherapy or chemotherapy for lymphoma, and were not observed when the analysis included only trials in which identical chemotherapeutic regimens were used in the G-CSF and non–G-CSF arms. A second meta-analysis including only patients with lymphoma found no reduction in mortality during the chemotherapy period, although the reduction in episodes of febrile neutropenia and documented infection remained significant.[20] A large meta-analysis of 148 studies of a mixed population of adults and children undergoing chemotherapy for solid tumors, for hematologic malignancies, or as conditioning regimens before hematopoietic stem cell transplant (HSCT) and randomized to receive either primary prophylactic G-CSF/GM-CSF or placebo/no treatment reported an overall reduction in febrile neutropenia and documented infections, but no difference in infection-related or all-cause mortality.[21] Important to note, only trials in which both arms used the same chemotherapeutic or conditioning regimen were included. This study also reported a reduction in febrile neutropenia and documented infection in the subgroup of patients with leukemia, albeit in a heterogeneous population of adult and pediatric patients receiving either G-CSF or GM-CSF. In adults with acute myelogenous leukemia (AML), CSF use has been shown to reduce the duration of neutropenia and hospitalization but not the incidence of documented infections or mortality.[17,22] Similarly, children with AML who were randomized to receive G-CSF after inductions 1 and 2 experienced a shorter duration of neutropenia but no reduction in febrile neutropenia, documented infection, infection-related mortality, or 5-year event-free survival, whereas children with ALL who received CSF support experienced fewer infections but not febrile neutropenic episodes.[23,24] Finally, in a meta-analysis of primary prophylactic G-CSF/GM-CSF before neutrophil engraftment during autologous or allogeneic HSCT, CSF use was associated with a reduction in documented infection but not infection-related mortality.[25] No increase in acute or chronic graft-versus-host disease (GVHD) was observed in recipients of allogeneic HSCT.

In aggregate, the available evidence suggests that the use of CSFs for primary prevention in patients undergoing chemotherapy for solid tumors, for hematologic malignancies excluding the acute leukemias, or as conditioning therapy before HSCT, can reduce the incidence of febrile neutropenia and proven infections and may, in certain patient subgroups, reduce infection-related and all-cause mortality. Updated clinical practice guidelines from ASCO recommend that the use of a CSF as primary prophylaxis be reserved for adult patients with a 20% or greater risk of febrile neutropenia and for some patients receiving dose-dense chemotherapy.[9] Calculation of risk for febrile neutropenia should include factors specific to the patient, his or her disease, and the planned treatment, with preference given to treatments that do not require CSF support, when such therapies are available and equivalent. No recommendation could be made for or against CSF support in myelodysplastic syndrome (MDS) or AML. As with the adult population, CSF therapy in pediatric patients should likewise be limited to those with a high risk for febrile neutropenia, and to enable dose-intensive chemotherapy that has been proven to provide a survival benefit. ASCO recommends against the use of CSFs in pediatric patients with non-relapsed ALL or AML.[9] ASCO also recommends that CSFs be used after both autologous and allogeneic HSCT to reduce the duration of severe neutropenia, albeit with the caveat that the evidence, and therefore strength of the recommendation, is much greater for CSF use in autologous HSCT. Although antibiotics have also been studied for the primary prevention of febrile neutropenia, this strategy is not addressed in the ASCO guidelines. A review found only two small studies comparing CSF support versus antibiotics for the primary prophylaxis of febrile neutropenia, and based on such limited evidence, no conclusions could be drawn.[26]

Secondary prophylaxis refers to the use of a CSF to prevent neutropenia in patients who developed a neutropenic complication, typically an episode of febrile neutropenia, during a previous cycle of chemotherapy. Secondary CSF prophylaxis has been shown to reduce episodes of febrile neutropenia and hospitalization in a mixed population of patients with solid and liquid tumors, and to reduce mortality in older patients with non-Hodgkin lymphoma.[18,27] More recent studies have focused on the use of secondary CSF prophylaxis to help achieve a target dose intensity for the chosen chemotherapeutic regimen, although the clinical relevance of this outcome may vary according to underlying disease and treatment regimen.[28] Accordingly, ASCO recommends that secondary prophylaxis be initiated in patients who have experienced a neutropenic complication in a prior chemotherapy cycle in which primary prophylaxis was not used, with the caveat that dose reduction or delay may be an alternative strategy provided it does not adversely affect outcome or survival.[9]

Unlike primary, or even secondary, prophylaxis, G-CSF is not routinely recommended to treat an established episode of febrile neutropenia. A meta-analysis of 14 RCTs that included 1553 participants who received G-CSF or GM-CSF in addition to antibiotics to treat an established episode of febrile neutropenia demonstrated shorter periods of neutropenia, antibiotic use, and hospitalization among those receiving CSFs, but no difference in overall or infection-related mortality.[29] Given the lack of demonstrable improvement in outcome, guidelines from ASCO suggest that G-CSF be considered as part of a treatment regimen for febrile neutropenia only in patients at the highest risk of infectious complications or poor clinical outcomes. Examples of the latter include prolonged or profound neutropenia, older age, uncontrolled malignancy, inpatient status at diagnosis, and infection attributable to pneumonia or invasive fungus or resulting in sepsis.[9] In keeping with these criteria, G-CSF is strongly recommended as adjunctive therapy in neutropenic

patients with hematologic malignancies and mucormycosis (zygomycosis) in clinical practice guidelines developed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM).[30]

