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SELECTED DRUG COMPLICATIONS AND TREATMENT CONFLICTS IN THE PRESENCE OF COEXISTENT DISEASES

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Rheumatologists treating patients with various rheumatic diseases are often faced with challenging clinical situations in which the available treatment options can adversely influence the course of a coexistent disease. The propensity of certain rheumatic diseases to involve multiple organs and the potential of various antirheumatic drugs to adversely affect different organs further complicates the selection of the appropriate treatment for the individual patient.

This article focuses on the treatment conflicts that are commonly encountered in the setting of underlying gastrointestinal (GI), liver, skin, kidney, or malignant diseases.

INTESTINAL DISEASES

Among the various medications that rheumatologists prescribe in their daily practice, nonsteroidal anti-inflammatory drugs (NSAIDs)

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have been predominantly associated with a number of complications affecting the upper and lower GI tract and the hepatobiliary and pancreatic systems.[45] The role of NSAIDs in the development of dyspepsia and peptic ulcer disease is well recognized among rheumatologists and is discussed elsewhere in this article. On the contrary, NSAID-induced, small and large intestinal toxicity is usually unrecognized and probably underreported.[49]

NSAID-Related Small Intestine Disease

NSAID use has been associated with various forms of small intestinal toxicity that varies from ulcer and stricture formation to perforation and bleeding (Table 1).[21, 45, 124] The most commonly described condition is the NSAID-induced enteropathy, which is characterized by diffuse intestinal inflammation and increased mucosal permeability.[124] Although it has been reported to occur in up to 70% of patients taking NSAIDs,[45]

Table 1. LOWER GASROINTESTINAL DISEASES ATTRIBUTABLE TO THE USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

GI Location	Lesion	Comments
Small intestine[21, 45, 124]	Ulcers	8% in a large autopsy study[4]
	Perforation/bleeding	Rare
	Strictures/diaphragms	Rare Presence of small intestine diaphragms is pathognomonic for NSAID-induced damage
	Enteropathy characterized by: Occult blood loss Protein-losing enteropathy Iron deficiency anemia Malabsorption	Usually mild without significant clinical findings
Colon[21, 45, 49, 75]		
No pre-existing colonic disease (de novo injury)	Ulcers Strictures Perforation Bleeding	Rare
	Colitis	Cases of NSAID-induced colitis due to a hypersensitivity reaction have been reported (reviewed in ref[49])
	Proctitis caused by suppositories	Mainly from indomethacin
Pre-existing colonic disease	Exacerbation of quiescent IBD	See text for details
	Complications from underlying diverticular disease (bleeding/perforation/peritonitis)	See text for details

NSAIDs = nonsteroidal anti-inflammatory drugs; IBD = inflammatory bowel disease

it is usually mild, without significant clinical manifestations. Its pathogenesis is unclear, but it has been proposed that direct NSAID-induced uncoupling of the oxidative metabolism in enterocyte mitochondria could lead to disruption of the small intestine mucosal barrier causing increased intestinal permeability.[201] NSAID-induced cyclooxygenase inhibition impairs the prostaglandin-dependent regenerative process, leading to prolongation of the increased intestinal permeability. Bacteria, various enzymes, and bile subsequently can penetrate easily the intestinal mucosa, perpetuating the mucosal injury. It has been shown that NSAIDs, such as indomethacin and piroxicam with extensive enterohepatic circulation, are causing the most injury compared with other agents.[191]

In patients with underlying rheumatic diseases who develop signs and symptoms of small intestinal injury, discontinuing the offending NSAID is the preferable approach. If this option is not possible or if the injury is mild, NSAIDs with limited enterohepatic circulation such as nabumetone may be tried.[139] In small trials, sulfasalazine[23, 90] and metronidazole[22] have been shown to decrease NSAID-induced intestinal inflammation and blood loss, but large scale prospective studies supporting this approach have not been reported.

NSAID-Related Large Intestine Disease

Most of the published information on NSAID-induced large intestinal damage has been from case reports or small retrospective studies, hence the true frequency of the NSAID-induced colonic toxicity is unknown (see Table 1). Overall, it appears to be less frequent compared with NSAID-induced small intestine toxicity.[21, 45] Most of the cases of de novo colitis induced by NSAIDs were caused by sustained release NSAIDs, fenemates or diclofenac.[49, 75] Its pathogenesis remains unclear.

Inflammatory Bowel Disease

NSAIDs have been associated with relapses of quiescent inflammatory bowel disease (IBD).[112] This seems to occur more often in patients with ulcerative colitis as compared with patients with Crohn's disease.[75] The frequency of exacerbation of IBD attributed to NSAIDs is unknown because large retrospective or prospective studies have not been done. In a recent case-control study, Evans et al reported an increased risk of admission to the hospital because of colitis from inflammatory bowel disease, in patients with current (less than 45 days) or recent (up to 6 months) exposure to NSAIDs (overall odds ratio 1.77–1.93).[56]

Different NSAIDs have been implicated in the reactivation of IBD, which histologically can range from mild sigmoid edema to pancolitis.[75] The time from initiation of NSAID therapy to IBD exacerbation ranges from a few hours to 8 weeks (median less than a week).[75] Each of the eight patients that has been rechallenged with NSAIDs showed evidence

of disease relapse, indicating a causal relationship between NSAID use and IBD exacerbation.[75] Most of the patients responded well to discontinuation of the responsible NSAID or to steroid treatment.

Diverticular Disease

Several case reports,[49] case-control studies,[33, 40, 96, 128] and a prospective study[224] have implicated NSAID intake with serious complications of diverticular disease, such as perforation and lower gastrointestinal bleeding. In a prospective study, Wilson et al found a statistically increased risk of perforation among patients with diverticular disease taking NSAIDs compared to age- and sex-matched controls from a general practice and patients with colorectal cancer taking NSAIDs.[224] In a recent retrospective case-control study from the USA, Holt et al observed a two-fold increased risk of lower GI bleeding in patients consuming NSAIDs at the time of admission compared with age- or sex-matched controls without evidence of GI disease.[96]

Further substantiating the above observations, a recent retrospective study from Finland found that NSAID-induced perforation or bleeding from the lower GI accounted for 36% of the NSAID-attributable deaths in a large population of rheumatoid arthritis (RA) patients ($n = 1666$).[149]

Although large epidemiologic studies linking NSAID use with exacerbation of IBD or with increased risk of complications from diverticular disease are still missing, the authors believe that NSAIDs should not be used in patients with known IBD and used very cautiously (if at all) in patients with known diverticulosis. An increased awareness of their potential life threatening complications is necessary and prompt discontinuation of the medication is indicated in patients who develop these complications.

