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Abatacept (Orencia)

[Clinical Policy Bulletins](#) | [Medical Clinical Policy Bulletins](#)

Number: 0720

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10/08/2025

Effective: 03/17/2006

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Brand Selection for Medically Necessary Indications for Commercial Medical Plans

Note: This policy applies only to members who are new to treatment with a targeted immune modulator for the first time.

As defined in Aetna commercial policies, health care services are not medically necessary when they are more costly than alternative services that are at least as likely to produce equivalent therapeutic or diagnostic results. Orencia IV (intravenous abatacept) is more costly to Aetna than other targeted immune modulators for certain indications. There is a lack of reliable evidence that Orencia IV (intravenous abatacept) is superior to other lower cost targeted immune modulators for the medically necessary indications listed below. Therefore, Aetna considers Orencia IV

(intravenous abatacept) to be medically necessary only for members who have a contraindication, intolerance or ineffective response to the available equivalent alternative targeted immune modulators per criteria below.

Moderately to Severely Active Rheumatoid Arthritis (RA)

Orencia intravenous (IV) formulation only: for the treatment of moderately to severely active RA, member has a contraindication, intolerance or ineffective response to all of the following available equivalent alternative targeted immune modulators (one-month trial each): Simponi Aria and either Avsola, Inflectra, or Renflexis.

Active Psoriatic Arthritis (PsA)

Orencia intravenous (IV) formulation only: for the treatment of PsA, member has a contraindication, intolerance or ineffective response to all of the following available equivalent alternative targeted immune modulators (one-month trial each): Simponi Aria, Stelara, and either Avsola, Inflectra, or Renflexis.

Policy

Scope of Policy

This Clinical Policy Bulletin addresses abatacept (Orencia) for commercial medical plans. For Medicare criteria, see [Medicare Part B Criteria](https://www.aetna.com/health-care-professionals/medicare/part-b-step.html) (<https://www.aetna.com/health-care-professionals/medicare/part-b-step.html>).

Note: Requires Precertification:

Precertification of intravenous abatacept (Orencia IV) is required of all Aetna participating providers and members in applicable plan designs. For precertification of intravenous abatacept, call (866) 752-7021 or fax

(888) 267-3277. For Statement of Medical Necessity (SMN) precertification forms, see [Specialty Pharmacy Precertification](#) (<https://www.aetna.com/health-care-professionals/health-care-professional-forms.html>).

Note: For commercial plans, Site of Care Utilization Management Policy applies. For information on site of service for intravenous Orencia, see [Utilization Management Policy on Site of Care for Specialty Drug Infusions](#) (<https://www.aetna.com/health-care-professionals/utilization-management/drug-infusion-site-of-care-policy.html>).

I. Prescriber Specialties

This medication must be prescribed by or in consultation with one of the following:

- A. Rheumatoid arthritis and articular juvenile idiopathic arthritis: rheumatologist;
- B. Psoriatic arthritis: rheumatologist or dermatologist;
- C. Prophylaxis of acute graft versus host disease (aGVHD), chronic GVHD, and immune checkpoint inhibitor-related toxicity: oncologist or hematologist.

II. Criteria for Initial Approval

Aetna considers abatacept (Orencia) medically necessary for the following indications when criteria are met:

- A. *Rheumatoid arthritis (RA)*
 - 1. For adult members who have previously received a biologic or targeted synthetic drug (e.g., Rinvoq, Xeljanz) indicated for moderately to severely active RA within the past 120 days; or
 - 2. For adult members for treatment of moderately to severely active RA when *both* of the following criteria are met:
 - a. Member meets *either* of the following criteria:

i. Member has been tested for either of the following biomarkers and the test was positive:

- Rheumatoid factor (RF); *or*
- Anti-cyclic citrullinated peptide (anti-CCP); *or*

ii. Member has been tested for *all* of the following:

- RF; *and*
- Anti-CCP; *and*
- C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR); *and*

b. Member meets *one* of the following criteria:

i. Member has failed to achieve a low disease activity after a 3-month trial of methotrexate (MTX) monotherapy at a maximum titrated dose of at least 15 mg per week and meets *any* of the following conditions:

- Member has had a documented inadequate response to MTX in combination with at least one other conventional synthetic drug (i.e., hydroxychloroquine and/or sulfasalazine) after a 3-month trial at a maximum tolerated dose(s); *or*
- Member has experienced a documented intolerable adverse event to hydroxychloroquine or sulfasalazine; *or*
- Member has a documented contraindication to hydroxychloroquine (see [Appendix A](#)) and sulfasalazine (e.g., porphyria, intestinal or urinary obstruction); *or*
- Member has moderate to high disease activity; *or*

ii. Member was unable to tolerate a 3-month trial of MTX monotherapy at a maximum titrated dose of at least 15 mg per week and meets *any* of the following conditions:

- Member has had a documented inadequate response to MTX in combination with at least one other conventional synthetic drug (i.e., hydroxychloroquine and/or sulfasalazine) after a 3-month trial at a maximum tolerated dose(s); *or*
 - Member has stopped taking MTX and has had a documented inadequate response to another conventional synthetic drug (i.e., leflunomide, hydroxychloroquine, and/or sulfasalazine) alone or in combination after a 3-month trial at a maximum tolerated dose(s); *or*
 - Member has experienced a documented intolerable adverse event to leflunomide, hydroxychloroquine, or sulfasalazine; *or*
 - Member has a documented contraindication to leflunomide, hydroxychloroquine (see Appendix A), and sulfasalazine (e.g., porphyria, intestinal or urinary obstruction); *or*
 - Member has moderate to high disease activity; *or*
- iii. Member has experienced a documented intolerable adverse event or has a documented contraindication to MTX (see Appendix A), discontinues MTX, and meets *any* of the following conditions:

- Member has had a documented inadequate response to another conventional synthetic drug (i.e., leflunomide, hydroxychloroquine, and/or sulfasalazine) alone or in combination after a 3-month trial at a maximum tolerated dose(s); *or*
- Member has experienced a documented intolerable adverse event to leflunomide, hydroxychloroquine, or sulfasalazine; *or*
- Member has a documented contraindication to leflunomide, hydroxychloroquine (see [Appendix A](#)), and sulfasalazine (e.g., porphyria, intestinal or urinary obstruction); *or*
- Member has moderate to high disease activity;

3. Articular juvenile idiopathic arthritis (JIA)

- a. For members 2 years of age or older who have previously received a biologic or targeted synthetic drug (e.g., Xeljanz) indicated for moderately to severely active articular juvenile idiopathic arthritis; *or*
- b. For members 2 years of age or older for treatment of moderately to severely active articular juvenile idiopathic arthritis when *any* of the following criteria is met:
 - i. Member has had an inadequate response to methotrexate or another conventional synthetic drug (e.g., leflunomide, sulfasalazine, hydroxychloroquine) administered at an adequate dose and duration; *or*
 - ii. Member has had an inadequate response to a trial of scheduled non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular glucocorticoids (e.g., triamcinolone hexacetonide) and *one* of the following risk factors for poor outcome:
 - Involvement of ankle, wrist, hip, sacroiliac joint, and/or temporomandibular joint (TMJ); *or*
 - Presence of erosive disease or enthesitis; *or*
 - Delay in diagnosis; *or*
 - Elevated levels of inflammation markers; *or*
 - Symmetric disease; *or*
 - iii. Member has risk factors for disease severity and potentially a more refractory disease course (see [Appendix B](#)) and member also meets *one* of the following:
 - High-risk joints are involved (e.g., cervical spine, wrist, or hip); *or*
 - Has high disease activity; *or*
 - Is judged to be at high risk for disabling joint disease.

4. Psoriatic arthritis (PsA)

- a. For members 2 years of age or older who have previously received a biologic or targeted synthetic drug

- (e.g., Rinvoq, Otezla) indicated for active psoriatic arthritis; or
- b. For members 2 years of age or older for treatment of active psoriatic arthritis when *either* of the following criteria is met:

i. Member has mild to moderate disease and meets *one* of the following criteria:

- Member has had an inadequate response to methotrexate, leflunomide, or another conventional synthetic drug (e.g., sulfasalazine) administered at an adequate dose and duration; *or*
- Member has an intolerance or contraindication to methotrexate or leflunomide (see Appendix A), or another conventional synthetic drug (e.g., sulfasalazine); *or*
- Member has enthesitis; *or*

ii. Member has severe disease.

5. *Prophylaxis of acute graft versus host disease (aGVHD)*

For prophylaxis of acute graft versus host disease in members 2 years of age or older when *both* of the following criteria are met:

- a. Member is undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor; *and*
- b. The requested medication will be used in combination with a calcineurin inhibitor (e.g., cyclosporine, tacrolimus) and methotrexate;

6. *Chronic graft versus host disease*

For treatment of chronic graft versus host disease when *either* of the following criteria is met:

- a. Member has had an inadequate response to systemic corticosteroids; *or*
- b. Member has an intolerance or contraindication to corticosteroids;

7. Immune checkpoint inhibitor-related toxicity

For the treatment of immune checkpoint inhibitor-related toxicity when the member has myocarditis and meets *any* of the following:

- a. Member has had an inadequate response to systemic corticosteroids; *or*
- b. Member has an intolerance or contraindication to corticosteroids; *or*
- c. Member has concomitant myositis and the requested medication will be used in combination with ruxolitinib.

Aetna considers all other indications as experimental, investigational, or unproven.

III. Continuation of Therapy

Aetna considers continuation of abatacept (Orencia) therapy medically necessary for the following indications:

A. Rheumatoid arthritis (RA)

For all adult members (including new members) who are using the requested medication for moderately to severely active RA and who achieve or maintain a positive clinical response as evidenced by disease activity improvement of at least 20% from baseline in tender joint count, swollen joint count, pain, or disability;

B. Articular juvenile idiopathic arthritis (JIA)

For all members 2 years of age or older (including new members) who are using the requested medication for moderately to severely active articular juvenile idiopathic

arthritis and who achieve or maintain a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in *any* of the following from baseline:

1. Number of joints with active arthritis (e.g., swelling, pain, limitation of motion); *or*
2. Number of joints with limitation of movement; *or*
3. Functional ability;

C. Psoriatic arthritis (PsA)

For all members 2 years of age or older (including new members) who are using the requested medication for psoriatic arthritis and who achieve or maintain a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition when there is improvement in *any* of the following from baseline:

1. Number of swollen joints; *or*
2. Number of tender joints; *or*
3. Dactylitis; *or*
4. Enthesitis; *or*
5. Skin and/or nail involvement; *or*
6. Functional status; *or*
7. C-reactive protein (CRP);

D. Chronic graft versus host disease

For all members (including new members) who are using the requested medication for chronic graft versus host disease and who achieve or maintain a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition;

E. Prophylaxis of acute graft versus host disease and immune checkpoint inhibitor-related toxicity

For all members (including new members) who meet all initial authorization criteria.

IV. Other

For all indications: Member has had a documented negative tuberculosis (TB) test (which can include a tuberculosis skin test [TST] or an interferon-release assay [IGRA]^{*} within 12 months of initiating therapy for persons who are naïve to biologic drugs or targeted synthetic drugs associated with an increased risk of TB.

* If the screening testing for TB is positive, there must be further testing to confirm there is no active disease (e.g., chest x-ray). Do not administer the requested medication to members with active TB infection. If there is latent disease, TB treatment must be started before initiation of the requested medication.

For all indications: Member cannot use the requested medication concomitantly with any other biologic drug or targeted synthetic drug for the same indication.