Finally, some investigators have reported differences among the various reference formulations of G-CSF when used in the prevention of chemotherapy-induced neutropenia. Neutrophils stimulated with lenograstim in vivo best maintain their phenotype and function when studied ex vivo, and consistent with this finding, use of lenograstim as compared with filgrastim resulted in fewer febrile episodes after initial neutrophil reconstitution (ANC $>0.5 \times 10^3/mm^3$) following high-dose cyclophosphamide-induced neutropenia before peripheral blood stem cell mobilization in patients with multiple myeloma.[31,32] Likewise, meta-analysis of five RCTs comparing once-daily filgrastim versus single-dose pegfilgrastim for the primary prevention of chemotherapy-induced neutropenia in a mixed population of patients with solid organ and hematologic malignancies demonstrated fewer episodes of febrile neutropenia with the use of pegfilgrastim.[33] Nonetheless, there is no strong evidence for clear superiority of any one agent, and they are considered equivalent (when dosed appropriately) for the purposes of the prevention of febrile neutropenia.[9]

In noncongenital, non–chemotherapy-induced neutropenia, the therapeutic benefits of G-CSF are less established. For example, in human immunodeficiency virus (HIV)–infected patients, mild-to-moderate neutropenia commonly occurs as a result of medications, opportunistic infections, and the direct impact of HIV on neutrophil production and function.[34] Neutropenia has been associated with an increased risk of bacterial infections and an increase in mortality in the setting of culture-confirmed bloodstream infections.[35] However, neutropenia has not been shown to increase overall mortality in HIV-infected patients, and G-CSF has not been rigorously studied for the prevention of neutropenia-associated infection in patients receiving the current standard of antiretroviral therapy (ART).[36] Likewise, in a small study of preterm infants with neutropenia, the addition of G-CSF to antimicrobial therapy hastened neutrophil recovery but did not improve in-hospital mortality rates.[37]

Similarly, mixed results have been seen when G-CSF has been studied as a potential therapeutic immunomodulator to enhance microbicidal activity of existing phagocytes in nonneutropenic disease states. For instance, treatment with G-CSF in addition to standard antimicrobial therapy in nonneutropenic patients with severe community-acquired pneumonia reduced neutrophil apoptosis and increased ANCs, expression of cell surface markers of neutrophil activation, and release of antiinflammatory cytokines.[38] However, a systematic review of six RCTs enrolling a total of 2018 patients with pneumonia found no reduction in 28-day mortality or length of stay in the intensive care unit.[39]

In critically ill postoperative patients, G-CSF produced enhanced oxidative burst activity and phagocytosis when neutrophils were studied ex vivo.[40] However, no improved neutrophil function was detected after administration of G-CSF to patients with systemic inflammatory response syndrome (SIRS), and no mortality benefit could be detected in studies of sepsis secondary to pneumonia, severe sepsis secondary to melioidosis, or undifferentiated septic shock.[41–43] In a meta-analysis of 12 RCTs evaluating nonneutropenic patients with sepsis who were randomized to receive either G-CSF/GM-CSF or placebo, administration of a CSF increased the likelihood of resolution of infection but not in-hospital or 28-day survival.[44] In patients with severe sepsis due to suspected melioidosis in Thailand, an RCT demonstrated longer survival but no overall mortality benefit, in contrast to data from prospectively-assembled databases from Northern Australia, in which the addition of G-CSF to standard therapy, contemporaneously with other changes to standard supportive care, reduced mortality in critically ill patients with melioidosis from 92% to 26%.[45,46]

In patients with diabetic foot infections, a meta-analysis of five small RCTs, enrolling 167 patients in total, reported that administration of G-CSF resulted in fewer surgical interventions, including amputations, but did not improve wound healing or resolution of infection.[47] However, disease severity among the enrolled patients varied greatly, from mild cellulitis to limb-threatening osteomyelitis, and guidelines from the Infectious Diseases Society of America (IDSA) concluded that there was insufficient evidence to recommend the routine use of G-CSF in these patients.[48]

TABLE 49.1 North American and European Approved Uses of Cytokines to Prevent or Treat Infection

CYTOKINE	INDICATIONS
G-CSF (filgrastim)	After myelosuppressive chemotherapy for nonmyeloid malignancies After induction or consolidation chemotherapy for AML Myeloid reconstitution after HSCT Severe chronic neutropenia in patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia Neutropenia in advanced HIV disease[a]
Pegylated G-CSF	After myelosuppressive chemotherapy for nonmyeloid malignancies
GM-CSF (sargramostim)[b]	After induction chemotherapy for AML in patients older than 55 yr Mobilization and after transplantation of autologous PBPCs Myeloid reconstitution after autologous HSCT for Hodgkin lymphoma, non-Hodgkin lymphoma, or ALL Following allogeneic bone marrow transplantation from an HLA-matched related donor HSCT failure or engraftment delay
IFN-α	Treatment of chronic HBV infection Treatment of chronic HCV infection Treatment of condylomata acuminata[b] Treatment of HIV-related Kaposi's sarcoma[b]
Pegylated IFN-α	Treatment of chronic HCV infection Treatment of chronic HBV infection
IFN-γ	Chronic granulomatous disease

[a]Canada and Europe only.
[b]United States only.
ALL, acute lymphoblastic leukemia; *AML,* acute myelogenous leukemia; *G-CSF,* granulocyte colony-stimulating factor; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *HLA,* human leukocyte antigen; *HSCT,* hematopoietic stem cell transplant; *IFN,* interferon; *PBPCs,* peripheral blood progenitor cells.

Table 49.1 summarizes the approved indications for G-CSF and other recombinant cytokines in North America and Europe.