LIVER DISEASES

Understanding the potential side effects of the antirheumatic medications in patients with compromised liver function is complicated by their occasional direct hepatotoxic effects on the "normal" liver[25, 210] and the concomitant involvement of the liver by certain autoimmune diseases.

NSAIDs[63] and methotrexate (MTX)[221] have been most commonly implicated in various forms of liver injury. Other antirheumatic drugs that may cause hepatoxicity include gold,[99] D-penicillamine,[181] allopurinol,[3] azathioprine (AZA),[117] and cyclosporine (CsA)[117] (Table 2).

RA and systemic lupus erythematosus (SLE) may affect the liver. Elevated alkaline phosphatase levels have been reported in 25% to 50% of patients with RA,[219] although significant abnormalities in liver biopsies rarely have been noted.[221] Liver enzyme abnormalities have been found in 23% to 60% of patients with SLE during the course of their disease[148, 184] and tend to correlate with disease activity.[123] Severe involve-

Table 2. HEPATOTOXICITY OF ANTIRHEUMATIC MEDICATIONS

Medication	Type of Hepatic Injury	Frequency/Comments
NSAIDs		
Phenylbutazone*	Hepatocellular	Minor AST/ALT elevation = 1%–15%
Diclofenac*		Severe liver injury = Rare (<0.1%)
Etodolac		
Ibuprofen		
Indomethacin		
Fenoprofen		
Piroxicam		
Phenylbutazone*	Cholestatic	
Sulindac*		
Naproxen		
Nabumetone		
Fenoprofen		
Diflunisal		
Sulindac*	Mixed	
Diflunisal		
Ibuprofen		
Phenylbutazone	Granulomatous	
Methotrexate	Fibrosis	Frequency of fibrosis in RA patients:
		Mild (Roenigk grade IIIA) = 14.3%
		Moderate (Roenigk grade IIIB) = 0.83%
		Cirrhosis (Roenigk grade IV) = 0.28%
Sulfasalazine	Hepatocellular	Occasionally manifesting as a hypersensitivity syndrome
Allopurinol	Hepatocellular	Rare, occasionally in older patients with underlying renal failure or on diuretic therapy
	Cholestatic	
	Granulomatous	
Azathioprine	Cholestatic (most common)	Rare (overall <0.1%)
	Hepatocellular	Mainly in the post-transplant setting
	Vascular liver disease (peliosis hepatis/ venoocclusive disease/ nodular regenerative hyperplasia)	
Cyclosporine	Cholestatic (most common)	Rare
	Hepatocellular	Mainly in the post-transplant setting (4%–7%), dose dependent
Gold	Cholestatic	Rare case reports
D-Penicillamine	Cholestatic	Rare case reports

*Most commonly reported.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; RA = rheumatoid arthritis.
Data from References 3, 57, 62, 63, 99, 117, 120, 181, 210

ment of the liver causing chronic hepatitis, fibrosis, or cirrhosis in SLE is rare (0.8%–2.4% in a recent autopsy series).[143] Rarely, Sjögren's syndrome, systemic sclerosis, Felty's syndrome, polymyalgia rheumatica/giant cell arteritis, and Still's disease can show evidence of liver involvement.[219]

An overview of the potential interactions of medications commonly used in the clinical practice of rheumatology in patients with underlying liver disease is presented in this article.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs have been associated with minor increases in liver enzymes in 1% to 15% of patients treated with these medications.[63] The pathogenesis of the liver injury has been attributed to immunologic or metabolic idiosyncratic mechanisms. Usually asymptomatic elevations in transaminase levels occur during the first few months of therapy and they usually subside after discontinuation of the offending NSAID. Based on the results of large retrospective studies, it seems that the risk of severe liver disease because of NSAIDs is low.[34, 62, 69]

Among the different NSAIDs, sulindac, diclofenac, and phenylbutazone have been associated with an increased reported incidence of liver injury.[144, 210] In a recent review of the reported cases of sulindac-induced liver injury, Tarazi et al showed that in 78% of the cases, liver damage occurred during the first 2 months of therapy and in almost half of the cases it was caused by a hypersensitivity type of reaction.[207] Similar results have been reported in association with diclofenac or phenylbutazone use.[63]

Although there are adequate scientific data to suggest a role of NSAID in direct liver injury, our knowledge of their effect in patients with pre-existing liver disease is limited. NSAIDs should be avoided in patients with cirrhosis of the liver and ascites regardless of its origin, because of the increased risk of NSAID-induced renal insufficiency.[9] Renal failure in these patients is caused by NSAID-induced inhibition of the vasodilating prostaglandins, which results in decreased renal blood flow and glomerular filtration rate (GFR).[18, 125] Although some studies have shown that misoprostol can minimize the renal dysfunction caused by NSAIDs,[7, 152] other studies did not reproduce these findings.[65, 100]

Patients with advanced liver disease characterized by decreased synthesis of coagulation factors or coexistent thrombocytopenia are prone to bleeding that can be exaggerated by the concomitant use of NSAIDs. In these patients NSAIDs should also be avoided.

Whether or not NSAIDs enhance liver damage in patients with underlying chronic viral hepatitis caused by hepatitis C virus (HCV) or hepatitis B virus (HBV) is unclear. There have been no studies examining their direct effect on liver function in these patients. Preliminary data have suggested an enhanced antiviral activity of interferon-alpha (IFN-α) when used in combination with NSAIDs in patients with chronic hepatitis.[6] Clinical studies have failed to show any additional efficacy in patients with chronic hepatitis C treated with a combination of IFN-α and NSAIDs in comparison with patients treated with IFN-α alone.[5, 230] In the study by Zarski et al,[230] administration of IFN-α and tenoxicam for 6 months did not result in worsened liver function (biochemical or histological) or in increased HCV RNA levels compared with patients treated with IFN-α alone.

Although it is difficult to extrapolate from these limited data, it seems that NSAIDs can be safely used in patients with chronic hepatitis (without evidence of cirrhosis) with close monitoring of the transaminase

levels, especially during the first 6 months of therapy.[63] NSAIDs with an increased risk for hepatotoxicity (e.g., phenylbutazone, diclofenac, Sulindac, see Table 2) probably should be avoided. NSAIDs should be discontinued if significant elevation of transaminase levels (> 3 times normal value) occurs. If other causes of elevated transaminase levels have been ruled out, the offending NSAID should not be used again.