V. Related Policies

- [CPB 0314 - Rituximab \(./300_399/0314.html\)](#)
- [CPB 0315 - Etanercept \(./300_399/0315.html\)](#)
- [CPB 0341 - Infliximab \(./300_399/0341.html\)](#)
- [CPB 0655 - Adalimumab \(./600_699/0655.html\)](#)
- [CPB 0761 - Certolizumab Pegol \(Cimzia\) \(0761.html\)](#)
- [CPB 0790 - Golimumab \(Simponi and Simponi Aria\) \(0790.html\)](#)
- [CPB 0905 - Secukinumab \(Cosentyx\) \(./900_999/0905.html\)](#)
- [CPB 0912 - Ustekinumab \(Stelara\) \(./900_999/0912.html\)](#)

Dosage and Administration

Note: Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. See

[Medical Specialty Medication Quantity Limits](#)
(<https://aetna.com/content/dam/aetna/pdfs/aetnacom/pdf/medical-specialty-medication-quantity-limits.pdf>)
for more information.

Below includes dosing recommendations as per the FDA-approved prescribing information.

Orencia (abatacept) is available for injection as:

- Intravenous (IV) injection for infusion: 250 mg lyophilized powder in a single-dose vial for reconstitution and dilution prior to IV infusion.
- Subcutaneous (SC) injection:
 - Injection: 50 mg/0.4 mL, 87.5 mg/0.7 mL, 125 mg/mL solution in single-dose prefilled syringes
 - Injection: 125 mg/mL solution in a single-dose prefilled ClickJect autoinjector.

The concomitant use of Orencia with other potent immunosuppressants [e.g., biologic disease-modifying antirheumatic drugs (bDMARDs), Janus kinase (JAK) inhibitors] is not recommended.

Adult Rheumatoid Arthritis (RA)

- For use in adults
- Dose may be administered as an IV infusion or SC injection.
- IV: dosing is based on body weight (see Table 1) and is administered at 0, 2, and 4 weeks, and every 4 weeks thereafter, as a 30-minute infusion.
- SC: prior to the first SC dose, Orencia may be administered with an optional loading dose as a single IV infusion (per body weight). SC dose of 125 mg is administered once weekly (within a day of the IV infusion, if given). Persons transitioning from Orencia IV therapy to SC use, the first SC dose is administered instead of the next scheduled IV dose.

Adult Psoriatic Arthritis

- Dose may be administered IV or SC injection.
- IV: dosing is based on body weight (see Table 1) and is administered at 0, 2, and 4 weeks, and every 4 weeks thereafter, as a 30-minute infusion.

- SC: 125 mg is administered by SC injection once weekly without an IV loading dose.
- Persons switching from Orencia IV therapy to SC administration should administer the first SC dose instead of the next scheduled IV dose.

Table 1: Orencia IV Dosing for Adult Rheumatoid Arthritis and Adult Psoriatic Arthritis

Body Weight	Dose	Number of Vials**
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
Greater than 100 kg	1,000 mg	4

** Each vial provides 250 mg of abatacept for administration

Pediatric Psoriatic Arthritis

- SC dosing: for pediatrics 2 years of age and older, Orencia dosing is based on body weight (see Table 2) and is administered subcutaneously without an IV loading dose. Note: IV administration is not approved for pediatrics with psoriatic arthritis.

Table 2: Orencia SC Dosing for Juvenile Idiopathic Arthritis and Pediatric Psoriatic Arthritis

Body Weight	Dose (once weekly)
10 to less than 25 kg	50 mg
25 to less than 50 kg	87.5 mg
Greater than 50 kg	125 mg

Polyarticular Juvenile Idiopathic Arthritis

- Dose may be administered as an IV infusion (6 years of age and older) or a SC injection (2 years of age and older). IV has not been studied in persons younger than 6 years of age.

- A person with polyarticular juvenile idiopathic arthritis may self-inject with Orencia, or the person's caregiver may administer Orencia if both the healthcare practitioner and the parent/legal guardian determines it is appropriate. The ability of pediatric persons to self-inject with the autoinjector has not been tested.
- IV: Orencia is administered as a 30-minute IV infusion based on body weight:
 - body weight less than 75 kg should be administered Orenica at a dose of 10 mg/kg.
 - body weight of 75 kg or more should be administered Orencia following the adult IV dosing regimen for adult rheumatoid arthritis (see Table 1), not to exceed a maximum dose of 1000 mg.
 - Following the initial administration, Orencia is given at 2 and 4 weeks and every 4 weeks thereafter.
- SC: should be initiated without an IV loading dose and administered utilizing the weight range-based dosing (see Table 2).

Prophylaxis of Acute Graft Versus Host disease (aGVHD)

- For persons 6 years and older, administer at a 10 mg/kg dose (maximum dose 1,000 mg) as a 60-minute infusion on the day before transplantation, followed by a dose on Day 5, 14, and 28 after transplant.
- For persons 2 to less than 6 years old, administer a 15 mg/kg dose as a 60-minute infusion on the day before transplantation, followed by a 12 mg/kg dose as a 60-minute infusion on Day 5, 14, and 28 after transplant.

Source: BMS, 2024

Experimental, Investigational, or Unproven

- I. Aetna considers concomitant use of abatacept with any other biologic drug (e.g., adalimumab, anakinra, etanercept, infliximab, rilonacept, tocilizumab) or targeted synthetic drug (e.g. tofacitinib)

for the same indication experimental, investigational, or unproven because the effectiveness of this approach has not been established.

II. Aetna considers abatacept experimental, investigational, or unproven for the treatment of the following indications (not an all-inclusive list) because its effectiveness for these conditions has not been established:

- ACPA-negative undifferentiated arthritis
- Ankylosing spondylitis
- Biliary cholangitis
- Common variable immunodeficiency
- Crohn's disease
- Dermatomyositis / polymyositis
- Encapsulated peritoneal sclerosis
- Focal segmental glomerulosclerosis
- Giant cell arteritis
- Interstitial lung disease
- Juvenile dermatomyositis (including juvenile dermatomyositis-associated calcinosis)
- Lupus nephritis
- Morphea (localized scleroderma)
- Multiple sclerosis
- Nephrotic syndrome
- Proteinuric kidney disease
- Psoriasis
- Reiter's syndrome
- Relapsing polychondritis
- Scleritis
- Sjogren's syndrome
- Spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis
- Systemic vasculitis
- Takayasu's arteritis
- Type 1 diabetes
- Ulcerative colitis
- Uveitis associated with Behcet's disease
- Wegener's granulomatosis.

CPT Codes/ HCPCS Codes / ICD-10 Codes

Code	Code Description
Other CPT codes related to the CPB:	
71045 - 71048	Radiologic examination, chest
85651	Sedimentation rate, erythrocyte; non-automated
85652	Sedimentation rate, erythrocyte; automated
86140	C-reactive protein
86141	C-reactive protein; high sensitivity (hsCRP)
86200	Cyclic citrullinated peptide (CCP), antibody
86430	Rheumatoid factor; qualitative
86431	Rheumatoid factor; quantitative
86480	Tuberculosis test, cell mediated immunity antigen response measurement; gamma interferon
86481	Tuberculosis test, cell mediated immunity antigen response measurement; enumeration of gamma interferon - producing T cells in cell suspension
86580	Skin test; tuberculosis, intradermal
96365 - 96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
96369 - 96371	Subcutaneous infusion for therapy or prophylaxis
HCPCS codes covered if selection criteria are met:	
J0129	Injection, abatacept, 10 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self administered)
Other HCPCS codes related to the CPB:	
<i>Rinvoq, Xeljanz, Otezla, Ruxolitinib, Hydroxychloroquine, Sulfasalazine - no specific code:</i>	
J0139	Injection, adalimumab, 1 mg

Code	Code Description
J0702	Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg
J0717	Injection, certolizumab pegol, 1 mg
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg
J1438	Injection, etanercept, 25 mg
J1600	Injection, gold sodium thiomalate, up to 50 mg
J1700	Injection, hydrocortisone acetate, up to 25 mg
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
J1745	Injection, infliximab, 10 mg
J2650	Injection, prednisolone acetate, up to 1 ml
J2793	Injection, rilonacept, 1 mg
J3262	Injection, tocilizumab, 1 mg
J3299	Injection, triamcinolone acetonide (xipere), 1 mg
J3300	Injection, triamcinolone acetonide, preservative free, 1 mg
J3301	Injection, triamcinolone acetonide, not otherwise specified, 10 mg
J3302	Injection, triamcinolone diacetate, per 5 mg
J3303	Injection, triamcinolone hexacetonide, per 5 mg
J3304	Injection, triamcinolone acetonide, preservative-free, extended-release, microsphere formulation, 1 mg
J7500	Azathioprine, oral, 50 mg
J7501	Azathioprine, parenteral, 100 mg
J7509	Methylprednisolone oral, per 4 mg
J7510	Prednisolone oral, per 5 mg
J7512	Prednisone, immediate release or delayed release, oral, 1 mg
J8540	Dexamethasone, oral, 0.25 mg
J8610	Methotrexate, oral, 2.5 mg
J8611	Methotrexate (jylamvo), oral, 2.5 mg

Code	Code Description
J8612	Methotrexate (xatmep), oral, 2.5 mg
J9255	Injection, methotrexate (accord) not therapeutically equivalent to j9250 or j9260, 50 mg
J9260	Methotrexate sodium, 50 mg
J9311	Injection, rituximab 10 mg and hyaluronidase
J9312	Injection, rituximab, 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (renflexis), 10 mg
Q5109	Injection, infliximab-qbtx, biosimilar, (ixifi), 10 mg
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg
Q5119	Injection, rituximab-pvvr, biosimilar, (ruxience), 10 mg
Q5123	Injection, rituximab-arrx, biosimilar, (riabni), 10 mg
Q5133	Injection, tocilizumab-bavi (tofidence), biosimilar, 1 mg
Q5135	Injection, tocilizumab-aazg (tyenne), biosimilar, 1 mg
Q5140	Injection, adalimumab-fkjp, biosimilar, 1 mg
Q5141	Injection, adalimumab-aaty, biosimilar, 1 mg
Q5142	Injection, adalimumab-ryvk biosimilar, 1 mg
Q5143	Injection, adalimumab-adbm, biosimilar, 1 mg
Q5144	Injection, adalimumab-aacf (idacio), biosimilar, 1 mg
Q5145	Injection, adalimumab-afzb (abrilada), biosimilar, 1 mg

ICD-10 codes covered if selection criteria are met:

D89.811	Chronic graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
I40.0 – I40.9	Acute myocarditis [immune checkpoint inhibitor-related cardiac toxicity]
I41	Myocarditis in diseases classified elsewhere [immune checkpoint inhibitor-related cardiac toxicity]
L40.50 - L40.59	Arthropathic psoriasis [age 2 and older]

Code	Code Description
M05.00 -	Rheumatoid arthritis [age 18 and older] [if the member has a contraindication, intolerance or incomplete response to at least 2 of the least cost brands of targeted immune modulators]
M05.09,	
M05.20 -	
M06.39,	
M06.80 -	
M06.9	
M08.00 -	Juvenile arthritis
M08.99	
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
D83.0 - D83.9	Common variable immunodeficiency
D89.810	Acute graft-versus-host disease
D89.813	Graft-versus-host disease, unspecified
E10.10 - E10.9	Type 1 diabetes mellitus
G35	Multiple sclerosis
J84.01 - J84.9	Other interstitial pulmonary diseases
H15.091 -	Other scleritis [non-infectious refractory scleritis]
H15.099	
K50.00 -	Crohn's disease (regional enteritis)
K50.919	
K51.00 -	Ulcerative colitis
K51.919	
K68.9	Other disorders of retroperitoneum [encapsulated peritoneal sclerosis]
K74.3	Primary biliary cirrhosis [immune checkpoint inhibitor-associated myocarditis]
K83.09	Other cholangitis [biliary cholangitis]
L40.0 - L40.4,	Psoriasis
L40.8 - L40.9	
L94.0	Localized scleroderma [morphea]
M02.30 -	Reiter's disease
M02.39	
M13.0	Polyarthritis, unspecified

Code	Code Description
M13.80 -	Other specified arthritis [ACPA-negative undifferentiated arthritis]
M13.89	
M31.30 -	Wegener's granulomatosis
M31.31	
M31.4	Aortic arch syndrome [Takayasu arteritis]
M31.5	Giant cell arteritis with polymyalgia rheumatica
M31.6	Other giant cell arteritis
M32.0 - M32.9	Systemic lupus erythematosus (SLE)
M33.00 -	Dermatopolymyositis
M33.99	
M34.0 - M34.9	Systemic sclerosis [scleroderma]
M35.00 -	Sicca syndrome
M35.0C	
M35.2	Behcet's disease
M45.0 -	Ankylosing spondylitis
M45.AB	
M47.819	Spondylosis without myelopathy or radiculopathy, site unspecified
M61.40 -	Other calcification of muscle [juvenile dermatomyositis-associated calcinosis]
M61.49	
M94.1	Relapsing polychondritis
N03.3	Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
N04.0 - N04.9	Nephrotic syndrome
N08	Glomerular disorders in diseases classified elsewhere

Background

U.S. Food and Drug Administration (FDA)-Approved Indications

- Moderately to severely active rheumatoid arthritis (RA) in adults
- Moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age or older
- Active psoriatic arthritis (PsA) in patients 2 years of age and older
- Prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor

Compendial Uses

- Oligoarticular juvenile idiopathic arthritis
- Chronic graft versus host disease
- Immune checkpoint inhibitor-related toxicity

Abatacept is branded as Orencia (Bristol-Myers Squibb). Abatacept is a selective co-stimulation modulator which inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a co-stimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA) and active psoriatic arthritis (PsA) and are found in the synovium of patients with RA, pJIA and PsA.