Adverse Effects of Granulocyte Colony-Stimulating Factor

G-CSF is usually well tolerated. The most common adverse effect is mild-to-moderate bone and/or musculoskeletal pain, which is estimated to occur in at least 25% of recipients but can be controlled with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs).[1,9,12,17,49] Other commonly reported adverse effects include mild local erythema at injection sites, headache, anemia, splenomegaly, thrombocytopenia, and asymptomatic elevations of lactate dehydrogenase and alkaline phosphatase. As a result of G-CSF–induced upregulation of osteoclast activity, osteopenia or osteoporosis has been reported in approximately 50% of patients receiving long-term G-CSF therapy.[50] More rarely, G-CSF has been associated with cutaneous neutrophilic vasculitis (Sweet syndrome), progression of autoimmune disorders, cancer chemotherapy–induced lung toxicity, severe pulmonary edema, and splenic rupture.[12]

The relationship between years of G-CSF use and subsequent leukemia remains a subject of debate. In severe congenital neutropenia, the overall cumulative incidence of MDS/AML after 15 years of G-CSF therapy was 22%, and increased to 34% in patients who required higher-than-usual doses of G-CSF.[51] However, a causal relationship has not been demonstrated, and it is possible that the specific underlying genetic cause of severe congenital neutropenia may be responsible for the elevated risk of leukemia.[13] Patients with cyclic and idiopathic neutropenia are at little risk of evolution to MDS/AML.[13]

Concern has also been raised about secondary MDS/AML in patients receiving G-CSF support during treatment for a primary malignancy, and caution has been advised for the use of G-CSF in children with

ALL for this reason. In a systematic review of 25 RCTs enrolling patients with solid tumors or lymphoma, both the relative and absolute risks of MDS/AML with G-CSF use were statistically significant at 1.92% and 0.41%, respectively.[52] Mortality, however, was significantly reduced in patients who had received G-CSF support, with relative and absolute risk reductions of 0.9% and 3.4%, respectively. There is currently no evidence that G-CSF is associated with hematologic malignancies in otherwise healthy individuals.[53,54]

Granulocyte Transfusions

Once G-CSF was established as a method of mobilizing large numbers of $CD34^+$ hematopoietic stem cells from bone marrow to peripheral blood (peripheral blood progenitor cells [PBPCs]) in healthy donors for use in HSCT, interest was rekindled in granulocyte (neutrophil) transfusions for the prevention or treatment of serious opportunistic bacterial and fungal infections in patients with neutropenia or inherited disorders of neutrophil function, including chronic granulomatous disease (CGD) and leukocyte adhesion deficiency, in which G-CSF therapy alone is inadequate. A systematic review of granulocyte transfusions in 44 neutropenic neonates with sepsis found no difference in all-cause mortality.[55] A systematic review of granulocyte transfusions for the prevention of infection in individuals with chemotherapy- or HSCT-induced neutropenia included 11 randomized or quasirandomized trials involving 653 participants and conducted between 1978 and 2006.[56] Although there were many caveats regarding risk of bias and imprecise outcome measures in the included studies, no difference was detected in 30-day all-cause mortality or 30-day infection-related mortality between those who received granulocyte transfusions and those who did not. However, bacteremia and fungemia were reduced in granulocyte recipients, as were local or systemic bacterial or fungal infections in those receiving an intermediate dose of granulocytes (1×10^{10} to 4×10^{10} per day). A separate systematic review of granulocyte transfusions for the treatment of established infection in patients with chemotherapy- or HSCT-related neutropenia identified 10 trials for inclusion, with a total enrollment of 587 individuals, conducted between 1975 and 2015.[57] In this instance there was insufficient evidence to determine the overall impact of granulocyte transfusion on 30-day all-cause mortality, but there was no detectable difference in clinical resolution of infection between those who received granulocyte transfusions and those who did not. This systematic review included the most recent randomized, controlled, open-label trial in this field, in which 114 patients with neutropenia due to chemotherapy, HSCT, or underlying bone marrow disease, and presumed, probable, or proven bacterial or fungal infection were randomized to antimicrobial therapy or antimicrobial therapy in combination with daily granulocyte transfusions until recovery of neutrophils or from infection, or to a maximum of 42 days.[58] The median dose transfused was 54.9×10^9 granulocytes per transfusion, and patients received a median of five transfusions. The primary outcome was survival and clinical response at day 42, which was met by similar numbers of patients in both arms, although patients who received higher doses of granulocytes (mean dose $\geq 0.6 \times 10^9$ per kilogram per transfusion) appeared to meet the primary outcome more often than those who received lower doses. Important to note, the study was stopped early owing to low accrual, with approximately half the target number of individuals enrolled.[58] At this time, granulocyte transfusions are not part of routine care for either the prevention or treatment of infection in neutropenic patients.

Nonetheless, granulocyte transfusions are recommended in several guidelines from the IDSA for treatment of refractory infections in patients with neutropenia, including persistent candidemia, although the authors acknowledge the low quality of evidence in support of the recommendation.[59] Likewise, clinical practice guidelines from ESCMID suggest that granulocyte transfusions may be used as adjunctive or salvage therapy in hematologic, cancer, and neutropenic patients with fusariosis (with a caveat in those who may undergo allogeneic HSCT); in HSCT recipients, neutropenic patients, and patients with CGD with scedosporiosis when used in combination with antifungal agents; and in neutropenic patients with disseminated candidiasis or candidemia.[60,61] However, in all cases it is acknowledged that the evidence for the recommendations is relatively weak and often based on small case reports or case series.[62]