Corticosteroids

Corticosteroids (CS) are used in the treatment of various liver diseases including autoimmune hepatitis,[47] granulomatous hepatitis,[232] severe alcoholic hepatitis,[174] and after liver transplantation. Although CS have been associated with the development of fatty liver, significant liver dysfunction from their use is rare.[117] CS should be used cautiously in patients with advanced liver failure with or without associated portal hypertension because of increased risk of infection and possibly gastrointestinal bleeding (especially in patients taking NSAIDs at the same time).[67, 164]

CS treatment leads to enhancement of HBV-antigen expression in hepatocytes,[129, 212] an increase in viral replication in animals,[64] an increase in serum hepatitis B surface antigen (HBsAg) and DNA polymerase levels in humans,[193] and clinical deterioration of patients with chronic HBV infection.[97, 126] Although liver inflammation decreases during treatment, withdrawal of steroids is usually followed by a rebound increase in transaminase levels because of an enhanced cellular immune response against the HBV-infected hepatocytes.[97] In some cases, this rebound phenomenon can lead to viral clearance[220] but can also cause fulminant hepatitis and death.[97] Antiviral therapy (IFN-α) following pretreatment with CS, has not been proven to be of additional benefit for the treatment of chronic hepatitis B,[38] but this regimen was not associated with an increased rate of liver decompensation.[161] These data emphasize the need for cautious use of CS in patients with chronic HBV infection, with close clinical and laboratory monitoring, especially after withdrawal of therapy. Antiviral therapy should be considered for each patient receiving steroids and consultation with a hepatologist is recommended, particularly in patients with HBV-associated polyarteritis nodosa.[141]

Taking into account that chronic hepatitis C affects 1% to 2% of the general population[93] and is frequently associated with various rheumatological/autoimmune manifestations,[86] rheumatologists are increasingly encountering patients requiring CS or other forms of immunosuppressive therapy for control of HCV-associated conditions (vasculitis, polyarthritis, renal disease, and so forth) or for the treatment of coexisting rheumatic diseases.

Short courses of CS treatment (1–6 months) increase viremia in HCV infected patients, whereas transaminase levels decrease during therapy.[60, 138, 209] Fong et al have found that discontinuation of prednisone therapy led to a return of viral RNA and transaminase levels to their pretreat-

ment values in patients with chronic HCV infection.[60] In contrast to hepatitis B, no cases of fulminant hepatitis were observed.[60] Furthermore, in HCV-positive patients who underwent kidney transplantation and were treated with different immunosuppressive regimens containing CS for 1 to 7 years, although elevations of transaminases and viral titers were seen, severe compromise of the liver function was rare (0%–4.3%).[114, 183] Addition of IFN to methylprednisolone in a long-term randomized controlled study of patients with HCV-associated mixed cryoglobulinemia prevented the rise of HCV RNA levels.[48]

These data suggest that although treatment with steroids leads to increased viremia in patients with hepatitis C, fulminant hepatitis or severe decompensation of the liver function is rare. Similarly to patients with hepatitis B, close monitoring of liver function and concomitant antiviral therapy (IFN ± ribavirin) should be considered in every patient with HCV infection receiving CS treatment.

Cyclosporine

CsA, an immunosuppressive agent that has been used successfully in the organ transplantation field for the last 20 years, has been recently included in the armamentarium of agents used for the treatment of various autoimmune and rheumatologic conditions.[127] Hepatotoxicity related to CsA use is rare[117]; it is usually manifested as a cholestatic syndrome with or without associated mild elevation of transaminases. A possible association with the formation of gallstones and biliary sludge also has been suggested. Most of the cases of CsA-induced hepatotoxicity have been reported in the post-transplant setting (ranging from 4%–7%), especially when a high dose of the medication was used.[117] The liver abnormalities usually subside after reduction of the dose of CsA.

CsA acts mainly by inhibiting interleukin-2 production by T lymphocytes, an essential cytokine for an effective immune response. Its potent immunosuppressive action can increase the risk of infection in all patients. Given its known nephrotoxic effect,[195] extreme caution should be paid to the renal function of patients with severe liver dysfunction who may have abnormal renal function.

The effect of CsA in patients with chronic liver disease has not been studied extensively. According to recent guidelines, CsA use is not recommended in patients with elevated liver enzymes (> 2 times the normal values).[157] Nevertheless, CsA has shown beneficial effects in patients with autoimmune hepatitis resistant to CS or AZA[54, 131, 162] and has been used with moderate success in patients with primary biliary cirrhosis (PBC) although an increased incidence of nephrotoxicity was noted.[133]

The impact of CsA in patients with chronic hepatitis B is controversial. CsA does not cause increased HBV antigen expression in hepatocyte cultures from patients with chronic hepatitis B[129] and does not lead to

increased rates of chronicity in an animal model of hepatitis B.[42] Most of the available data in humans are derived from the study of patients with HBV infection receiving immunosuppressive regimens containing CsA after renal transplantation. Unfortunately, the interpretation of these data is complicated by the concomitant use of CS or AZA by these patients. Huang et al observed a 50% incidence of chronic hepatitis in renal allograft recipients treated with CsA and prednisone but the mortality rate was low (5%).[101] These results were not different from patients treated with prednisone and AZA. Similarly, Stempel et al found no increased mortality in HBsAg-positive renal transplant patients treated with CsA and prednisone over a 4-year period.[204] On the other hand, Kliem et al followed renal transplant patients for almost 7 years and found that 60% of HBsAg-positive patients died from liver failure compared with 2% of HBsAg-positive patients.[114] Furthermore, Bang et al reported a 25% mortality in HBsAg-positive patients treated with CsA/prednisone (45% because of liver-related diseases) compared with a mortality of 7.8% in a similar group of HCV positive patients (0% from liver diseases).[13]

A milder course of hepatitis C after kidney transplantation in patients receiving different immunosuppressive regimens containing CsA has been suggested from different studies,[13, 114, 183] although in some studies an increased incidence of sepsis was found.[114, 159] Elevated levels of CsA metabolites in patients with chronic hepatitis C receiving CsA have been reported, but the clinical significance of these findings is unclear.[98, 114] In the nontransplant setting, CsA given for 3 months at a dose of 1.5 to 4.0 mg/kg/day, did not have any effect in the HCV RNA levels in patients with chronic hepatitis C.[108] CsA also has been used successfully for the treatment of HCV-associated cryoglobulinemia without any reported worsening of liver function.[12]

In conclusion, CsA appears to have a milder effect on the clinical course of patients with chronic viral hepatitis. Close monitoring of liver and kidney function is mandatory in these patients as is a high alert state for the development of infections.