The label carries the following warnings and precautions for Orencia:

- Concomitant use with a TNF antagonist can increase the risk of infections and serious infections
- Hypersensitivity and anaphylaxis have occurred
- Serious infections reported. Patients with a history of recurrent infections or underlying conditions predisposing to infections may experience more infections.
- Screen for latent TB infection prior to initiating therapy. Patients testing positive should be treated prior to initiating Orencia

- Should screen for viral hepatitis prior to initiating Orencia
- Update vaccinations prior to initiating Orencia. Live vaccines should not be given concurrently or within 3 months of discontinuation, as it may blunt the effectiveness of some immunizations
- Chronic obstructive pulmonary disease (COPD) patients may develop more frequent respiratory adverse events
- Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) reactivation in patients treated for aGVHD prophylaxis.

The most common adverse events (10% or more) in rheumatoid arthritis are headache, upper respiratory tract infection, nasopharyngitis, and nausea. The most common adverse reactions (10% or more) in prophylaxis of aGVHD are anemia, hypertension, CMV reactivation/CMV infection, pyrexia, pneumonia, epistaxis, CD4 lymphocytes decreased, hypermagnesemia, and acute kidney injury.

According to the CDC's (Centers for Disease Control and Prevention) Quality ID #176 measure, tuberculosis (TB) screening should be performed within the 12 months prior to initiating a first course of biologic and/or immune response modifier therapy that carries a warning for potential reactivation of latent infections. This applies to adult patients (18 years and older) who are newly prescribed such therapies and have not received similar treatment in the preceding 15 months. The goal is to ensure that TB testing is documented in the medical record before starting treatment to mitigate the risk of reactivating latent TB infection.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disorder characterized by inflammation of synovial joints resulting in progressive erosion of cartilage and bone. The main objectives of treatment of RA are three-fold: to interfere with the disease process (i.e., inflammation and destruction of the joints), preserve physical function, and prevent long-term disability. The American College of Rheumatology (ACR)'s guidelines for the treatment of RA (1996) recommend that newly diagnosed patients with RA begin treatment with disease-modifying anti-

rheumatic drugs (DMARDs) within 3 months of diagnosis. Methotrexate remains the most commonly prescribed DMARD and is the standard by which recent new and emerging therapies are measured.

In addition to traditional DMARDs, TNF antagonists (e.g., adalimumab, etanercept, infliximab, and golimumab) are currently being used for the treatment of RA. However, only 60 to 70 % of RA patients respond to treatment with a TNF antagonist. Furthermore, the majority of patients show only a partial response according to ACR20 (20 % improvement) criteria (Voll and Kalden, 2005). Contraindications such as infection and cardiac failure also add to the number of patients who need alternative treatment.

A better understanding of the inflammatory pathway in RA has led to the development of a number of targeted biological therapies. One of these targeted biological agents is abatacept, a novel fusion protein designed to modulate the T cell co-stimulatory signal mediated through the CD28-CD80/86 pathway. It inhibits T-cell activation and interrupts the process leading to inflammation in RA (Pollard and Choy, 2005; Ruderman and Pope, 2005).

Published clinical studies have found that patients with severe RA who received abatacept with at least one other DMARD showed statistically significant improvement in tender, swollen joints and other clinical measures compared with placebo. However, abatacept should not be administered in conjunction with other biological agents because of reported increased rates of serious adverse events, including serious infections.

In a 12-month, multi-center, randomized, double-blind, placebo-controlled phase 2 clinical trial, Kremer and colleagues (2005) ascertained the safety and effectiveness of abatacept in patients with RA that has remained active despite methotrexate therapy. A total of 339 patients were randomly assigned to one of the 3 groups: (i) 10 mg/kg abatacept ($n = 115$), (ii) 2 mg/kg abatacept ($n = 105$), or placebo ($n = 119$). A significantly greater percentage of patients treated with 10 mg/kg abatacept met the ACR20 response criteria at 1 year compared with patients who received placebo (62.6 % versus 36.1 %; $p < 0.001$). Greater percentages of patients treated with 10 mg/kg abatacept also

achieved ACR50 responses (41.7 % versus 20.2 %; p < 0.001) and ACR70 responses (20.9 % versus 7.6 %; p = 0.003) compared with patients who received placebo. For patients treated with 10 mg/kg abatacept, there were also statistically significant and clinically important improvements in modified Health Assessment Questionnaire (HAQ) scores compared with those who received placebo (49.6 % versus 27.7 %; p < 0.001). Abatacept at a dosage of 10 mg/kg resulted in an increase in rates of remission (Disease Activity Score in 28 joints of less than 2.6) compared with placebo at 1 year (34.8 % versus 10.1 %; p < 0.001). The incidence of adverse events was comparable between the groups, and no significant formation of neutralizing antibodies was noted. These researchers concluded that abatacept was associated with significant reductions in disease activity and improvements in physical function that were maintained over the course of 12 months in patients with RA that had remained active despite methotrexate treatment. Abatacept was found to be well tolerated and safe over the course of 1 year.

In a randomized, double-blind, phase 3 clinical trial (n = 322), Genovese and colleagues (2005) assessed the safety and effectiveness of abatacept in patients with active RA and an inadequate response to at least 3 months of anti-TNF-alpha therapy. Patients were randomly assigned in a 2:1 ratio to receive abatacept (n = 223) or placebo (n = 99) on days 1, 15, and 29 and every 28 days thereafter for 6 months, in addition to at least one DMARD. Patients stopped anti-TNF-alpha therapy before randomization. The rates of ACR20 responses and improvement in functional disability, as reflected by scores for the HAQ disability index, were evaluated. After 6 months, the rates of ACR20 responses were 50.4 % in the abatacept group and 19.5 % in the placebo group (p < 0.001); the respective rates of ACR50 and ACR70 responses were also significantly higher in the abatacept group than in the placebo group (20.3 % versus 3.8 %, p < 0.001; and 10.2 % versus 1.5 %, p = 0.003). At 6 months, significantly more patients in the abatacept group than in the placebo group had a clinically meaningful improvement in physical function, as indexed by an improvement from baseline of at least 0.3 in the HAQ disability index (47.3 % versus 23.3 %, p < 0.001). The incidence of adverse reactions as well as peri-infusional adverse events was 79.5 % and 5.0 %, respectively, in the abatacept group and 71.4 % and 3.0 %, respectively, in the placebo group. The incidence of serious

infections was 2.3 % in each group. These investigators concluded that abatacept produced significant clinical and functional benefits in patients who had had an inadequate response to anti-TNF-alpha therapy.

Schiff et al (2006) reported on the results of a randomized multi-center clinical trial comparing abatacept (n = 156) to infliximab (n = 165) and placebo (n = 110) in adults with moderate to severe RA an inadequate response to methotrexate and no previous treatment with a TNF antagonist. At the end of 6 months, the mean reduction in Disease Activity Score-28 using Erythrocyte Sedimentation Rate (DAS28 [ESR]) from baseline was - 1.48 for placebo, -2.53 for abatacept ($p < 0.001$ versus placebo), and -2.25 for infliximab ($p < 0.001$ versus placebo). After 12 months, the change in DAS28[ESR] from baseline was -2.88 for abatacept and -2.25 for infliximab. (The placebo group was placed on abatacept after 6 months and not included in the 12 month analysis). The investigators found that abatacept was associated with fewer serious infections or discontinuations due to adverse events than infliximab. The rate of serious adverse events after six months was 5.1 % for abatacept, 11.8 % for placebo and 11.5 % for infliximab). The rate of discontinuation due to adverse events was 1.9 % for abatacept, 0.9 % for placebo, and 4.8 % for infliximab. At 12 months, the rate of serious adverse events was 9.6 % for abatacept and 18.2 % for infliximab. The rate of discontinuation due to adverse events at 12 months was 3.2 % for abatacept and 7.3 % for infliximab.

The United States Food and Drug Administration (FDA) initially approved abatacept (Orencia) for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs such as methotrexate or a TNF antagonist. Combinational therapy with abatacept and a targeted biological agent is not recommended. In clinical trials, patients receiving concomitant abatacept and TNF antagonist therapy experienced more infections (63 %) and serious infections (4.4 %) compared to patients treated with only TNF antagonists (43 % and 0.8 %, respectively), without an important improvement in effectiveness. The most common side effects associated with the use of abatacept were dizziness, headache, hypertension, upper respiratory tract infection, nasopharyngitis, and nausea. Although the

requirement for a trial of DMARDs was subsequently removed from the FDA labeling, an assessment of abatacept for rheumatoid arthritis by the National Institute for Health and Clinical Excellence (NICE, 2008) outlined the uncertainties regarding the comparative effectiveness of abatacept to DMARDs and tumor necrosis factor inhibitors.

Weinblatt et al (2013) evaluated the overall safety, including rare events, of intravenous (IV) abatacept treatment in rheumatoid arthritis (RA). Data from 8 clinical trials of IV abatacept in RA were pooled. Safety events were assessed during the short-term (duration less than or equal to 12 months) and cumulative (short-term plus long-term extensions) abatacept treatment periods. Incidence rates per 100 patient-years were calculated. Standardized incidence ratios (SIR) for hospitalized infections and malignancies were compared with external RA cohorts and, for malignancies, with the US general population. There were 3,173 IV abatacept-treated patients with 2,331 patient-years of exposure in the short-term periods, and 4,149 IV abatacept-treated patients with 12,132 patient-years of exposure in the cumulative period. Incidence rates for serious infections were low and consistent over time (3.68 for abatacept versus 2.60 for placebo during the short-term, and 2.87 for abatacept during the cumulative period). Hospitalized infections were generally similar to external RA patient cohorts and were consistent over time. Incidence rates of malignancies were similar for abatacept- and placebo-treated patients during the short-term period (0.73 versus 0.59) and remained low during the abatacept cumulative period (0.73). SIR of some tissue-specific malignancies (e.g., colorectal and breast) in the cumulative period tended to be lower, while others (lymphoma and lung) tended to be higher, compared with the general population; however, incidence rates were comparable with RA cohorts. Autoimmune events were rare and infusion reactions uncommon. The authors concluded that long-term safety of IV abatacept was consistent with the short-term, with no unexpected events and low incidence rates of serious infections, malignancies, and autoimmune events. (This study addressed the use of abatacept for RA, not PsA. Moreover, there were no direct comparisons in infection rates between abatacept with anti-TNF alpha agents).