Granulocyte-Macrophage Colony-Stimulating Factor

GM-CSF is a 127–amino-acid glycoprotein that is available in various recombinant forms, including sargramostim (produced in yeast), molgramostim (produced in *E. coli*), and regramostim (produced in Chinese hamster ovary cells), which differ slightly in amino-acid sequence and degree of glycosylation. The principal sources of endogenous GM-CSF are T lymphocytes, monocytes-macrophages, fibroblasts, and endothelial cells.[1] Administration of GM-CSF increases peripheral blood counts and stimulates the function of neutrophils, monocytes, and eosinophils.[1] Unlike G-CSF, GM-CSF does not play an essential role in neutrophil development: GM-CSF knockout mice have normal numbers of peripheral blood cells and bone marrow progenitors. However, GM-CSF knockout mice have impaired leukocyte function, increased susceptibility to bacterial and fungal pneumonia, and alveolar proteinosis as a result of impaired macrophage clearance of surfactant.[63,64] Similarly, neutralizing anti-GM-CSF antibodies have been associated with cryptococcal disease (particularly *Cryptococcus gattii*), nontuberculous mycobacterial infection, and idiopathic pulmonary alveolar proteinosis in humans.[65–68]

In the United States, GM-CSF is approved for human use only as sargramostim and has been used primarily as an alternative to G-CSF to prevent neutropenia and its infectious risks in oncology patients after myelosuppressive chemotherapy.[1] Sargramostim is not approved in Canada or Europe, and there are no widely available biosimilars. In healthy volunteers, GM-CSF stimulates the release of mature neutrophils from the bone marrow, resulting in an increase in ANC to 3.5 times baseline levels.[69] GM-CSF also enhances the induced neutrophil oxidative burst in vitro and induces eosinophilia when administered in vivo.

Several studies have reported differences in the clinical effects of G-CSF and GM-CSF when used for the prevention of neutropenia in patients with malignancies. After myelosuppressive chemotherapy, patients who received GM-CSF experienced a longer duration of neutropenia (14 vs. 12 days) than did those who received G-CSF.[70] In a mixed population of patients undergoing chemotherapy for solid tumors or hematologic malignancies, GM-CSF reduced the incidence of febrile neutropenia and documented infections, but less so than G-CSF.[21] However, neither CSF reduced all-cause or infection-related mortality. Compared with G-CSF, hospitalization rates for patients receiving GM-CSF for the prevention of neutropenia have been variously reported to be lower (infection related), equivalent (febrile neutropenia related), or higher (neutropenic complications including both fever and infection) depending on the outcome studied.[28,71,72] In a meta-analysis of patients with lymphoma, G-CSF, but not GM-CSF, reduced the incidence of neutropenia and documented infection; however, few included studies used GM-CSF exclusively.[20]

In post-HSCT patients, the population in whom GM-CSF has been most widely studied, GM-CSF, but not G-CSF, reduced the incidence of documented infection. Once again, however, neither reduced all-cause or infection-related mortality.[25] In contrast, cumulative mortality and transplant-related mortality were lower at 100 days in patients who received GM-CSF while neutropenic after allogeneic HSCT than in those who received G-CSF.[73] Furthermore, although there was no difference in the incidence of invasive fungal infection between the groups at 100 days, those who had received GM-CSF had lower infection-related and fungal infection-related mortality after a median follow-up of 600 days. One-year overall and disease-free survival rates did not differ between the groups. Prolonged use of GM-CSF after allogeneic HSCT may confer some antitumor activity (an effect related to GM-CSF–mediated increases in myeloid dendritic (antigen-presenting) cells and IL-12–stimulated cytotoxic T cells) but does not exacerbate GVHD.[73,74]

When used for treatment of an established episode of febrile neutropenia, GM-CSF, like G-CSF, does not reduce mortality.[75] Neither the 2006 nor the 2015 ASCO guidelines found enough evidence to make recommendations regarding the equivalency of G-CSF and GM-CSF.[9,76]

Nonetheless, like G-CSF, GM-CSF has been studied for use in non-neutropenic patients. In patients with SIRS but without hemodynamic

instability, a 72-hour course of treatment with GM-CSF in addition to standard therapy resulted in multilineage leukocyte activation and a greater number of patients with clinical or microbiologic resolution of infection.[77] However, GM-CSF had no impact on organ failure or 28-day mortality. Similarly, an RCT of a 5-day course of GM-CSF in 18 patients with sepsis and pulmonary dysfunction found no difference in the incidence of acute respiratory distress syndrome (ARDS), extrapulmonary organ failure, or 30-day mortality, despite increased superoxide production by peripheral blood neutrophils.[78] An RCT of 38 patients with severe sepsis or septic shock and sepsis-induced immunosuppression (as defined by monocytes with decreased human leukocyte antigen [HLA] class II expression) found a shorter duration of mechanical ventilation and improved APACHE II scores with GM-CSF treatment.[79] Once again, 28-day mortality was unchanged. Finally, when 132 critically ill patients with acute lung injury (ALI) or ARDS, most commonly due to sepsis and pneumonia, were randomized to receive either GM-CSF for 14 days or placebo, no difference in ventilator-free days or 28-day mortality was found between the groups.[80] Given the small numbers of enrolled patients, all of these studies should be regarded as preliminary and hypothesis generating, and conclusions regarding the use of GM-CSF in adults with sepsis should be withheld pending larger RCTs adequately powered to detect an impact on survival.