Methotrexate

MTX is currently one of the most commonly used medications for the treatment of RA. Its hepatotoxicity has been well documented, although significant controversy exists regarding its frequency and severity.[221]

The American College of Rheumatology (ACR) recently has published guidelines regarding the monitoring for hepatotoxicity in patients with RA receiving MTX.[120] In patients with history of excessive alcohol consumption, persistently elevated aspartate aminotransferase (AST) levels or with underlying chronic hepatitis B or C infection, consultation with a gastroenterologist for consideration for a pretreatment liver biopsy is recommended.[120] If there is evidence of persistent AST abnormal-

ities over a year, a repeat liver biopsy is recommended. Presence of advanced histologic changes, such as moderate to severe fibrosis or cirrhosis (Roenigk grade IIIB or IV, respectively),[180] in the liver biopsy is an indication for discontinuation of therapy.[120]

When MTX is used for treatment of psoriasis or psoriatic arthritis, a higher incidence of liver toxicity has been observed.[179] Based on these findings, a recent consensus conference proposed that patients without risk factors for liver disease should undergo a liver biopsy when 1 to 1.5 gm of cumulative MTX has been reached and thereafter at intervals of approximately 1.5 gm of cumulative MTX dose.[179] In patients with risk factors for liver disease, such as excessive alcohol consumption, persistent abnormal liver chemistry studies, family history of inheritable liver diseases, history of liver diseases like chronic hepatitis B or C, diabetes mellitus, obesity, or history of significant exposure to hepatotoxic drugs or chemicals, an initial liver biopsy is indicated during the first 2 to 4 months of therapy, with repeat biopsies at 1.0 to 1.5, 3.0, and 4.0 gm of cumulative MTX dose. Similarly to the ACR guidelines, discontinuation of MTX is recommended if severe fibrosis or cirrhosis (Roenigk grade IIIB or IV) are present.

Although these guidelines emphasize the importance of close monitoring in patients with pre-existing liver diseases, the mere presence of an underlying liver disease should not be a contraindication for treatment. MTX should be avoided in patients with advanced liver disease or cirrhosis regardless of its cause because of concerns of increased risk of infection and drug-related toxicities (renal, pulmonary, bone marrow, liver, and so forth). MTX also should be avoided in patients with underlying alcoholic liver disease because that represents a significant risk factor for MTX-induced hepatotoxicity.[221] On the other hand, MTX has been used over the last decade in patients with various inflammatory liver diseases including PBC,[110] primary sclerosing cholangitis,[222] and idiopathic granulomatous hepatitis[115] with promising results.

Although a case report of fulminant hepatitis caused by reactivation of hepatitis B infection after discontinuation of low-dose MTX has been reported,[59] the short and long term effects of MTX treatment in patients with underlying chronic hepatitis B or C are unknown. As mentioned previously, a baseline liver biopsy is indicated and then a decision should be made, balancing the risk to benefit ratio for each individual patient. Close monitoring of liver function and virologic parameters, as discussed with the other immunosuppressive agents, is mandatory.

Azathioprine

Liver disease caused by AZA is rare (< 0.1%).[57] AZA-induced hepatotoxicity has been more commonly reported in the post-transplant setting and it can present with a wide spectrum of manifestations, including asymptomatic elevation of liver tests, cholestasis, cholestatic hepatitis, and vascular liver disease (peliosis hepatis, veno-occlusive

disease and nodular regenerative hyperplasia).[117] Despite its potential hepatotoxic effect, AZA is being used successfully for the treatment of autoimmune hepatitis[46] particularly, as a steroid-sparing agent.

In patients with advanced liver disease, the same precautions that have been mentioned previously for the other immunosuppressive agents apply to AZA. A recent report by Pol et al[166] suggested that AZA-induced hepatitis in renal transplant patients was facilitated by an underlying chronic viral hepatitis B or C. Similarly, Hestin et al found a correlation between AZA use and histologically proven chronic active hepatitis C in renal transplant patients.[94] Although data from patients with chronic viral hepatitis treated with AZA in the nontransplant setting are lacking, caution is recommended in patients with chronic viral hepatitis receiving AZA therapy. Differentiating between AZA-induced liver injury and exacerbation of the underlying viral process may require liver biopsy in addition to drug discontinuation.

PSORIASIS

The skin is frequently involved in different rheumatologic or autoimmune diseases including SLE, scleroderma, dermatomyositis, psoriatic arthritis (PsA), Reiter's syndrome, Still's disease, sarcoidosis, Behçet's disease, and various vasculitides.[70] Successful treatment of the underlying rheumatologic condition usually leads to improvement of the coexistent skin lesions. In some cases, treatment of the underlying rheumatic disease has been associated with exacerbations of the skin manifestations. Typically, this has been described in patients with psoriasis undergoing treatment for associated PsA or coexistent rheumatic diseases (e.g., SLE).[1, 30, 83]

Several medications have been associated with induction or exacerbation of psoriatic lesions. These medications are listed below:

Definite association
- Lithium[2]
- β-blockers[2]
- Corticosteroid withdrawal[185]
- Antimalarials[1]

Possible association
- NSAIDs[1]
- Interferons:
  - α[19, 66, 68, 74, 107, 134, 140, 227]
  - β[116, 218]
  - γ[58]
- ACE-inhibitors[43, 76, 87, 102, 206, 226]
- Potassium iodide[1]
- Amiodarone[1]
- Digoxin[1]
- Antibiotics (tetracycline,[1] penicillin,[1] sulfonamides,[1] terbinafine[84])
- Alcohol[165]
- Calcium channel blockers[113]

Most of the drug-induced psoriasis cases have been reported as sporadic case reports or as small retrospective studies.[1, 30] The absence of well-designed, prospective placebo-controlled studies makes the interpretation of the available data problematic.[30]

Among the medications that rheumatologists frequently prescribe, antimalarials, CS, NSAIDs, and gold have been frequently implicated in the exacerbation of psoriasis.