A systematic evidence review of targeted immunomodulators by the Drug Effectiveness Review Project (DERP) (Thaler, et al., 2012) found one fair-quality, double-blinded head-to head trial provided evidence of

moderate strength that abatacept and infliximab do not differ in efficacy for the treatment of rheumatoid arthritis up to 6 months. The safety profile, however, appeared to be better for abatacept than for infliximab with fewer serious adverse events (9.6% compared with 18.2%) and fewer serious infections (1.9% compared with 8.5%). The review found that other direct comparisons of targeted immune modulators for the treatment of rheumatoid arthritis were limited to one small randomized controlled trial and multiple observational studies rendering evidence of low strength. The review stated that adjusted indirect comparisons suggested greater efficacy for etanercept than abatacept, adalimumab, anakinra, and infliximab for the treatment of rheumatoid arthritis.

The American College of Rheumatology (ACR) conducted a systematic review to synthesize the evidence for the benefits and harms of various treatment options. Their goal was to develop evidence-based, pharmacologic treatment guideline for rheumatoid arthritis. *The 2015 American College of Rheumatology Guidelines for the Treatment of Rheumatoid Arthritis* provided “strong” recommendations for established RA and symptomatic early RA.

For established RA, the guidelines state “if the disease activity is low, in patients who have never taken a DMARD, the recommendation is to use DMARD monotherapy (methotrexate preferred) over TNFi”. “If disease activity remains moderate or high despite DMARD monotherapy, the recommendation is to use combination traditional [conventional] DMARDs or add a TNFi or a non-TNF biologic or tofacitinib (all choices with or without methotrexate, in no particular order of preference), rather than continuing DMARD monotherapy alone”. Recommendations for patients with symptomatic early RA state that “if disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (methotrexate preferred) over double or triple therapy”. “If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi or a non-TNF biologic (all choices with or without methotrexate, in no particular order of preference), rather than continuing DMARD monotherapy alone”. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the

undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation (Singh et al., 2016).

The 2022 EULAR (European Alliance of Associations for Rheumatology) guidelines for RA management emphasize a treat-to-target approach, aiming for sustained remission or low disease activity through early intervention, regular monitoring, and shared decision-making.

Recommendations include use of methotrexate (MTX) as the preferred first-line therapy, typically initiated at 15 mg/week and escalated up to 25-30 mg/week as tolerated, with folic acid supplementation to reduce side effects. If MTX is contraindicated or not tolerated, alternatives such as leflunomide, sulfasalazine, or hydroxychloroquine can be considered.

Hydroxychloroquine is particularly appropriate for patients with mild disease or when used in combination with other DMARDs, but is not recommended as monotherapy in individuals with poor prognostic indicators due to its limited efficacy in preventing joint damage. If treatment targets are not met within 3 to 6 months, escalation to a biologic DMARD (bDMARD) or targeted synthetic DMARD (tsDMARD) (e.g., tofacitinib, upadacitinib) is advised. Among bDMARDs, TNF inhibitors such as abatacept are recommended, typically in combination with MTX but may be used as monotherapy when MTX is unsuitable. The guidelines also stress the importance of considering comorbidities and safety profiles when selecting and escalating therapy (Smolen et al., 2023).

Juvenile Idiopathic Arthritis

Abatacept has been approved by the FDA for use in reducing signs and symptoms of moderately to severely active polyarticular juvenile RA (juvenile idiopathic arthritis) in pediatric patients 6 years and older. The approval was based on data from the AWAKEN study (Abatacept Withdrawal study to Assess efficacy and safety in Key Endpoints in juvenile idiopathic arthritis Not responding to current treatment), a 3-part study including an open-label extension in children with polyarticular juvenile RA. Overall, the 3-part trial showed that abatacept therapy yielded improvements across 3 major subtypes of juvenile RA through 1 year in patients aged 6 to 17 years whose disorder had not responded to 1 or more DMARDs, such as methotrexate or tumor necrosis factor

(TNF) antagonists. Patients had a disease duration of approximately 4 years with moderately to severely active disease at study entry, as determined by baseline counts of active joints (mean of 16) and joints with loss of motion (mean of 16); patients had elevated C-reactive protein (CRP) levels (mean of 3.2 mg/dL) and ESR (mean of 32 mm/h).

In the first part of the study, a total of 190 patients received 16 weeks of intravenous abatacept on days 1, 15, and 29, and every month thereafter. Efficacy was assessed with the Rheumatology Pediatric American College of Rheumatology (ACR Pedi) 30 response, defined as a 30 % or greater improvement in at least 3 of the 6 ACR Pedi response variables and no more than 1 indicator worsening by 30 % or more.

Results at 4 months showed that ACR Pedi 30 responses were consistent across all juvenile RA subtypes, including oligoarticular extended (59.3 %), polyarticular rheumatoid factor-positive (68.4 %), polyarticular rheumatoid factor-negative (64.3 %), and systemic juvenile RA with polyarticular course (64.9 %). Children who were new to biologic therapy appeared to have higher rates of ACR 30, 50, 70, and 90 versus those in whom previous biologic treatments had failed (76 % versus 38.6 %; 60 % versus 24.6 %; 36 % versus 10.5 %; and 17 % versus 1.8 %, respectively).

Patients with an ACR Pedi 30 response in the first part of the study ($n = 122$) were then randomized in the second part of the study to receive abatacept or placebo for an additional 24 weeks or until disease flare. A flare was defined as a 30 % or greater worsening in at least 3 of the 6 ACR Pedi response variables, a minimum of 2 active joints, and no more than 1 indicator improving by 30 %. Data from the second phase of the study showed that continued abatacept therapy significantly reduced the incidence of disease flare vs placebo (20 % versus 53 %; $p < 0.001$; hazard ratio [HR], 0.31; 95 % confidence interval [CI]: 0.16 to 0.59).

Furthermore, abatacept-treated children were significantly more likely to show ACR responses of 30, 50, and 70, which were maintained for up to 1 year in the open-label study extension (third phase of AWAKEN).

The investigators reported that, in general, adverse reactions in pediatric patients were similar in type and frequency to those observed in adult studies. The overall frequency of adverse events during the first part of

the study was 70 %; infections (36 %) most commonly involved the upper respiratory tract and nasopharyngitis and were consistent with those observed in outpatient pediatric populations. Other events that occurred in 5 % or more of patients were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.

According to the FDA-approved labeling, abatacept may be used alone or with methotrexate for juvenile rheumatoid arthritis. The labeling states that abatacept should not be administered concomitantly with TNF antagonists, and that abatacept is not recommended for use concomitantly with other biologic rheumatoid arthritis therapy, such as anakinra. The recommended dose of the intravenous formulation of abatacept for patients 6 to 17 years of age with juvenile RA who weigh less than 75 kg is 10 mg/kg calculated based on the patient's body weight at each administration. Pediatric patients weighing 75 kg or more should be administered abatacept following the adult dosing regimen, not to exceed a maximum dose of 1,000 mg. Following the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Although the FDA-approved labeling does not limit use of abatacept to persons with juvenile RA that have failed DMARDs, clinical studies submitted to the FDA have focused on JRA patients who have failed DMARDs.

The FDA has approved the subcutaneous formulation of abatacept for juvenile idiopathic arthritis for persons 2 years of age and older. Dosing of the subcutaneous formulation is based upon the body weight of the patient.

The DERP review (Thaler et al, 2012) found no head-to-head trials comparing the efficacy and safety of targeted immune modulators for the treatment juvenile idiopathic arthritis. The review stated that the general efficacy of abatacept, adalimumab, etanercept, infliximab, and tocilizumab for the treatment of juvenile idiopathic arthritis is supported by one randomized controlled trial for each drug. The review noted, however, that sample sizes of these studies were small and active run-in periods limited the applicability of results. In efficacy trials statistically significantly fewer patients on targeted immune modulators (20 % to 37 %) experienced disease flares than children treated with placebo (53 % to 83 %).

Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic, inflammatory disease that can affect the skin and musculoskeletal system, which can cause joint pain, stiffness and reduced range of motion.

In July 2017, the U.S. Food and Drug Administration (FDA) approved abatacept for the treatment of adults with active psoriatic arthritis (PsA). FDA approval of abatacept for active PsA was based on the results from two randomized, double-blind, placebo-controlled studies (Studies PsA-I and PsA-II) in 594 adult patients with disease duration more than seven years. Patients had active PsA (\geq 3 swollen joints and \geq 3 tender joints) despite prior treatment with DMARD therapy and had one qualifying psoriatic skin lesion of at least 2 cm in diameter. In PsA-I and PsA-II, 37% and 61% of patients, respectively, were treated with TNF inhibitors (TNFi) previously. A higher proportion of patients treated with abatacept 10 mg/kg IV or 125 mg SC achieved an ACR20 response at Week 24 compared to placebo, 47.5% versus 19.0% and 39.4% versus 22.3% ($p < 0.05$), respectively. Responses were seen regardless of prior anti-TNF α treatment and regardless of concomitant non-biologic DMARD treatment. Improvements in enthesitis and dactylitis were seen with abatacept treatment at Week 24 in both IV and SC (BMS, 2017).

In October 2023, the FDA approved the subcutaneous formulation of Orencia to include patients 2 to 17 years of age with active PsA. Previously, treatment with Orencia for PsA was limited to adults with active PsA. FDA approval is based on data from "adequate and well-controlled studies" of abatacept in adults with PsA, pharmacokinetic (PK) data from adults with rheumatoid arthritis (RA), adults with PsA, and pediatrics with polyarticular juvenile idiopathic arthritis (pJIA), as well as, safety data from clinical studies in pediatrics 2 to 17 years old with pJIA using the subcutaneous formulation (BMS, 2023).

Immune Checkpoint Inhibitor-Related Toxicity

Muller and associates (2018) noted that immune checkpoint inhibitors (ICIs) have started revolutionizing the treatment of numerous advanced oncological diseases by restoring immune resistance against cancer cells. ICI-associated cardiac adverse effects are rare, but severe.

Approximately 50 % of cardiac complications comprise myocarditis with variable clinical presentation and a high rate of fatality. The pathomechanism is incompletely understood and may involve pre-existing autoimmunity such as autoantibodies or common epitopes shared by cardiomyocytes and tumor cells. Especially patients at risk might be followed-up by serial troponin measurements in order to allow an early identification of ICI-associated myocarditis. Therapeutic options are limited and consist of early discontinuation of ICI treatment and initiation of an immunosuppression. The authors stated that further studies are needed to elucidate the mechanism, define diagnostic criteria, improve surveillance of patients at risk, and finally refine therapy.

An expert consensus on “Myocarditis associated with immune checkpoint inhibitors” compiled on behalf of the Checkpoint Inhibitor Safety Working Group (Neilan et al, 2018) did not mention abatacept as a therapeutic option.

An UpToDate review on “Patient selection criteria and toxicities associated with checkpoint inhibitor immunotherapy” (Postow and Wolchok, 2019) states that “Cardiotoxicity may develop in the absence of a history of significant cardiac risk factors and may be associated with a more general myositis as well as other irAEs. Venous thromboembolism may also be seen, although its relationship to checkpoint inhibitor immunotherapy is less clear. The time to onset was variable, but fatal myocarditis has been reported after a single treatment with the combination of nivolumab plus ipilimumab. In pharmacovigilance studies, the incidence of myocarditis was higher in patients treated with the combination of nivolumab plus ipilimumab compared with nivolumab alone (0.27 versus 0.06 %). High-dose steroids have been used to treat cardiac complications, but symptoms may progress in some cases despite aggressive therapy. Immediate transfer to a coronary care unit or, if available, cardiac transplant unit should be considered for patients with elevated troponin or conduction abnormalities. The early institution of cardiac transplant rejection doses of steroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin should be considered in patients without an immediate response to high-dose steroids”; abatacept is not listed as a therapeutic option.