Similarly promising but inconclusive findings have emerged from studies of GM-CSF in pediatric sepsis. A meta-analysis of treatment studies using G-CSF or GM-CSF in critically ill neonates found no survival benefit (14-day mortality) with the addition of CSF support to standard antimicrobial therapy, except in the small subgroup with severe neutropenia.[81] In a relatively large RCT of 280 low-birth-weight, preterm infants, a 5-day course of prophylactic GM-CSF started within 72 hours of birth did not reduce the incidence of sepsis or mortality (within 14 days or up to hospital discharge), even among the 21% of participants who were neutropenic.[82] Results of long-term follow-up from this study (at 2 and 5 years, respectively) demonstrated no differences in neurodevelopmental, health. or educational outcomes between the infants who received GM-CSF and those who did not.[83,84] Finally, in a small study of 14 critically ill children with failure of at least three major organs and immunoparalysis (as defined by blunted tumor necrosis factor [TNF] production in response to lipopolysaccharide [LPS] ex vivo), pediatric patients who received GM-CSF had significantly fewer nosocomial infections than those who received the standard of care without CSF support.[85]

Similarly, no definitive benefit to GM-CSF treatment has been found in the other infectious diseases for which its use has been proposed. In postoperative patients in the intensive care unit, 1 to 3 days of therapy with GM-CSF did not reduce infections in the short term (up to postoperative day 9).[86] In contrast, a small RCT of 58 patients with nontraumatic generalized peritonitis who received GM-CSF for 4 days in addition to protocol-specified broad-spectrum antimicrobial therapy for at least 5 days found fewer infectious complications in those receiving GM-CSF therapy.[87] Based on ex vivo studies that demonstrated enhanced antifungal activity in human neutrophils, GM-CSF has been used, both alone and in combination with IFN-γ, as adjunctive therapy for refractory invasive fungal infections in nonneutropenic patients, and ongoing GM-CSF therapy has been used to suppress relapsing *Candida* meningoencephalitis in a patient with CARD9 (caspase recruitment domain-containing protein 9) deficiency.[88,89]

Adverse Effects of Granulocyte-Macrophage Colony-Stimulating Factor

Compared with G-CSF, GM-CSF–associated toxicity in adults is more frequent and more severe, possibly because of stimulation of proinflammatory responses in monocytes-macrophages. Fever is the most common adverse effect, often accompanied by myalgias and malaise, and occurs in more than 20% of recipients.[1] First-dose reactions, consisting of dyspnea, hypoxemia, hypotension, tachycardia, flushing, musculoskeletal pain, nausea, and vomiting, have been reported in 5% of patients receiving GM-CSF.[90] Adverse effects are more common when GM-CSF is administered intravenously and with doses greater than 3 μg/kg. High doses (20 μg/kg/day) of GM-CSF have been reported to cause a generalized capillary leak syndrome.

Macrophage Colony-Stimulating Factor

M-CSF or CSF-1 is a glycoprotein that was first cloned and produced in recombinant form in 1985. It is produced endogenously by monocytes-macrophages, fibroblasts, and endothelial cells. M-CSF acts specifically on cells of the monocyte-macrophage lineage to stimulate their production and enhance their functional activity.[91] Clinical experience with M-CSF for the treatment of infectious diseases has been limited, and it is not currently approved for human use in either the United States or Europe.

INTERFERONS

IFNs are a class of cytokines distinguished by their intrinsic antiviral properties but produced in response to a variety of stimuli, including intracellular pathogens and bacterial toxins. Although three families of IFNs have been identified in humans, this chapter will focus on the two best studied in infectious diseases in humans: type I IFNs (IFN-α and IFN-β), produced primarily by leukocytes and fibroblasts; and type II IFN (IFN-γ), produced primarily by NK cells and T lymphocytes. Whereas IFN-α and IFN-β are primarily antiviral IFNs, IFN-γ activates macrophages and contributes to host defense against intracellular pathogens.

Interferon-α

The antiviral activity of IFN-α is discussed in Chapter 4. The term *IFN-α* actually refers to a class of molecules, of which there are 12 subtypes. Currently, IFN-α is available for clinical use as recombinant IFN-alfa-2a and IFN-alfa-2b, which differ by a single amino acid; IFN-alfa-n3, which is a mixture of subtypes of IFN-α purified from human leukocytes; and IFN-alfacon-1, a bioengineered form of IFN-α based on a "consensus" amino-acid sequence of the most common forms of naturally occurring IFN-α. Pegylated forms of IFN-alfa-2a and IFN-alfa-2b have extended biologic half-lives.

IFN-α has been most widely used as treatment for chronic hepatitis B and C virus infections (see Chapters 48, 143, 145, and 154); however, it is also an effective therapy for various manifestations of human papillomavirus infection, including condylomata acuminata (genital warts) and recurrent respiratory papillomatosis.[92,93]

As an immunomodulatory agent, IFN-α has been studied as an adjunct to conventional antimicrobial agents. A combination of topical trifluorothymidine and IFN-α was reported to be effective in three HIV-infected individuals with refractory cutaneous herpes simplex virus infection, and combined use of IFN-α with foscarnet was reportedly successful in treating a single case of severe acyclovir-resistant perianal herpes simplex virus infection in an individual with advanced HIV disease.[94,95]

In virologically suppressed patients with HIV on ART, fewer patients who received pegylated IFN-α-2a had virologic failure when ART was subsequently stopped for 12 weeks than did historical control subjects.[96] In a phase II, multicenter RCT of 259 patients with HIV in whom current ART therapy was failing (based on a detectable and increasing viral load), pegylated IFN-α-2b administered subcutaneously once weekly for 4 weeks resulted in a significant decrease in plasma HIV RNA levels (mean 0.53 $\log_{10}$ copies/mL) despite an unchanged ART regimen.[97] $CD4^+$ T-cell counts were also unchanged, but 15% of patients discontinued IFN-α therapy owing to adverse events. At this time, there is no clear role for IFN-α as adjunctive treatment in HIV disease.