ANTIMALARIALS

Antimalarials are prescribed to patients with psoriasis for treatment of associated PsA, coexistent SLE or RA, or for prophylaxis against malaria in patients traveling to endemic areas.[1] Although there have been no controlled trials indicating efficacy in PsA, recent reports have suggested a potential role for antimalarials in the treatment of PsA.[77, 109] Concerns about their potential toxicity have limited their use. In a study by Gladman et al only 5% of patients with PsA were receiving antimalarials.[78]

Earlier reports suggested an increased incidence of psoriasis exacerbation, especially in patients taking quinacrine[41] or chloroquine.[11, 20, 41, 121, 153, 155, 231] Similarly, there have been several case reports in the literature describing exacerbation of psoriasis, resistance to treatment, and erythroderma, following treatment with hydroxychloroquine (HCQ).[10, 61, 82, 91, 137, 199, 216] Some in vitro studies suggested a potential role of these agents in the induction of epidermal injury in normal and psoriatic skin.[50, 192, 225] Chloroquine enhances mitogen-induced lymphocyte proliferation[192] and the allostimulatory properties of fresh and cultured epidermal antigen presenting cells from patients with psoriasis.[50] HCQ has been shown to inhibit the epidermal transglutaminase in normal cultured human skin, leading to epidermal injury and subsequent irregular keratinization of the upper and lower epidermis.[225] Chloroquine, however, in contrast to lithium and propranolol, had no enhancing effect in tyrosine phosphorylation of mitogen-stimulated T cells from psoriatic patients.[154]

Clinical studies have portrayed a safer profile for antimalarials in the treatment of psoriatic arthritis. Gladman et al[77] found no differences in psoriasis exacerbation between a group of patients with PsA treated with chloroquine for 6 months compared to a control group (18% and 25%, respectively). Only 1 out of 32 patients had to discontinue the medication because of psoriasis exacerbation.[77] Two retrospective studies in patients with PsA treated with HCQ did not show also any significant incidence of skin exacerbations.[109, 190] Specifically, Kammer et al reported no cases of psoriasis exacerbation in 50 trials of HCQ, although drug-induced cutaneous eruptions developed in 4 cases (8%).[109] Wilke and Sayers, reviewing the experience at the Cleveland Clinic, showed that only 3 of 32 patients (9%) treated with HCQ for 4 to 6 years had a "possible flare" of their psoriatic lesions.[223]

Collectively, these limited data suggest that the incidence of antima-

larial-induced exacerbation of psoriasis is low. It also seems that HCQ is safer compared with chloroquine and quinacrine. Nevertheless, these medications should be used cautiously in psoriatic patients with close monitoring of their skin lesions.[30]

CORTICOSTEROIDS

The impression that systemic CS aggravate psoriasis is derived from the seminal observations of Ryan and Baker[185] in the treatment of 73 patients with generalized pustular psoriasis. Prednisolone alone was used in 24 patients in doses ranging from 30 to 300 mg/day. Triamcinolone was used in 17 patients in doses of 8 to 60 mg daily. Smaller numbers of patients received betamethasone, ACTH, dexamethasone, or hydrocortisone alone, and 21 patients received varying combinations together or in sequence. Six months or longer seemed to be a typical treatment course. The authors concluded that CS-treated patients tended to experience increasingly severe generalized pustular relapses, often precipitated by attempting to withdraw the steroid. Satisfactory control with acceptable side effects was achieved in only 12 of 73 (17%) patients.

They later expanded their experience to 155 patients and reported that 37 (24%) endured their first attack of generalized pustular psoriasis within a month of first receiving CS or within a month of their withdrawal; 25 (16%) had common plaque-type psoriasis before the pustular phase.[186] They concluded that systemic CS used for plaque or erythrodermic psoriasis may precipitate and perpetuate the severe phase of the disease. Moreover, MTX seemed to be less efficacious in patients previously treated with steroids. MTX was valuable during steroid withdrawal in patients who became refractory to steroids; however, rebound flares after steroid withdrawal were not always controllable with MTX.

The least common form of psoriasis is exfoliative dermatitis or psoriatic erythroderma, representing only 1% to 2% of all forms. Erythrodermic psoriasis usually develops gradually or abruptly during the course of ordinary chronic psoriasis, but it may be the initial manifestation. The most important precipitating factor is thought to be the preceding use of systemic steroids or excessive potent topical steroids (>60 gm/week). Of 50 patients admitted to Baylor University for psoriatic erythroderma, 25 (50%) received excessive topical steroids or systemic steroids (oral or intramuscular).[24] Some patients received both oral and intramuscular steroids.

Because of the foregoing indirect clinical evidence, whenever possible, the use of high-dose systemic CS therapy should be eschewed in patients with psoriasis. Their use is associated with the majority of extremely unstable (inflammatory) psoriasis as well as the conversion of ordinary cases into generalized pustular or erythrodermic psoriasis.[31] Despite these concerns, systemic CS are still used in approximately 20% of patients with PsA.[78, 211] Short courses of low-dose CS (such as prednisone at 10–20 mg/d) and local intra-articular CS injections may be

justifiable for severe flares of PsA but always in combination with disease modifying agents like MTX, sulfasalazine, AZA, CsA, and so forth. A prior consultation with a dermatologist is recommended for better planning and coordination of the therapeutic strategy for these patients.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are the most commonly used medications in the treatment of PsA.[78, 81] Although there have been anecdotal case reports of psoriasis exacerbations in patients receiving various NSAIDs (including indomethacin,[111, 168, 194] phenylbutazone,[175] ibuprofen,[15] and oxyphenbutazone[175]) two double-blind placebo controlled trials using NSAIDs for treatment of psoriasis did not substantiate these findings.[55, 118] Kragballe et al compared the efficacy of benoxaprofen (n = 20) with placebo (n = 20) in an 8-week double-blind randomized trial.[118] There was a significant improvement of the psoriatic lesions in the benoxaprofen group compared with placebo, without any cases of worsening psoriasis in the NSAID group. A higher incidence of photosensitivity was observed in patients receiving benoxaprofen (11 of 20) compared with placebo (3 of 19). In a similar study, Ellis et al randomized patients to receive either meclofenamate (n = 47) or placebo (n = 56) in a double-blind fashion for 4 weeks followed by an open trial of the medication for 4 more weeks.[55] Although there was no evidence of improvement with meclofenamate, the incidence of worsening psoriatic lesions did not differ between the meclofenamate and the placebo group (13% versus 13% at 4 weeks and 8% versus 10% at 8 weeks, respectively).

Overall, it appears that NSAIDs are well tolerated in patients with psoriasis without significant skin side effects.

Gold

Gold therapy has been shown to have modest efficacy in patients with PsA. Both oral (auranofin) and intramuscular (IM) (gold sodium thiomalate) gold have been used.[81, 223] In a recent double-blind trial, Palit et al found a marginal improvement of PsA in patients treated with IM gold compared to auranofin.[156] The incidence of psoriasis exacerbation is low for both routes of administration, but it seems to be higher in patients treated with IM gold. In a recent review of published studies, Bruckle et al reported an overall incidence of 3.4% of psoriasis exacerbation in patients receiving auranofin.[26] In contrast, in patients treated with IM gold, the incidence ranges from 0% to 18% (7.8% from 4 published studies).[26, 52, 156, 177]

Gold therapy is well tolerated in patients with PsA, although its efficacy is modest. Auranofin has a lower incidence of psoriasis exacerbations but is less effective compared with IM gold.[105]

Treatment Conflicts in the Presence of Coexistent SLE

Based on the prevalence of psoriasis in the US and UK population (1%–2%),[32] the coexistence of all forms of lupus with psoriasis seems to be less than expected. Dubois reported that 0.6% of 520 patients with SLE had concurrent psoriasis.[53] The coexistence of psoriasis and lupus raises issues of diagnosis and treatment.[91] Subacute cutaneous lupus erythematosus (SCLE) lesions may be either annular or psoriasiform. Biopsy, direct immunofluorescence, and serologic testing are necessary to distinguish some cases of SCLE from psoriasis.