Furthermore, Salem and colleagues (2019) stated that evaluation of the risk-benefit balance of the use of abatacept in immune checkpoint inhibitor-induced myocarditis is needed, given the possible risks of infectious complications and effects that promote tumor growth.

Prophylaxis of Acute Graft Versus Host Disease

In December 2021, the U.S. FDA approved Orencia (abatacept) for the prophylaxis of acute graft versus host disease (aGVHD), a potentially fatal condition that occurs when donor bone marrow or stem cells attack the graft recipient, in combination with certain immunosuppressants. Orencia may be used in adults and pediatric patients two years of age or older undergoing hematopoietic stem cell transplantation (commonly known as bone marrow transplantation or stem cell transplantation) from an unrelated donor. The chances of developing aGVHD increase when the donor and recipient are not related or are not a perfect match (FDA, 2021).

FDA approval was based on the safety and efficacy from two separate studies on the use of abatacept in combination with immunosuppressant therapy in patients 6 years of age and older who underwent stem cell transplantation from a matched or mismatched unrelated donor.

Study 1 (GVHD-1) was a multicenter, double-blind, placebo-controlled trial that evaluated 186 patients who underwent stem cell transplantation from a matched unrelated donor and randomly received abatacept or a placebo in combination with immunosuppressive drugs (a calcineurin inhibitor (CNI) and methotrexate (MTX)). Abatacept was administered at a dose of 10 mg/kg (1,000 mg maximum dose) as an intravenous infusion over 60 minutes, beginning on the day before transplantation (Day -1), followed by administration on Days 5, 14, and 28 after transplantation. The study measured severe (grade III-IV) aGVHD-free survival, overall survival and moderate-severe (grade II-IV) aGVHD-free survival 6 months after transplantation. While severe aGVHD-survival was not significantly improved in patients who received abatacept (87%) compared to patients who received a placebo (75%), patients who received abatacept saw a 97% overall survival rate compared to 84% for patients who received a

placebo. For moderate-severe aGVHD-free survival, patients who received abatacept saw a 50% rate compared to 32% for patients who received a placebo (FDA, 2021).

Additional evidence of effectiveness was provided by Study 2 (GVHD-2), a registry-based clinical study conducted using real world data from the Center for International Blood and Marrow Transplant Research in patients who underwent stem cell transplantation from a mismatched unrelated donor. This study analyzed outcomes of 54 patients treated with abatacept in combination with standard immunosuppressive drugs (CNI and MTX), versus 162 patients treated with standard immunosuppressive drugs alone (CNI and MTX), for the prophylaxis of aGVHD, in patients 6 years of age or older who underwent hematopoietic stem cell transplant (HSCT) from a 1 allele-mismatched unrelated donor between 2011 and 2018. The study measured overall survival 6 months after transplantation. Patients who received abatacept saw a 98% overall survival rate compared to 75% for patients who received standard immunosuppression alone (BMS, 2021; FDA, 2021).

Other Indications

ACPA-Negative Undifferentiated Arthritis

Buch and colleagues (2017) stated that no proven treatment exists for anti-citrullinated protein antibodies (ACPA)-negative undifferentiated arthritis (UA). In a proof-of-concept, open-label, prospective study, these researchers examined if abatacept is effective in treating poor prognosis, ACPA-negative UA, including its effect on power Doppler on US (PDUS). A total of 20 patients with DMARD-naïve, ACPA-negative UA (greater than or equal to 2 joint synovitis) and PDUS greater than or equal to 1 with clinical and 20-joint US (grey scale/PDUS) assessments at baseline, 6, 12, 18 and 24 months were enrolled in this trial. All patients received 12 months of abatacept (monotherapy for minimum first 6 months). The primary end-point was a composite of the proportion of patients that at 6 months achieved DAS44 remission, a maximum of 1 swollen joint for at least 3 consecutive months and no radiographic progression (over 0 to 12 months); 20 of the 23 patients screened were enrolled [14 women; mean (SD) age of 53.4 (11.2) years, symptom duration of 7.5 (0.9) months]; 2 (10 %) achieved the composite primary end-point. A reduction in the

mean (SD) DAS44 was observed from a baseline value of 2.66 (0.77) to 2.01 (0.81) at 6 months and to 1.78 (0.95) at 12 months. The DAS44 remission rates were 6/20 (30 %; 95 % CI: 15 % to 51 %) at 6 months and 8/20 (40 %; 95 % CI: 22 % to 62 %) at 12 months. A striking decrease in the median (interquartile range; IQR) total PDUS score was noted from 10 (4 to 23) at baseline to 3 (2 to 12) and 3 (0 to 5) at 6 and 12 months, respectively. The authors concluded that this report was a first in potentially identifying an effective therapy, abatacept monotherapy, for poor-prognosis, ACPA-negative UA, supported by a clear reduction in PDUS. They stated that these findings justify evaluation in a controlled study.

Ankylosing Spondylitis (AS)

In a prospective, open-label, pilot study, Song et al (2011) examined the short-term safety and effectiveness of abatacept in patients with ankylosing spondylitis (AS). Abatacept (10 mg/kg) was administered intravenously on days 1, 15, 29 and every 28 days thereafter up to week 24 in 15 TNF α -inhibitor naive patients (group 1) and 15 patients with inadequate response to TNF α inhibitors (group 2) with active AS. The primary end point was the proportion of patients with 40 % improvement according to the Assessment of SpondyloArthritis international Society criteria (ASAS40) in both groups at week 24. At week 24, ASAS40 was reached by 13 % of group 1 and 0 % of group 2; 20 % improvement (ASAS20) was reached by 27 % and 20 %, respectively. There was no significant change of Bath Ankylosing Spondylitis Disease Activity Index score, patient global assessment or C reactive protein. Overall, abatacept was well-tolerated. The authors concluded that in this pilot open-label AS study a major response was not observed.

Biliary Cholangitis

Popp and associates (2018) reported on the case of a 51-year old woman who was diagnosed with primary biliary cholangitis (PBC) in 2012 and rheumatic factor (RF)-positive, ACPA-positive RA in 2013. The diagnosis of a PBC was confirmed by liver biopsy showing portal inflammatory infiltrates with non-suppurative inflammatory lesions of the biliary duct; PBC has been treated with ursodeoxycholic acid (UDCA) since 2012. After an increase of activity of RA under sulfasalazine, abatacept 750 mg

every 4 weeks was added to treatment in January 2015. Under this treatment strategy remission was achieved in April 2015 and maintained thereafter. The authors stated that abatacept could be a significant therapeutic option in T cell-mediated diseases; however, they stated that further studies are needed, especially for diseases like PBC, in which abatacept is not a recognized standard treatment.

Bowlus and colleagues (2019) stated that PBC is a classic autoimmune disease in which humoral, cytotoxic, and innate immune responses have been implicated with the specific targeting of a mitochondrial antigen.

The mainstay of treatment remains UDCA. Corticosteroids may have some benefits, but to-date, clinical trials of biologics targeting B cells and IL-12/23 have not shown any efficacy. Because activated T cells target the intra-hepatic bile ducts in PBC and pre-clinical models suggested that blocking CD80/CD86 with CTLA-4 Ig might have therapeutic benefit in PBC, these researchers performed an open-label trial to determine if abatacept is safe and potentially effective in PBC patients with an incomplete response to UDCA. PBC patients with an alkaline phosphatase (ALP) of greater than $1.67 \times$ the upper limit of normal after 6 months on UDCA treatment or who were intolerant of UDCA received subcutaneous abatacept 125 mg weekly for 24 weeks. The co-primary end-point was ALP normalization or a greater than 40 % reduction from baseline. Among 16 subjects enrolled and who received at least 1 dose of abatacept, 1 (6.3 %) met the co-primary end-point. Absolute and percent changes in ALP [median (95 % CI) were +2.8 U/L (-90.9 to 96.6) and -0.28 % (-21.1 to 15.5), respectively. No significant changes were observed in ALP, ALT, total bilirubin, albumin, immunoglobulins, or liver stiffness. Abatacept treatment decreased several non-terminally differentiated CD4+; but not CD8+ T cell populations, including decreases in CD4+ CCR5+ ($p = 0.02$) and CD4+ PD1+ ($p = 0.03$) lymphocytes. In contrast there were increases in CD4+ CCR7+ lymphocytes ($p = 0.034$); treatment emergent adverse events (AEs) occurred in 4 subjects. The authors concluded that abatacept was well-tolerated in this population of PBC patients but like other biologics in PBC was ineffective in achieving biochemical responses associated with improved clinical outcomes.

Common Variable Immunodeficiency (CVID) adverse event

Mullighan et al (1999) stated that variation in clinical phenotype is a hallmark of many complex diseases. The cause of this clinical heterogeneity is unknown, but it may be determined by genetic factors distinct from those conferring disease susceptibility. Common variable immunodeficiency (CVID) is a complex disease of unknown etiology and diverse clinical manifestations. These researchers have developed a unified polymerase chain reaction and sequence-specific primer (PCR-SSP) method to simultaneously genotype multiple polymorphisms under identical conditions and have used this method to test the hypothesis that the clinical phenotype of CVID is determined by immunoregulatory gene polymorphism. A total of 23 polymorphisms in 13 genes were studied in 163 CVID patients. Vitamin D receptor and interleukin (IL)-6 alleles were associated with immunophenotypic abnormalities characteristic of more severe disease; and tumor necrosis factor and IL-10 alleles conferred susceptibility to the granulomatous form of CVID in an interacting fashion. The authors concluded that these findings demonstrated that different clinical features of a disease may have unique pathogenetic abnormalities, determined by multiple interacting genetic factors. The ease of application of this efficient, robust genotyping technique to polymorphisms throughout the genome will make it a powerful tool in the investigation of the genetic basis of phenotypic variability in a wide variety of diseases.

Adams et al (2012) noted that parvovirus B19 infection in healthy hosts is self-limited, but persistent infection has been described in patients with cellular immune defects. These investigators reported the case of a 6-year old boy who presented with a 6-month history of weight loss and malaise and a 1-month history of fever and polyarticular arthritis.

Parvovirus DNA was detected in plasma at 10 300 copies/ml. Levels of immunoglobulin (Ig)G, IgA, IgM, IgG-1, and IgG-2 were low, and antibody responses to vaccine antigens were impaired. HIV antibody and DNA PCR were negative, and the patient had normal immunophenotype, mitogen stimulation response, CD40 ligand and inducible co-stimulator expression, transmembrane activator and CAML interactor sequencing, genomic analysis, and fluorescent in situ hybridization for deletions at 22q11.2. Common variable immunodeficiency was diagnosed and replacement therapy with immune globulin intravenous was initiated. The parvovirus DNA level declined by 50 % over 3 months and was undetectable at 15 months. Constitutional symptoms improved but

arthritis persisted, and eosinophilic fasciitis eventually developed. The authors concluded that this case demonstrated that persistent parvovirus infection may be a presenting feature of humoral immune deficiency and can mimic juvenile rheumatoid arthritis. The infection may respond to immune globulin intravenous therapy.

Furthermore, UpToDate reviews on “Treatment and prognosis of common variable immunodeficiency” (Ahn and Cunningham-Rundles, 2014) and “Common variable immunodeficiency in children” (Hogan and Wilson, 2014) do not mention abatacept as a therapeutic option.