Given the recent outbreaks of hand, foot, and mouth disease due to enterovirus 71, there has been interest in the use of IFN-α to treat affected individuals. In an RCT of 305 non–critically ill children hospitalized with hand, foot, and mouth disease, IFN-α administered via either aerosolization or intramuscular injection reduced the time to defervescence, time to healing of skin and mucosal lesions, and stool viral load when compared with standard supportive care.[98] Clinical outcomes were not affected by route of IFN-α administration. A second clinical trial randomized 400 non–critically ill children with hand, foot, and mouth disease, primarily due to enterovirus 71 or coxsackievirus A16, to receive either IFN-α2b oral spray for 7 days or standard care and placebo spray.[99] Patients who received the IFN-α spray experienced a shorter duration of fever, oral ulcers, and rash than did those who received

placebo, although the absolute differences between groups were not large. At this time, it is not clear that the small reductions in duration of clinical symptoms (<1 day) with the use of IFNs to treat hand, foot, and mouth disease are either clinically relevant or cost-effective.

IFN-α has also been used to treat severe HSV infections in patients with heritable immunodeficiencies, such as dedicator of cytokinesis 8 (DOCK8) deficiency.[100] Finally, preliminary studies have suggested that IFN-α may have clinical benefit in human T-cell lymphotropic virus type 1 (HTLV-1)–associated myelopathy and pulmonary tuberculosis (TB), the latter in combination with standard antimycobacterial therapy.[101,102]

The major adverse effects of systemic IFN-α therapy are dose-dependent and influenza-like, with fever, headache, myalgias, arthralgias, and nausea common.[103] These symptoms are usually alleviated by pretreatment with acetaminophen or NSAIDs. At higher doses, bone marrow suppression, neuropsychiatric effects (depression, change in mental status or cognition, or seizures), and elevated serum hepatic aminotransferase levels may be observed. Rash and erythema at the injection site are also reported. Intralesional IFN-α can cause local discomfort, inflammation, and mild systemic effects.

Interferon-β

IFN-β is available as IFN-beta-1a and is approved for treatment of relapsing multiple sclerosis. It has been studied in the treatment of infectious diseases less frequently than its type I counterpart IFN-α, but has been explored for its potential antiviral properties in some small studies. For instance, an inhaled form of IFN-β was investigated for the prevention of asthma exacerbations when used at the onset of a viral upper respiratory tract infection.[104] Although not found to be significantly different from placebo in the study population as a whole, those with more severe asthma may have experienced a reduction in symptoms. IFN-β shares many of the potential adverse effects of IFN-α, including depression and suicidal ideation, seizures, liver dysfunction, cytopenias, and thrombotic microangiopathy, along with influenza-like symptoms and injection site reactions.

Interferon-γ

Recombinant human IFN-γ is available as IFN-gamma-1b. In vivo, IFN-γ is produced by $CD4^+$, $CD8^+$, and NK cells and targets monocytes, macrophages, and neutrophils, in addition to nonprofessional host defense cells such as fibroblasts, hepatocytes, astrocytes, microglia, and endothelial cells.[1] IFN-γ plays a critical regulatory role in macrophage-mediated killing and granuloma formation in response to important intracellular pathogens, including *Mycobacterium, Leishmania, Rickettsia, Legionella,* and *Chlamydia* species.[1] Individuals with autoantibodies against IFN-γ develop an adult-onset immunodeficiency syndrome characterized by multiple opportunistic infections by organisms including *Mycobacterium* species (tuberculous and nontuberculous, slow and rapid growing), *Salmonella* species, *Cryptococcus neoformans, Talaromyces marneffei (*previously *Penicillium marneffei),* and varicella-zoster virus.[105,106]

Recombinant IFN-γ is approved by the US Food and Drug Administration (FDA) for the prevention of infection in individuals with CGD, characterized by dysfunction of the NAPDH oxidase needed for the phagocytic respiratory burst (see Table 49.1). In an early clinical trial, IFN-γ–treated patients developed significantly fewer infections and required fewer days of hospitalization.[107] An observational study of 76 patients with CGD documented persistent efficacy for up to 9 years when IFN-γ was used in combination with prophylactic trimethoprim-sulfamethoxazole and itraconazole.[108] However, a more recent study reported decreasing long-term use of IFN-γ, largely due to discontinuation as a result of adverse events.[109] Although this was a nonrandomized study of a small group of patients, a prospective 5-year comparison of those receiving IFN-γ in combination with trimethoprim-sulfamethoxazole and itraconazole versus those receiving standard antimicrobial prophylaxis alone did not demonstrate differences in the rates of infections or severe infections. A subsequent meta-analysis that combined the results of this study with the original 1991 trial for a total of 163 patients found a significant reduction in severe infection with IFN-γ therapy, albeit with the caveat that standard of care with regard to antimicrobial prophylaxis differed significantly between the two trials.[110] To date, no RCTs comparing current standard antimicrobial prophylaxis alone with that with IFN-γ have been published.

Hyperimmunoglobulin E syndrome (hyper-IgE syndrome; previously known as Job syndrome) is a primary (congenital) immunodeficiency syndrome most commonly caused by mutations in the gene encoding STAT3 and characterized by recurrent skin and pulmonary abscesses, pneumonia, eczema, eosinophilia, and elevated serum IgE levels.[111] Lymphocytes of patients with hyper-IgE syndrome have a depressed response to IL-12, resulting in decreased IFN-γ production after challenge with bacterial antigens.[112] On the basis of these observations, a small, uncontrolled trial was performed, and it suggested possible improvement in the clinical course of hyper-IgE patients when treated with systemic IFN-γ therapy.[113] No RCTs have been performed in this patient population.