Photochemotherapy with longwave ultraviolet (UV) light and oral 8-methoxypsoralen (PUVA) is being used for the treatment of psoriasis and has shown some benefit in the treatment of patients with peripheral PsA.[160] UV light exposure (UVA or UVB) can induce significant flares of the skin disease in patients with lupus, especially in those with SCLE who are positive for anti-Ro/SSA antibodies.[89, 132] Hence, UV therapy should be avoided in patients with coexistent psoriasis and SLE.

The control of serious SLE manifestations (renal, CNS, hematologic, and so forth) often requires systemic CS therapy, but a rebound flare of psoriasis is possible upon withdrawal of the CS. Antimetabolites such as AZA and MTX used as steroid-sparing agents may prevent this as well as be beneficial for the psoriasis.[31]

KIDNEY DISEASES

Kidney involvement is a common finding in different rheumatic diseases and represents an important determinant of morbidity and mortality.[29] SLE, systemic sclerosis, mixed connective tissue disease (MCTD), and vasculitides like Wegener's granulomatosis, microscopic polyarteritis, polyarteritis nodosa, mixed cryoglobulinemia, and Henoch-Schönlein purpura, are the diseases that are most commonly associated with renal injury. Kidney involvement also can be secondary to amyloidosis because of chronic inflammatory conditions like RA and ankylosing spondylitis or more rarely caused by complications from chronic gout.[29]

In addition to kidney abnormalities caused by the underlying rheumatologic conditions, a number of antirheumatic drugs have been shown to possess nephrotoxic properties. The most commonly used potentially nephrotoxic medications are listed in Table 3.

Renal insufficiency either caused by the underlying rheumatic condition or by unrelated causes (e.g., hypertension, diabetes mellitus, hereditary causes, and so forth) complicates the appropriate treatment of the affected patients. For most antirheumatic drugs, renal insufficiency can lead to inappropriately high levels in the blood and prolonged half-life of the medications, causing increased toxicity (see Table 4). Certain medications, like NSAIDs, MTX, gold (oral or intramuscular), D-penicillamine, and probenecid should be avoided in the setting of advanced

Table 3. RENAL TOXICITY OF ANTIRHEUMATIC MEDICATIONS

Drug	Renal Toxicity	Risk Factors	Comments
NSAIDs[18]	Acute renal failure	Plasma volume contraction	
		Congestive heart failure	
		Cirrhosis of the liver with ascites	
	Hyperkalemia	Concomitant drug use, e.g., β-blockers, α-agonists, K^+-sparing diuretics, ACE-inhibitors	
		Insulin-dependent diabetes mellitus	
		Moderate-severe renal failure (GFR <30 mL/min)	
	Sodium retention		Transient effect
	Water retention		
	Acute interstitial nephritis ± minimal-change glomerulopathy/nephrotic syndrome		Usually reversible
	Chronic renal failure	Concomitant use of OTC analgesics	
	Renal papillary necrosis		Rare
Corticosteroids[14, 37]	↑ protein catabolic rate, azotemia		
	↑ GFR (high-dose)		"False" evidence of improvement in renal function
	Hypokalemic alkalosis		
Gold[79] (mainly with IM route)	Proteinuria		Mild/transent = 10%–20% Severe = 1%–3%
	Hematuria		1%–3%
	Nephrotic syndrome caused by membranous glomerulopathy	HLA-B8/DR3	Occurs in 1%–2% Usually reversible (70%)
	Renal insufficiency		Rare

D-Penicillamine[79]	Proteinuria			Common (10%–20%)
	Nephrotic syndrome			Rare
	Membranous glomerulonephritis			Rare
	Microscopic hematuria			Usually benign
	Rapidly progressive glomerulonephritis			Rare
	Goodpasture-like syndrome			Rare Granular deposits in basement membrane Anti-GBM = (−)
Cyclosporine[178, 195]	Acute nephrotoxicity	↑ Creatinine HTN ↑ K^+ Mild distal RTA		Dose-related Usually reversible
	Chronic nephrotoxicity	Slowly progressive renal failure Proteinuria HTN	Increasing age Dose >5 mg/kg/d ↑ of pretreatment creatinine by >50% CsA-induced HTN	10% in RA patients treated for ~3 yr
	Hemolytic-uremic syndrome			Renal transplant patients
FK-506/Tacrolimus[145, 167, 202, 208, 215]	Acute/chronic toxicity similar to cyclosporine		↑ dose	Most of the data derived from renal/liver transplant recipients Usually reversible after dose reduction ? autoimmune diseases

GFR = glomerular filtration rate; OTC = over the counter; RTA = renal tubular acidosis; CsA = cyclosporine; GBM = glomerular basement membrane; RA = rheumatoid arthritis; HTN = hypertension; ACE = angiotensin converting enzyme.

Table 4. TOXICITY OF ANTIRHEUMATIC DRUGS IN THE PRESENCE OF RENAL INSUFFICIENCY

Drug	Major Toxicity	Comments
Allopurinol[88, 198]	Allopurinol hypersensitivity syndrome manifested by: Skin rash (erythematous desquamative) Fever Hepatitis Eosinophilia Worsening renal function	Renal insufficiency present in 81% of reported cases Mortality = 26% Dose adjustment required (see Table 5) for patients with renal failure
Colchicine[72, 122, 170, 230]	Proximal myopathy with ↑ creatinine kinase Neuropathy (mild, axonal)	Usually reversible after drug discontinuation ↓ dose by 50% for GFR <10 mL/min Special precautions for posttransplant patients receiving CsA
Methotrexate[85, 95, 176]	Pancytopenia ↑ Overall severe toxicity	54% of all reported cases of bone marrow suppression had evidence of renal insufficiency Odds ratio for overall severe toxicity ranging from 3 to 5.7 Probably avoid for patients with creatinine >2.0 mg/dL
NSAIDs[18]	Hyperkalemia ↑ Risk of GI bleeding (?)	NSAIDs should be probably avoided for patients with GFR <50 m/min and used cautiously in hemodialysis patients
Cyclophosphamide/ azathioprine	Possible potentiation of bone marrow suppressive effects	Close monitoring of cell counts is mandatory

GFR = glomerular filtration rate; CsA = cyclosporine; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.

renal failure. For other medications, appropriate adjustment of their dose is imperative in the presence of mild or severe renal failure. An overview of the pharmacokinetics of different antirheumatic medications and their dosage adjustment in patients with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis is presented in Table 5.