Crohn's Disease (CD)

Sandborn et al (2012) evaluated the safety and effectiveness of abatacept as induction (IP) and maintenance (MP) therapy in adults with active, moderate-to-severe Crohn's disease (CD) (CD-IP; CD-MP) and ulcerative colitis (UC) (UC-IP1; UC-MP). In CD-IP and UC-IP1, 451 patients with CD and 490 patients with UC were randomized to abatacept 30, 10, or 3 mg/kg (according to body weight) or placebo, and dosed at weeks 0, 2, 4, and 8. In MP, 90 patients with CD and 131 patients with UC who responded to abatacept at week 12 in the induction trials were randomized to abatacept 10 mg/kg or placebo every 4 weeks through week 52. In CD-IP, 17.2 %, 10.2 %, and 15.5 % of patients receiving abatacept 30, 10, and 3 mg/kg achieved a clinical response at weeks 8 and 12, versus 14.4 % receiving placebo ($p = 0.611$, $p = 0.311$, and $p = 0.812$, respectively). In UC-IP1, 21.4 %, 19.0 %, and 20.3 % of patients receiving abatacept 30, 10, and 3 mg/kg achieved a clinical response at week 12, versus 29.5 % receiving placebo ($p = 0.124$, $p = 0.043$, and $p = 0.158$, respectively). In CD-MP, 23.8 % versus 11.1 % of abatacept versus placebo patients were in remission at week 52. In UC-MP, 12.5 % versus 14.1 % of patients receiving abatacept versus placebo were in remission at week 52. Safety generally was comparable between groups. The studies showed that abatacept is not efficacious for the treatment of moderate-to-severe CD or UC.

Dermatomyositis / Polymyositis (Adult)

In a randomized, phase-IIb clinical trial, Tjamlund and colleagues (2018) examined the effects of abatacept on disease activity and on muscle biopsy features of adult patients with dermatomyositis (DM) or polymyositis (PM). A total of 20 patients with DM (n = 9) or PM (n = 11) with refractory disease were enrolled in a randomized treatment delayed-start trial to receive either immediate active treatment with intravenous abatacept or a 3 month delayed-start. The primary end-point was number of responders, defined by the International Myositis Assessment and Clinical Studies Group definition of improvement (DOI), after 6 months of treatment. Secondary end-points included number of responders in the early treatment arm compared with the delayed treatment arm at 3 months. Repeated muscle biopsies were investigated for cellular markers and cytokines. A total of 8 of 19 patients included in the analyses achieved the DOI at 6 months. At 3 months of study, 5 (50 %) patients were responders after active treatment but only 1 (11 %) patient in the delayed treatment arm; 8 AEs were regarded as related to the drug, 4 mild and 4 moderate, and 3 serious AEs, none related to the drug. There was a significant increase in regulatory T cells (Tregs), whereas other markers were unchanged in repeated muscle biopsies. The authors concluded that in this pilot study, treatment of patients with DM and PM with abatacept resulted in lower disease activity in nearly 50 % of the patients. In patients with repeat muscle biopsies, an increased frequency of Foxp3+ Tregs suggested a positive effect of treatment in muscle tissue. These preliminary findings need to be further investigated in phase-III clinical trials.

Diabetes Mellitus Type 1

In a randomized, double-blind, placebo-controlled trial, Orban et al (2011) evaluated the effect of abatacept in recent-onset type 1 diabetes. Patients aged 6 to 45 years recently diagnosed with type 1 diabetes were randomly assigned (2:1) to receive abatacept (10 mg/kg, maximum 1,000 mg per dose) or placebo infusions intravenously on days 1, 14, 28, and monthly for a total of 27 infusions over 2 years. Computer-generated permuted block randomization was used, with a block size of 3 and stratified by participating site. Neither patients nor research personnel were aware of treatment assignments. The primary outcome was baseline-adjusted geometric mean 2-hr area-under-the-curve (AUC) serum C-peptide concentration after a mixed-meal tolerance test at 2

years' follow-up. Analysis was by intention-to-treat for all patients for whom data were available. A total of 112 patients were assigned to treatment groups (35 placebo, 77 abatacept). Adjusted C-peptide AUC was 59 % (95 % CI: 6.1 to 112) higher at 2 years with abatacept (n = 73, 0.378 nmol/L) than with placebo (n = 30, 0.238 nmol/L; p = 0.0029). The difference between groups was present throughout the trial, with an estimated 9.6 months' delay (9.5 % CI: 3.47 to 15.6) in C-peptide reduction with abatacept. There were few infusion-related adverse events (36 reactions occurred in 17 [22 %] patients on abatacept and 11 reactions in 6 [17 %] on placebo). There was no increase in infections (32 [42 %] patients on abatacept versus 15 [43 %] on placebo) or neutropenia (7 [9 %] versus 5 [14 %]). The authors concluded that co-stimulation modulation with abatacept slowed reduction in β-cell function over 2 years. The beneficial effect suggested that T-cell activation still occurs around the time of clinical diagnosis of type 1 diabetes. Yet, despite continued administration of abatacept over 24 months, the decrease in β-cell function with abatacept was parallel to that with placebo after 6 months of treatment, causing these researchers to speculate that T-cell activation lessens with time. They stated that further observation is needed to establish whether the beneficial effect continues after cessation of abatacept infusions.

Encapsulated Peritoneal Sclerosis

Brican and associates (2017) noted that encapsulated peritoneal sclerosis (EPS) is a rare complication of long-term peritoneal dialysis (PD) and is usually associated with mortality. Inflammation is a leading factor for developing EPS. These researchers examined the effect of abatacept on peritoneal fibrosis and inflammation using the EPS rat model. A total of 24 Wistar albino rats were randomly divided into 4 groups. Group I (control group) was administered isotonic saline (IS) via the intra-peritoneal (ip) route during weeks 0 to 3. Chlorhexidine gluconate (CG) ip was administered to group II (CG group) during weeks 0 to 3. Group III (CG + IS group) received CG for the first 21 days and IS solution for the following 3 weeks. Group IV (abatacept group) received CG during weeks 0 to 3, and subsequently, 50 mcg/day abatacept during weeks 4 to 6. Peritoneal thickness, fibrosis, and inflammation were examined using light microscopy. Expressions of matrix metalloproteinase-2 (MMP-2) and transforming growth factor-beta 1

(TGF- β 1) were detected by immunohistochemical staining. Lesser peritoneal thickness and lower inflammation score were observed in the abatacept group than in the CG and CG + IS groups ($p < 0.05$). Furthermore, the abatacept group had a lower fibrosis score than the CG + IS group ($p < 0.05$). MMP-2 and TGF- β 1 scores were lower in the abatacept group than in the CG + IS group ($p < 0.05$). The authors concluded that these findings demonstrated that abatacept had a histopathological beneficial effect on peritoneal fibrosis, inflammation, MMP-2, and TGF- β 1 scores, which were induced by CG. They stated that abatacept could be a new therapeutic option for treating EPS. These preliminary pre-clinical findings need to be further investigated in well-designed studies.

Evans Syndrome

Per the National Organization for Rare Diseases (NORD), "Evans syndrome is a rare disorder in which the body's immune system produces antibodies that mistakenly destroy red blood cells, platelets and sometimes certain white blood cell known as neutrophils. This leads to abnormally low levels of these blood cells in the body (cytopenia). The premature destruction of red blood cells (hemolysis) is known as autoimmune hemolytic anemia or AIHA". First-line therapy for Evans syndrome often consists of corticosteroids such as prednisolone. Intravenous immunoglobulin (IVIg) therapy has also been used to treat individuals with Evans syndrome. New therapies are being explored for Evans syndrome.

NORD and An UpToDate review on "Warm autoimmune hemolytic anemia (AIHA) in adults" (Brugnara and Brodsky, 2022) do not mention abatacept as a therapeutic option.

Giant Cell Arteritis

Koster and colleagues (2016) reviewed the advances in medical management of giant cell arteritis (GCA) and Takayasu arteritis (TAK) with a focus on recent developments in targeted biologic therapy. The role of biologics in the treatment of large vessel vasculitis (LVV) is expanding; TNF-alpha inhibitors appear to be effective in the treatment of TAK but have little benefit in GCA. Preliminary clinical trial data

suggested that abatacept and tocilizumab reduce the risk of relapse in GCA. Increasing observational evidence supports the use of IL-6 inhibitors in TAK. Based on a small open-label study, ustekinumab appeared safe and potentially effective for refractory GCA. A possible role of B cell dysregulation may contribute to pathogenic mechanisms in LVV, but support for the use of B cell depleting therapy is limited. The authors concluded that IL-6 inhibitors appeared effective in the treatment of refractory cases of LVV; however, utility in newly diagnosed immunosuppressive-naïve patients is less well-established. They stated that abatacept and ustekinumab are promising targets for therapy in LVV; however, further investigation is needed before routine use is considered.

In a randomized, double-blind, multi-center trial, Langford and colleagues (2017a) compared the effectiveness of abatacept to that of placebo for the treatment of GCA. Patients with newly diagnosed or relapsing GCA were treated with abatacept 10 mg/kg intravenously on days 1, 15, and 29 and week 8, together with prednisone administered daily. At week 12, patients in remission underwent a double-blinded randomization to continue to receive abatacept monthly or switch to placebo. Patients in both study arms received a standardized prednisone taper, with discontinuation of prednisone at week 28. All patients remained on their randomized assignment until meeting criteria for early termination or until 12 months after enrollment of the last patient. The primary end-point was duration of remission (relapse-free survival rate). A total of 49 eligible patients with GCA were enrolled and treated with prednisone and abatacept; of these, 41 reached the week 12 randomization and underwent a blinded randomization to receive abatacept or placebo.

Prednisone was tapered using a standardized schedule, reaching a daily dosage of 20 mg at week 12 with discontinuation in all patients at week 28. The relapse-free survival rate at 12 months was 48 % for those receiving abatacept and 31 % for those receiving placebo ($p = 0.049$). A longer median duration of remission was seen in those receiving abatacept compared to those receiving placebo (median duration 9.9 months versus 3.9 months; $p = 0.023$). There was no difference in the frequency or severity of AEs, including infection, between the treatment arms. The authors concluded that in patients with GCA, the addition of abatacept to a treatment regimen with prednisone reduced the risk of

relapse and was not associated with a higher rate of toxicity compared to prednisone alone. This study had a relatively small sample size and short-term follow-up.

On the other hand, an UpToDate review on “Treatment of giant cell (temporal) arteritis” (Hunder, 2017a) does not mention abatacept as a therapeutic option.

Granulomatosis with Polyangiitis (Wegener's Granulomatosis)

In an open-label study, Langford et al (2014) examined the safety and effectiveness of abatacept in non-severe relapsing granulomatosis with polyangiitis (GPA; also known as Wegener's granulomatosis).

Intravenous abatacept was administered in 20 patients with non-severe relapsing GPA. Prednisone up to 30 mg daily was permitted within the first 2 months, and patients on methotrexate, azathioprine, or mycophenolate mofetil continued these agents. Patients remained on study until common closing or early termination. Of the 20 patients, 18 (90 %) had disease improvement, 16 (80 %) achieved remission (BVAS/WG = 0) at a median of 1.9 months, and 14 (70 %) reached common closing. Six patients (30 %) met criteria for early termination due to increased disease activity; 3 of 6 achieved remission and relapsed at a median of 8.6 months. The median duration of remission before common closing was 14.4 months, with the median duration of time on study for all patients being 12.3 months (range of 2 to 35 months); 11 of the 15 (73 %) patients on prednisone reached 0 mg. Nine severe adverse events occurred in 7 patients, including 7 infections that were successfully treated. The authors concluded that in this study of patients with non-severe relapsing GPA, abatacept was well-tolerated and was associated with a high frequency of disease remission and prednisone discontinuation. These preliminary findings from a small study ($n = 20$) need to be validated by well-designed studies.