IFN-γ has also been administered as adjunctive therapy for infections caused by intracellular pathogens in patients without immunodeficiency. Administration of IFN-γ with pentavalent antimony in visceral leishmaniasis was reported to significantly improve the response rate compared with historical control groups treated with pentavalent antimony alone.[114] However, a prospective RCT of a 30-day course of pentavalent antimony, with or without adjunctive IFN-γ, failed to demonstrate any treatment benefit for the combination therapy.[115] Adjunctive IFN-γ has also been reported to be effective for treatment of cutaneous leishmaniasis when combined with pentavalent antimony.[116] When administered in lepromatous leprosy, IFN-γ has been shown to increase the macrophage response to *Mycobacterium leprae* and to enhance clearance of mycobacteria from skin.[117] However, a small RCT involving 21 patients with multibacillary leprosy failed to show a significant beneficial effect on clinical or microbiologic outcomes when IFN-γ was added to standard multidrug therapy.[118]

When administered as adjunctive therapy to HIV-infected patients with disseminated *Mycobacterium avium* complex infection, systemic IFN-γ therapy decreased mycobacterial load.[119] A study of HIV-negative patients with nontuberculous mycobacterial infection of the lungs found significant clinical improvement, persisting for 12 months after completion of therapy, when a 5-month course of IFN-γ was combined with standard antimycobacterial therapy.[120] An aerosolized form of IFN-γ has been used successfully in patients with antimicrobial-refractory nontuberculous mycobacterial infection of the lungs and in patients with pulmonary TB.[121,122] In a meta-analysis of studies of adjunctive IFN-γ for the treatment of TB, the aerosolized form was associated with significantly higher rates of sputum clearance both at 1 month and at the end of treatment as compared with standard therapy alone.[123] Chest radiograph improvement was also more likely in the IFN-γ–treated group. However, none of the included studies were considered to be of high methodologic quality by the authors.

Although many studies have focused on the potential usefulness of IFN-γ for the treatment of invasive fungal infections, few RCTs have been conducted. One notable exception is an RCT of two doses of adjunctive IFN-γ for the treatment of HIV-associated cryptococcal meningitis, which demonstrated significantly faster fungal clearance of the CSF with IFN-γ therapy versus amphotericin and 5FC alone.[124] There was no difference in mortality or adverse events between the groups. A small case series of eight patients with refractory invasive candidiasis or aspergillosis who were treated with IFN-γ three times weekly for 2 weeks in addition to standard antifungal therapy at the discretion of their attending physician revealed an ex vivo improvement in proinflammatory cytokine response and HLA-DR expression on monocytes, the latter a marker of immune paralysis.[125] Published case reports document the successful use of IFN-γ, in combination with G-CSF, GM-CSF, or granulocyte transfusions, to treat or stabilize refractory invasive fungal infections in patients with leukemia or persistent and prolonged neutropenia.[126,127] IFN-γ was also reported to be safe and well tolerated when used in combination with standard antifungal therapy to successfully treat disseminated fungal infections in seven renal transplant patients.[128]

Although IFN-γ has been studied as adjunctive therapy for a variety of infections and infectious syndromes, there have been no large-scale RCTs demonstrating improvement in clinically relevant end points with

the addition of IFN-γ to standard treatment regimens, and therefore its use is not typically recommended in patients other than those with CGD.

Adverse effects of systemic IFN-γ administration include fever, myalgias, and headache, all of which are common. Although IFN-γ–associated influenza-like symptoms are typically mild, decrease over time, and can usually be managed with prophylactic antipyretics, these adverse effects are largely avoided if IFN-γ is administered via inhalation.[1] Reversible neutropenia can occur; however, clinically significant hematologic abnormalities are infrequent, even in patients who have received IFN-γ therapy for years.[1]

INTERLEUKINS

A variety of IL cytokines have been studied for the treatment of infectious diseases—some for their ability to stimulate the immune system in conditions of immunodeficiency, and others for their ability to suppress excessive immune activation in situations of fulminant infection. Clinical trials involving these cytokines as immunomodulatory therapy for the treatment of infectious diseases are outlined in the following sections; however, as of the time of publication, no ILs are in routine clinical use for the treatment of infection.

Interleukin-1

The IL-1 family of cytokine agonists and receptor antagonists plays a pivotal role in multiple aspects of infection and immunity. Three molecules are currently available for clinical use in IL-1 blockade: anakinra, a recombinant human IL-1 receptor antagonist; canakinumab, an IL-1β inhibitor; and rilonacept, a bispecific anti-IL-1β antibody. Although these molecules have been used successfully for the treatment of autoimmune and autoinflammatory diseases (see Table 49.3, later), they have yet to demonstrate similar usefulness in the treatment of infection. RCTs published in 1994 and 1997 explored the use of anakinra as a treatment for severe sepsis but found no impact on overall 28-day survival.[129,130] However, preliminary data may indicate a role of IL-1 blockade in patients with sepsis and certain features of the macrophage activation syndrome. A post hoc analysis from the 1997 trial was published in 2016 and reported improved 28-day survival in the small subgroup of patients with hepatobiliary dysfunction and disseminated intravascular coagulation (DIC), mimicking findings of an eight-patient retrospective observational study of critically ill children with sepsis and features of the macrophage activation syndrome.[131,132] Trials of immunomodulators in patients with sepsis have previously been hampered by the heterogeneity of the patient population, so future studies that focus on specific subgroups may help to define those in whom blockade of a particular cytokine, such as IL-1, is of benefit.