Special precautions also should be taken in order to avoid hazardous interactions between different medications, especially in the setting of underlying renal failure. A complete review of the multiple interactions between different antirheumatic medications is beyond the scope of this review. Most antirheumatic drugs should be used very cautiously in patients with renal insufficiency, with close laboratory monitoring and increased alertness for any signs of clinical toxicity.

Table 5. PHARMACOKINETICS AND DOSAGE ADJUSTMENT OF ANTIRHEUMATIC DRUGS

Drug	Clearance/ Metabolism	Protein Binding (%)	Half-life Normal (t 1/2)	Half-life ESRD (t 1/2)	Adjustment for Renal Failure by GFR (mL/min)			Supplementation After Hemodialysis	Supplementation After Peritoneal Dialysis
					> 50 (%)	10–50 (%)	< 10 (%)		
Acetylsalicylic acid	Hepatic metabolism	80–90	15 min	Unchanged	100	?	Avoid	Yes	None
NSAIDS	Hepatic metabolism	95–99	Variable (1–100 h)	Unchanged except Diflunisal (5–20 h → 62 h) Ketorolac (4–6 h → 10 h)	100	100 ↓ by 50 for Diflunisal Ketorolac	100 ↓ by 50 for Diflunisal Ketorolac Ketoprofen Oxaprozin Sulindac	None	None
Prednisone	Hepatic metabolism	75	2.5–3.5 h	Unchanged	100	100	100	None	Unknown
Methylprednisolone	Hepatic metabolism	40–60	1.9–6 h	Unchanged	100	100	100	Yes	Unknown
Cyclophosphamide	Hepatic metabolism	14 (metabolites ~ 60)	4–7.5 h	10 h	100	100	75	Half dose	Unknown
Sulfasalazine	Colon → SP/5-ASA	99	4–14 h	↑	100	?	?	Unknown	Unknown
Azathioprine	Hepatic metabolism/ renal excretion of metabolites	20	15 min (metabolites ~ 5 h)	↑	100	75	50	Yes	Unknown
Methotrexate	Renal excretion	45–50	7 h	↑	100	50	Avoid	None	None
Cyclosporine	Hepatic metabolism	96–99	5–18 h	Unchanged	100	100	50	None	None
FK-506	Hepatic metabolism	75–99	4–40 h	Unchanged	100	100	?	Unknown	Unknown
Auranofin	Renal excretion	60	Plasma = 17–26 d Whole body = 70–80 d	Unknown	50	Avoid	Avoid	None	None
Gold sodium thiomalate	Renal excretion	95	Variable (7–250 d)	Unknown	50	Avoid	Avoid	None	None
Penicillamine	Hepatic metabolism Renal excretion	80	1.5–3 h	↑	100	Avoid	Avoid	One-third dose	Unknown
Allopurinol	Oxidation to oxipurinol Renal excretion	<5	Allopurinol = 2–3 h Oxypurinol = 15 h	Unchanged	75	50	25	Half dose	Unknown
Colchicine	Renal excretion	31	19 h	40 h	100	100	50	None	Unknown
Probenecid	Renal excretion	85–95	5–8 h	Unchanged	100	Avoid	Avoid	Unknown	Unknown
Chloroquine	Renal excretion	50–65	2–4 d	5–50 d	100	100	50	None	None

SP = sulfapyridine; 5-ASA = 5-aminosalicylic acid; ESRD = end stage renal disease; GFR = glomerular filtration rate.
Data from references 16, 17, 39, 163, 173, 202.

MALIGNANT DISEASES

Treating patients with various rheumatologic conditions in the setting of an underlying malignancy is a challenging task. Rheumatologists are faced with this situation in patients with:

De novo appearing rheumatologic conditions caused by underlying malignancies or as a complication of cancer treatment (chemotherapy, radiation therapy, etc)
Exacerbation of pre-existing rheumatic diseases caused by malignancy or cancer therapy
Development of malignancies in the course of a chronic rheumatic disease

The choice of the appropriate therapeutic regimen should be influenced by several factors. Obviously, the nature and the severity of the coexistent malignant condition, which usually determines the expected survival for the individual patient, is the most important factor. In patients with projected short life expectancy, therapy aiming primarily at relief of symptoms should be offered. Because most of these patients have coexistent conditions such as cytopenias, infections, or evidence of different organ dysfunction (liver, lung, gastrointestinal, etc.) selecting medications with the least possible toxicity is appropriate.

In patients with projected longer life expectancy after treatment of their primary malignancy, several issues must be taken into account before designing the appropriate therapy. Differentiating between a primary rheumatologic condition versus a malignancy or drug-associated musculoskeletal syndrome is an important first step.

Various musculoskeletal syndromes have been described in association with malignant diseases.[27, 35, 150] An overview of the most commonly described conditions is summarized in Table 6. Treatment of the underlying malignant disease occasionally leads to improvement of the associated rheumatic conditions like carcinoma-associated polyarthritis,[28] malignancy-associated polymyositis (PM)/dermatomyositis (DM),[35] and so forth. In other conditions, conventional antirheumatic therapy is required for symptom control and improvement of the patient's quality of life. Certain conditions like myelodysplastic syndrome (MDS)-associated polyarthritis, polymyalgia rheumatica, malignancy-associated PM/DM, and various malignancy-associated vasculitides may respond to steroid therapy.[35] George and Newman observed a good response to steroids in 5 out of 8 patients with seronegative inflammatory arthritis associated with MDS.[71] Similar responses in various MDS-associated rheumatologic conditions have been reported in a study from the Mayo Clinic.[36] When steroids are used for the treatment of these disorders, increased vigilance for early diagnosis and aggressive treatment of emerging infections is required. The use of cytotoxic immunosuppressive agents should be avoided because of concerns about recurrence of the underlying malignant process or transformation of a premalignant condition to frank malignancy (e.g., MDS to leukemia). A similar approach should be taken in patients with pre-existing rheumatic diseases that are exacerbated