Interstitial Lung Disease

Vicente-Rabaneda et al (2021) noted that interstitial lung disease (ILD) is a serious complication that represents the 2nd leading cause of death in patients with RA. Treatment of RA-ILD remains controversial. The absence of randomized clinical trials and specific ACR or EULAR

therapeutic guidelines makes it difficult to establish solid therapeutic recommendations on this issue. In this setting, real-world data are especially valuable. In a systematic review, these investigators examined the available evidence on the safety and effectiveness of abatacept (ABA) for the treatment of ILD associated with RA, given its clinical relevance and the lack of consensus on its therapeutic management. PubMed and Embase were searched from the date of approval of ABA to the end of 2020 using a combination of RA, ILD and ABA terms following PRISMA guidelines. Identified studies were evaluated by 2 independent investigators. A total of 9 original studies (1 case series and 8 observational studies) were selected for inclusion in the systematic review. No randomized trial or meta-analysis were identified. The mean age of patients ranged from 61.2 to 75 years and the mean RA duration varied from 7.4 to 18 years. Subcutaneous ABA (74.5 % to 91 %) predominated in combination with conventional synthetic DMARDs (csDMARDs) (58 % to 75 %), and it was used as 1st-line biologic agent in 22.8 % to 64.9 % of the patients. The mean course of ILD ranged from 1 to 6.7 years, being usual and non-specific interstitial pneumonia the most frequent patterns. Improvement or stabilization of ILD imaging (76.6 % to 92.7 %) and forced vital capacity (FVC) or diffusion capacity of the lung for carbon monoxide (DLCO) (greater than 85 %) was described after a mean follow-up of 17.4 to 47.8 months, regardless of the pattern of lung involvement, being more remarkable in patients with shorter evolution of ILD. ABA led to significantly lower ILD worsening rates than TNF inhibitors (TNFi) and was associated with a 90 % reduction in the relative risk of deterioration of ILD at 24 months of follow-up compared to TNFi and csDMARDs. Combination with methotrexate may have a corticoid-sparing effect. No unexpected AEs were identified. The authors concluded that current evidence suggested that ABA may be a plausible alternative to treat RA patients with ILD. It would be highly desirable to develop prospective RCTs to confirm these findings.

Tardella et al (2021) stated that RA-ILD is an extra-articular involvement that impairs the prognosis and for which there is still no well-coded treatment. These researchers examined the safety and effectiveness of ABA in patients with RA-ILD. Patients with RA-ILD who started ABA treatment were consecutively enrolled. Chest high-resolution computed tomography (HRCT), clinical, laboratory and respiratory function variables were collected at baseline and after 18 months of ABA treatment. HRCT

abnormalities were evaluated using a computer-aided method (CaM). ABA response was established based on the change in the percentage of fibrosis evaluated at HRCT-CaM, dividing patients into "worsened" (progression of 15 % or more), "improved" (reduction of 15 % or more), and "stable" (changes within the 15 % range). The multi-variate regression model was used to evaluate the associations between RA characteristics and ABA response. A total of 46 patients (81 % women, mean age of 59.1 ± 8.0 years, mean disease duration of 7.5 ± 3.1 years) were studied; 5 patients (11.4 %) showed RA-ILD progression, 32 patients (72.6 %) were considered stable, and 7 patients (16.0 %) showed an RA-ILD improvement. The proportion of current smokers was significantly different between "worsened" patients, with respect to those defined as "improved/stable" ($p = 0.01$). Current smoking habit ($p = 0.005$) and concomitant methotrexate treatment ($p = 0.0078$) were the 2 variables related to RA-ILD progression in multi-variate regression analysis. The authors concluded that treatment with ABA was associated with a RA-ILD stability or improvement in the 88.6 % of patients. Current smoking habit and concomitant treatment with methotrexate were the modifiable factors associated with RA-ILD worsening.

The authors stated that this study had several drawbacks. First, a small sample size ($n = 46$). Second, the absence of a control group. Third, these researchers did not have data on the onset of ILD. Fourth, short-term follow-up (1.5 years).

Juvenile Dermatomyositis / Juvenile Dermatomyositis-Associated Calcinosis

Arabshahi et al (2012) reported the successful use of abatacept and sodium thiosulfate in a patient with severe recalcitrant juvenile dermatomyositis (JDM) complicated by ulcerative skin disease and progressive calcinosis. This combination therapy resulted in significant reductions in muscle and skin inflammation, decreased corticosteroid dependence, and halted the progression of calcinosis.

Also, an UpToDate review on "Treatment and prognosis of juvenile dermatomyositis and polymyositis" (Hutchinson and Feldman, 2013) states that "Abatacept is a soluble fusion protein comprised of the extracellular domain of cytotoxic T lymphocyte antigen 4 (CTLA-4) and

the Fc portion of immunoglobulin G1 (IgG1). It binds to CD80/CD86, preventing CD28 binding and thereby downregulating T cell activation. A 14-year-old girl with severe, refractory JDM with ulcerations and calcinosis was reported to have improvement in disease scores, ulcerations, pain medication and glucocorticoid use, and laboratory values after treatment with abatacept and thiosulfate. The utility of this agent in children with JDM remains to be determined".

Sukumaran and Vijayan (2020) noted that calcinosis is a feared complication of JDM that may be observed in up to 40 % of children with JDM. It is associated with negative impact on the patients' QoL due to weakness, functional disability, joint contractures, muscle atrophy, skin ulcers, and secondary infections. Calcinosis could present as superficial nodules or plaques, larger nodular deposits extending into deeper tissue layers, accumulation of calcifications along the fascial planes of muscles or tendons, or an exoskeleton of calcium leading to limitations in mobility and joint contractures. Currently, there are no known effective treatments for calcinosis and current therapy is based on anecdotal retrospective studies and cases series. These researchers reported the case of a child with JDM-associated calcinosis with extensive intra-muscular calcifications who failed conventional therapies but demonstrated improvement as evident by decrease in calcinosis and improved physical function with use of abatacept. They found that use of abatacept was associated with improvement in functional outcome and recurrence did not occur. The authors concluded that the findings of this case suggested that the use of abatacept as a safe and effective therapeutic option for calcinosis due to JDM. Moreover, these researchers stated that further, large-scale clinical studies are needed to validate these findings and to evaluate the long-term outcomes.

Kidney Disease

Yu and colleagues (2013) stated that abatacept (cytotoxic T-lymphocyte-associated antigen 4-immunoglobulin fusion protein [CTLA-4-Ig]) is a co-stimulatory inhibitor that targets B7-1 (CD80). The present report described 5 patients who had focal segmental glomerulo-sclerosis (FSGS) (4 with recurrent FSGS after transplantation and 1 with primary FSGS) and proteinuria with B7-1 immuno-staining of podocytes in kidney-biopsy specimens. Abatacept induced partial or complete remissions of

proteinuria in these patients, suggesting that B7-1 may be a useful biomarker for the treatment of some glomerulopathies. The authors concluded that the findings of this study indicated that abatacept may stabilize β 1-integrin activation in podocytes and reduce proteinuria in patients with B7-1-positive glomerular disease. (This was a small study of 4 patients with FSGS after transplantation).

In an editorial that accompanied the afore-mentioned study, Haraldsson (2013) stated that "If corroborated, these observations -- and the approach described -- may signal the start of a new era in the treatment of patients with proteinuric kidney disease. However, only time will tell how many patients will benefit from the proposed podocyte-targeted treatment with abatacept or similar agents".

Alkandari et al (2016) noted that FSGS is a common cause of end-stage renal disease in children. Focal segmental glomerulo-sclerosis recurrence in renal transplants is a challenging disease and can cause graft dysfunction and loss. Different therapies exist with varying responses, from complete remission to resistance to all modes of treatment. Abatacept was recently introduced as a treatment for primary FSGS in native kidneys and in recurrent disease after transplant. These researchers presented a pediatric case with immunosuppression-resistant primary NPHS2-negative FSGS recurrence after renal transplant. The standard therapy for recurrent FSGS (rituximab, plasmapheresis, high-dose cyclosporine, and corticosteroids) was tried but failed to induce remission. Abatacept (10 mg/kg) was given at 0, 2, and 4 weeks (total, 3 doses) with no good response. The authors concluded that abatacept may work in patients with B7-1-positive FSGS recurrence and its efficacy is uncertain in disease with B7-1-negative or unknown staining status.

Also, an UpToDate review on "Overview of the management of chronic kidney disease in adults" (Rosenberg, 2014) does not mention the use of abatacept as a therapeutic option.

Localized Scleroderma

Kalampokis and colleagues (2020) stated that localized scleroderma (LS) is a rare chronic immune-mediated skin condition of unknown etiology characterized by an inflammatory response in the skin and subcutaneous tissues resulting in collagen deposition and subsequent fibrosis. There is no cure for LS. No therapies have been licensed specifically for the treatment of LS and the clinical management of the disease remains largely empirical. Abatacept has been reported to be effective in adult cases of LS. These investigators reported the successful use of abatacept in a juvenile LS (jLS) cohort and carried out a systematic literature review to examine the evidence supporting the use of abatacept in the treatment of LS. They compiled retrospectively the clinical data on 8 cases of jLS that were treated with abatacept in their academic center. A systematic review protocol was developed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines and has been registered with the international prospective register of systematic reviews (PROSPERO). Standardized searches of Medline/PubMed and Embase were undertaken to identify studies reporting the use of abatacept in the treatment of LS. Heterogeneity in study design, interventions and reported outcomes necessitated a qualitative data synthesis. The use of abatacept was effective and safe in the authors' cohort of jLS patients. Their standardized searches identified 30 articles, of which 3 were deemed eligible for full data extraction. All 3 studies were small (total of 18 subjects; mean of 6 per study), single-center, open-label, uncontrolled and non-randomized. The Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) identified high risk-of bias for confounding variables and blinding of assessors in each of the 3 studies evaluated and in the authors' pediatric case series. The authors concluded that the evidence-base to support the use of abatacept in the treatment of LS is currently limited and clinical practice guidelines should take a measured approach to such recommended therapy.

Nonetheless, as the empirical evidence on the clinical effectiveness of abatacept in the treatment of LS accumulates, a double-blind, placebo-controlled, randomized clinical trial is needed to formally evaluate the observations documented by case-based reports.

The authors stated that this study was limited in being a single-center, uncontrolled retrospective case series of 8 patients that were treated with abatacept in the context of combination therapy with corticosteroids (CS) and mycophenolate mofetil (MMF) or methotrexate (MTX). All 8 patients

were treated during the first 3 months with intravenous (IV) pulses of methylprednisolone in combination with abatacept and MMF or MTX. The therapeutic effect of methylprednisolone in LS is well established; these researchers were unaware how much of the therapeutic effect of methylprednisolone contributed initially to the treatment responses in their cohort. However, all patients had been treated with systemic CS prior to abatacept and none of them had a sustained response. Furthermore, 5 of 8 patients had also failed maintenance therapy with MTX and/or MMF in the past. After the initiation of combination therapy with abatacept, treatment responses were sustained in all 8 cases for up to 30 months. Thus, the authors concluded that the sustained treatment responses in their cohort were due to the addition of abatacept. The lack of control patients in this study made it impossible to examine if the sustained therapeutic responses were exclusively due to abatacept or due to potential synergy of abatacept with MMF or MTX. Another important limitation of this study was that these investigators did not use a formal disease activity monitoring tool such as the modified Rodnan Skin Score (mRSS) or the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) in all 8 patients at all their clinic visits and relied on clinical photographs and physician clinical assessment. However, they used the LoSCAT in 5 of 8 patients at some of their clinic visits and both the modified Localized Scleroderma Skin Severity Index (mLoSSI) and the Localized Scleroderma Skin Damage Index (LoSDI) improved with treatment. It appeared that the magnitude of LoSCAT score improvement in this study was larger than what was reported by Fage et al (2018); this difference may relate to the pediatric nature of this study population and/or the fact that, in this study, abatacept was used as part of combination therapy instead of monotherapy as in the study by Fage et al [2018]. Nonetheless, the clinical outcomes observed in the authors' pediatric case series confirmed the outcomes reported in adult cases of LS and in the recently presented conference abstract of a jLS case series. Systematic literature review of studies reporting the effectiveness of abatacept in the treatment of LS revealed overall moderate risk-of-bias. The evaluation of the existing literature by a systematic literature review and the authors' clinical experience in a jLS case series suggested that abatacept therapy in LS is safe and effective in both adults and children. Nevertheless, more robust studies are needed to evaluate these findings and determine the therapeutic potential of abatacept in the treatment of LS.