Interleukin-2

IL-2 plays an important role in the proliferation, differentiation, and activation of lymphocytes and, in particular, promotes the development of $CD4^+CD25^+FoxP3^+$ T-regulatory cells (Tregs), and inhibits differentiation of Th17 and follicular helper T cells.[133] By doing so, IL-2 can effectively limit or downregulate the immune response. However, IL-2 can also exert proinflammatory effects, by inducing the production of other proinflammatory cytokines, stimulating the proliferation of activated B cells, and enhancing the activity of NK cells and cytotoxic T lymphocytes. Recombinant human IL-2 was first approved by the FDA in 1992 for the treatment of metastatic renal cell carcinoma and metastatic melanoma but has since been proposed as an antiinfective immunomodulatory therapy. In that role, IL-2 has been best studied as adjunctive treatment for HIV disease. Two multicenter, randomized, open-label trials were conducted in patients with HIV and varying degrees of immunodeficiency: SILCAAT (Subcutaneous IL-2 in HIV Infected Subjects with Low CD4 Counts Under Active Antiretroviral Therapy), which enrolled 1695 patients with $CD4^+$ cell counts between 50 and 299 cells/mm^3, and ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial), which enrolled 4111 patients with $CD4^+$ cells counts greater than or equal to 300 cells/mm^3.[134] In both, participants were randomized to receive ART alone or ART plus IL-2. IL-2 was administered on 5 consecutive days every 8 weeks with trial-specific doses and durations: 4.5 million international units (IU) of IL-2 twice daily for six cycles in SILCAAT and 7.5 million IU twice daily for three cycles in ESPRIT. Despite significant and sustained increases in $CD4^+$ T-cell counts in both studies, addition of IL-2 to standard ART did not change the risk of opportunistic disease, grade 4 clinical events, or death. A third randomized trial (Study of Aldesleukin With and Without Antiretroviral Therapy [STALWART]) enrolled patients with HIV and $CD4^+$ cell counts greater than or equal to 300 cells/mm^3 who had not received ART in at least a year.[135] Participants were randomized to receive no therapy, IL-2 alone, or IL-2 and a maximum of 10 days of pericycle ART beginning 2 days before IL-2 administration. The STALWART study was halted early based on results from SILCAAT and ESPRIT; however, analysis of the preliminary data demonstrated that participants receiving IL-2 therapy experienced a significantly greater increase in $CD4^+$ cell counts compared with those receiving no therapy, but also experienced a greater number of opportunistic diseases and deaths. To assess the longer-term impact of IL-2 therapy, 222 of the 267 patients initially enrolled in the STALWART study were followed for an additional 24 months.[136] No increase in adverse events was detected after discontinuation of IL-2 therapy, nor was there a detectable impact on subsequent $CD4^+$ cell count or viral load responses to ART. IL-2 has also been studied in patients with TB, hepatitis C, and hepatitis C virus (HCV)–HIV coinfection, with similarly negative results.[137–139]

Interleukin-7

IL-7 plays a key role in leukocyte development, most critically for T cells.[140] Secreted constitutively and at low levels by stromal cells, IL-7 provides continuous survival signals to T cells under normal conditions and is markedly increased during periods of lymphopenia, most notably in inverse proportion to levels of $CD4^+$ T cells. In humans, administration of recombinant human IL-7 produced a dose-dependent increase in $CD4^+$ and $CD8^+$ T cells, particularly naïve and central memory T cells, and enhanced the T-cell receptor repertoire but did not expand the $CD4^+CD25^+FoxP3^+$ Treg population.[141] IL-7 has therefore been proposed as an immune stimulant without the confounding enhancement of immunosuppressive Tregs, and in this role has been best studied in patients with HIV.

In patients who were classified as poor or nonresponders to at least 1 year of ART on the basis of $CD4^+$ T-cell counts of 101 to 400 cells/mm^3 for more than 6 months despite virologic control (plasma HIV RNA <50 copies/mL), three weekly doses of IL-7 yielded a sustained, dose-dependent increase in $CD4^+$ T cells that persisted for up to a year.[142] As expected, patients randomized to receive placebo demonstrated no such increase. However, IL-7 administration also resulted in low-level viremia in some patients. Two subsequent phase II trials, enrolling HIV-infected individuals with similar immunologic and virologic parameters (INSPIRE 2 and INSPIRE 3), were conducted with repeated cycles of three weekly doses of IL-7 (every 3 months to a maximum of three cycles in the first year) whenever $CD4^+$ T-cell counts reached <550 cells/mm^3.[143] Although the studies were terminated prematurely because of closure of the sponsoring company, leaving some cycles incomplete, IL-7 administration resulted in increased $CD4^+$ T-cell counts but also increased viral loads. Large-scale RCTs would be needed to determine the clinical impact of these results; at the time of publication, no such studies are registered on ClinicalTrials.gov.

Given its immunobiology and promising initial results in patients with HIV, IL-7 has also been studied in idiopathic $CD4^+$ lymphocytopenia; researchers conducting a phase I/IIa open-label clinical trial of 21 patients reported significant increases in circulating $CD4^+$ and $CD8^+$ T cells above baseline.[144] Similarly, a phase I study in recipients of T-cell–depleted allogeneic HSCT demonstrated increased $CD4^+$ T-cell counts (primarily effector memory T cells) and improved T-cell receptor diversity after IL-7 administration.[145] Finally, two phase II studies were initiated to explore the use of IL-7 for the restoration of lymphocyte counts in patients with septic shock and lymphopenia (ClinicalTrials.gov identifiers NCT02640807 and NCT02797431), although no results are yet available and the latter study was terminated owing to lack of IL-7 availability.

Interleukin-10

Endogenous IL-10 is produced primarily by T cells and acts to suppress the functional activity of macrophages. A clinical trial examining