Table 6. MUSCULOSKELETAL SYNDROMES ASSOCIATED WITH MALIGNANCIES

Musculoskeletal Syndrome	Malignancy	Comments
Inflammatory polyarthritis (RA-like)	Carcinomas* (most common) MDS Lymphoma (especially NHL) Paraproteinemias (MM/WM/MGUS) Leukemias (rare/children)	Predominantly asymmetric with lower extremity involvement ↑ acute phase reactants/RF(-) Occasionally good response to steroids
Mono/oligo-articular involvement	Leukemia Lymphoma Metastatic cancer with local invasion Primary bone tumors	Common knee involvement Nonspecific synovial biopsy changes Pain a prominent feature
Hypertrophic osteoarthropathy	Mainly lung neoplasms Intrathoracic carcinomas	Knee/ankle/MTP/wrist involvement/+ clubbing Bone scan (+)/periosteal thickening in radiographs
Polymyalgia rheumatica	Various malignancies (ovary, prostate, kidney)/ Questionable relationship	Occasional improvement with steroids
Palmar fasciitis	Ovarian tumors	Accompanied by polyarthritis
Relapsing polychondritis	MDS (rare) Lymphoma Leukemia	
Dermatomyositis/ polymyositis	Carcinomas (breast, ovary, lung, GI)	Most common with DM Variable response to steroid treatment
Necrotizing myopathy	Carcinomas (lung/breast/ GI/bladder)	Shoulder girdle>>lower extremities Steroid-resistant
Systemic sclerosis	Carcinoma of the stomach/ melanoma	
Eosinophilic fasciitis	Hematopoietic malignancies	
Panniculitis	Pancreatic cancer	Accompanied by ankle arthritis
Vasculitides	Hematopoietic malignancies (hairy cell leukemia/ lymphomas/MDS, etc.) Solid tumors (Lung/colon/ renal cell, etc.)	Usually leukocytoclastic but any size vessel can be affected

*Typically seronegative, explosive onset arthritis.

MDS = myelodysplastic syndrome; MM = multiple myeloma; WM = Waldenström macroglobulinemia; MGUS = monoclonal gammopathy of undetermined significance; NHL = non-Hodgkin's lymphoma; MTP = metatarsophalangeal; RF = rheumatoid factor; DM = dermatomyositis.

Data from references 28, 35, 150.

because of the underlying malignancy or as a consequence of the cancer treatment (see below).

Rheumatologists should also be aware of the potential of anticancer drugs to induce various rheumatologic syndromes or to exacerbate underlying rheumatic diseases. In Table 7 the most commonly reported drug-induced musculoskeletal conditions are presented. Identifying and discontinuing the offending medication, after appropriate consultation

Table 7. ANTICANCER DRUG INDUCED RHEUMATOLOGICAL SYNDROMES

Drug	Musculoskeletal Syndrome	Comments
Intravesical bacille Calmette-Guérin (BCG)[51, 80, 104, 169, 189, 213, 228]	Arthralgias/reactive arthritis	Usually symmetric polyarthritis involving small joints HLA-B27 (+) = 44% Good response to NSAIDs
Interleukin-2[130, 142]	Symmetric polyarthritis (RA-like) Reactivation of quiescent RA or Reiter's syndrome	Usually few days to weeks after IV infusion Occasional improvement with NSAIDs
G-CSF/GM-CSF[103, 146, 188, 203]	Cutaneous vasculitis Sweet's syndrome Pyoderma gangrenosum Psoriasis exacerbation Gout/pseudogout exacerbation (G-CSF)	
Interferons (-α, -β, -γ)[146, 151]	Induction/exacerbation of various autoimmune diseases (SLE/RA/psoriasis/vasculitis) Arthritis (IFN-α) Raynaud's (rare) Leukocytoclastic vasculitis (rare)	Polyarthritis (50%) with RF(+) = 34% Arthritis usually improves with drug discontinuation and/or addition of NSAIDs ± steroids
Tamoxifen[44, 217]	Induction/exacerbation of inflammatory polyarthritis	
Various chemotherapeutic agents[44, 135, 147, 171, 182, 196, 200, 217]	"Post-chemotherapy rheumatism"	See text for details

NSAIDS = non-steroidal anti-inflammatory drugs; RA = rheumatoid arthritis; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; RF = rheumatoid factor; SLE = systemic lupus erythematosus; IFN = interferon.

with the patient's hematologist/oncologist, could lead to improvement of patient's symptoms and avoidance of an extensive diagnostic work-up. In some cases, addition of NSAIDs or low-dose CS is indicated.

Loprinzi et al have recently described a syndrome of widespread arthralgias associated with mild inflammation in a few cases, occurring 1 to 3 months after completion of chemotherapy for breast cancer.[136] They called this syndrome *postchemotherapy rheumatism.* Since then, 24 more cases have been described.[135, 147, 171, 182, 196, 200, 217] Most patients were women (31 of 32) receiving chemotherapy for breast cancer (27 of 31). Symmetric polyarthralgias/myalgias, morning stiffness, and absence of laboratory findings suggestive of an inflammatory process characterize this syndrome. In a few cases objective findings suggestive of synovitis were present. Treatment with NSAIDs has been ineffective in the major-

ity of patients, whereas CS provided little additional benefit. The symptoms usually subside spontaneously 4 to 12 months later. The pathogenesis of this condition is unknown. It is interesting that all reported patients had received cyclophosphamide as part of their chemotherapy regimen. Still, though, it remains unclear if this condition represents a syndrome with a common origin or a heterogeneous collection of musculoskeletal conditions caused by chemotherapy withdrawal, chemotherapy-induced menopause, steroid-withdrawal, tamoxifen-induced polyarthritis, or fibromyalgia.

Certain rheumatic conditions have been associated with an increased risk of malignancy. These include RA (hematopoietic malignancies), Sjögren's syndrome (lymphomas), Felty's syndrome (non-Hodgkin lymphomas), scleroderma (lung cancer), SLE (non-Hodgkin's lymphomas), discoid lupus erythematosus (squamous cell epithelioma), Paget's disease (osteogenic sarcoma), and lymphomatoid granulomatosis (lymphoma).[35] Cytotoxic agents that are commonly used for the treatment of various rheumatic diseases, such as AZA,[106, 197] cyclophosphamide,[172, 205] chlorambucil,[92, 158] and CsA[8] have been shown to further increase this risk. A highly controversial issue is the possible oncogenic potential (mainly for lymphomas) of MTX when it is used in low doses for the treatment of RA.[73, 119] Regardless of the exact contribution of cytotoxic agents in the development of certain malignant disorders, recent evidence suggests that occasionally discontinuation of these agents can lead to reversal of the malignant process.[187, 214] It is prudent to discontinue all cytotoxic agents when a malignancy is identified in patients with a chronic rheumatic disease. Whether or not these agents should be used for life-threatening complications of the underlying rheumatic disease or for symptomatic relief of these patients is a question that has to be addressed on an individual basis, taking into account all the factors that have been mentioned previously.

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