Lupus Nephritis

Wofsy et al (2012) stated that recent lupus nephritis trials have all used different criteria to assess complete response (CR). These investigators compared several previously proposed criteria using the same data set from a large trial of abatacept in lupus nephritis. By so doing, they sought: (i) to determine which criteria are most sensitive to differences among treatment groups; and (ii) to further examine the potential of abatacept in lupus nephritis. Subjects in BMS study number IM101075 received either abatacept or placebo on a background of mycophenolate mofetil and corticosteroids. Using data from this trial, these researchers assessed CR rates at 12 months according to 5 sets of criteria from: (i) the trial protocol; (ii) the ALMS trial of mycophenolate mofetil; (iii) the LUNAR trial of rituximab; (iv) an ongoing NIH trial of abatacept (ACCESS); and (v) published recommendations of the American College of Rheumatology. The per-protocol CR definition showed no difference among groups. In contrast, the ALMS, LUNAR, and ACCESS definitions each showed significantly higher CR rates in both treatment groups relative to control. The largest differences were observed using the LUNAR criteria (CR rates of 6 % among control subjects, compared to 22 % and 24 % in the 2 abatacept groups). The authors concluded that the choice of definition of complete response can determine whether a lupus nephritis trial is interpreted as a success or a failure. This analysis provided an evidence-based rationale for choosing among alternative definitions, and it offered a strong rationale for conducting further studies of abatacept in lupus nephritis.

Morphea (Localized Scleroderma)

Stausbol-Gron et al (2011) stated that morphea profunda is a rare disease that mainly affects young women and often has a progressive course with physical and psychological sequelae. The skin becomes sclerotic after an initial inflammatory reaction and joint contractures can develop. The etiology is unknown. Until now, no successful therapy has been proven for this morphea variant. On the basis of new insights into the key role of effector T cells in scleroderma, in particular Th-17, T-cell directed therapies are expected to have promising effects. The authors

reported the first 2 cases of morphea profunda treated with abatacept. They stated that abatacept had a clinical effect on the active disease, in addition to softening old sclerotic lesions.

In a prospective, open-label, case-series study, Adeeb et al (2017) examined the potential efficacy of abatacept in patients presenting with morphea subtypes and deep tissue involvement. A total of 3 patients with established morphea subtypes and deep tissue involvement and with no contraindication to abatacept were included in this study. The index patient was exceptionally severely affected with a mean modified Rodnan skin score (MRSS) of 38/51. At baseline, whole-body MRI and skin biopsy were performed which confirmed classical deposition of dense fibrous tissue in the appropriate layer of the skin. MRSS was performed independently by 3 clinicians and VAS scores (10 cm) were measured at baseline for Patient Global Disease Activity (PGDA), Patient Global Pain (PGP), Patient Day Pain (PDP), Patient Night Pain (PNP), and Physician Global Disease Activity (PhGDA). Patients 2 and 3 were similarly screened at baseline except for MRI. Patients were commenced on abatacept as per body weight (10 mg/kg) given intravenously with concomitant tapering dose of oral prednisolone. All 3 were re-assessed at 6 months and the index case was further re-assessed at 18 months. All patients tolerated the abatacept well and showed dramatic improvement. The index patient's clinical signs and symptoms, whole-body MRI, and mean MRSS improved dramatically from baseline by 37 % at 6 months and by 74 % at 18 months. There were no clinically significant adverse outcomes noted. The authors concluded that they presented 3 cases, 1 with exceptionally severe disease, which demonstrated excellent clinical response to abatacept. These researchers stated that abatacept is a promising option for the treatment of severe or resistant morphea, especially in those with deep tissue involvement.

In a retrospective, case-series study, Fage and colleagues (2018) examined if abatacept may have a positive effect on disease activity in patients with treatment-resistant localized scleroderma (LoS). These researchers noted that the scleroderma clinic at the Department of Dermato-Venereology of Aarhus University Hospital manages approximately 650 patients with scleroderma and scleroderma-like diseases. Each week a total of 2 to 4 new patients were admitted and 25

to 45 patients attended for regular control of disease and treatments. Through 2009 to 2016, these investigators followed-up on all adult treatment-resistant LoS patients who were treated experimentally with abatacept. The patients were treated with either 500 mg (patients weighing less than 60 kg) or 750 mg (patients weighing more than 60 kg) abatacept intravenously on days 1, 15, 30, and thereafter every 4 to 6 weeks. Some patients switched to subcutaneous injection of 125 mg abatacept/week during treatment. Evaluations, including either modified Rodnan skin score (MRSS) or localized scleroderma cutaneous assessment tool (LoSCAT) (8), were performed by well-trained doctors. Medical records review were conducted to extract data at 2 time-points: At the beginning of abatacept treatment (the day the 1st abatacept treatment was injected) 1st assessment and either the latest follow-up during treatment (the patient is still treated with abatacept) or at the determination (2nd assessment) of abatacept treatment. Regarding patients with generalized LoS, MRSS and LoSCAT, data were collected at any time, prior to, during, and after abatacept treatment. Primary end-points were changes in MRSS, LoSCAT, and/or change of size of lesions; secondary end-points were changes in CRP, C3c, C4, and/or PIIINP. A total of 13 adults with treatment-resistant LoS were treated with abatacept (11 women and 2 men). Through-out 2016, 8 patients were still receiving treatment with abatacept and 5 patients had stopped treatment. Primary end-points were missing in 2 patients, both with "en coup de sabre" disease. The duration between assessment points ranged from 3 to 32 months, with a mean of 16 months. When measured, CRP, C3c, C4, and PIIINP were within reference ranges and without significant deviations in all patients. A reduction in activity of LoS was observed in this small group of patients with previously treatment-resistant LoS. The treatment was generally well-tolerated, but some patients had transient adverse effects, such as fatigue, nausea and diarrhea. The authors concluded that an improvement/reduction in size of lesions or MRSS/mLoSSI score were observed in this series of adult patients with LoS treated with abatacept. Thus, abatacept may be an appropriate therapeutic option for treatment-resistant LoS disease of different subtypes. However, they stated that further studies are needed.

The authors stated that this descriptive case study had several limitations in design, as well as the well-known difficulty of assessing disease severity in various forms of scleroderma. The clinical course of the

disease with a general improvement over time, partially depending on subtype, was not regarded as a significant confounding factor in interpretation of the collected data, since the mean time between assessments of disease severity was 16 months, which was a short time relative to the activity of each lesion and mean duration of disease activity prior to treatment with abatacept. Moreover, they stated that it is worth noticing that this is a highly selected group of treatment-resistant cases with severe disease. The effects in cases with milder disease, or of abatacept as 1st- or 2nd-line of systemic treatment, could not be evaluated in a descriptive case series.

Furthermore, UpToDate review on "Treatment of morphea (localized scleroderma) in adults" (Jacobe, 2018) and "Localized scleroderma in childhood" (Zulian, 2018) do not mention abatacept as a therapeutic option.

Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE)

Blockade of antigen non-specific co-stimulatory signals is also being investigated for the treatment of autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus (Dumont, 2004; Davidson et al, 2005). However, there is currently insufficient evidence that abatacept is effective in treating patients with autoimmune diseases.

Nephrotic Syndrome

Trachtman and colleagues (2017) stated that treatment-resistant nephrotic syndrome (TRNS) is a rare form of glomerular disease that occurs in children and adults. No FDA-approved treatments consistently achieve remission of proteinuria and preservation of kidney function.

CD80 (B7-1) can be expressed on injured podocytes, and administration of abatacept (modified CTLA4-Ig based on a natural ligand to CD80) has been associated with sustained normalization of urinary protein excretion and maintenance of glomerular filtration rate (GFR) in experimental and clinical settings. In this report, these researchers described the rationale for and design of a randomized, placebo-controlled, clinical trial of abatacept in patients with TRNS caused by FSGS or minimal change disease (MCD). The design is a hybrid of a parallel-group and cross-over design (switch-over) with the primary objectives assessed in the 1st

period of the study and the secondary objectives assessed using data from both periods. All participants will receive the active agent in 1 of the periods. The duration of treatment will be 4 months per period. The primary outcome will be improvement in nephrotic-range proteinuria to sub-nephrotic range, that is, reduction from baseline to 4 months in urine protein-creatinine ratio (UPCR) of greater than or equal to 50 % and to a level of less than 3. The projected sample size is 90 patients, which has 80 % power to detect a treatment difference of 28 %. The authors concluded that they described the design of a pilot randomized clinical trial to test the efficacy of abatacept in patients with TRNS. They adopted a trial design that should promote enrollment, and they will conduct the study using a network of experienced academic nephrology centers. These investigators specifically intend for this pilot study to guide the execution of subsequent studies of abatacept, based on biomarkers derived from analysis of bio-samples from responders versus non-responders in this pilot study. They stated that future studies may therefore use these specific biomarkers for patient enrollment, thus greatly increasing the potential for a substantial treatment effect. It is hoped that this trial will spur the identification of biomarkers of CD80 involvement in TRNS, and will initiate a precision medicine-based approach to this serious kidney disease in which the selection of a therapeutic agent is guided by the underlying disease mechanism operating in each individual patient.

Oligoarthritis and Polyarthritis

Wevers-de Boer et al (2013) stated that undifferentiated arthritis (UA) is defined as an inflammatory oligoarthritis or polyarthritis in which no definitive diagnosis can be made. These investigators performed a literature review to assess the efficacy of various drug therapies in patients with UA. The literature search was conducted using electronic databases PubMed, EMBASE and MEDLINE in adults with UA or early arthritis (not fulfilling the American College of Rheumatology (ACR) 1987 or ACR/ EULAR 2010 criteria for rheumatoid arthritis). Drug therapy consisted of DMARDs, biological agents and oral, intra-muscular or intra-articular corticosteroids. A total of 9 publications on 8 RCTs, 2 publications on 2 uncontrolled open-label trials, and 7 publications on 3 cohort studies were included. Temporary treatment with methotrexate (MTX), abatacept and intra-muscular corticosteroids were demonstrated

in RCTs with 12 months to 5 years follow-up to be more effective than placebo in suppressing disease activity or radiological progression. One study suggested that DMARD combination therapy is, at least after 4 months, superior to MTX monotherapy in patients with UA at high-risk of developing persistent arthritis. The open-label uncontrolled trials and cohort studies also suggested that early treatment may provide immediate suppression of inflammation. The long-term benefit of early treatment in UA remains unclear. The authors concluded that patients with UA benefit from early treatment with MTX. Combining multiple DMARDs or DMARDs with corticosteroids and biological agents may be even more beneficial. However, which treatment may provide the best results or may alter the disease course has still to be determined. Moreover, they stated that more RCTs with longer follow-up time are needed.

Organ Transplant

Wojciechowski and Vincenti (2011) noted that signaling through the co-stimulatory pathway is critical in the regulation of T cell activation. Abatacept, a selective co-stimulatory antagonist FDA approved for the treatment of moderate to severe rheumatoid arthritis, binds to CD80 and CD86 on antigen presenting cells, blocking the interaction with CD28 on T cells. Belatacept, a second generation CTLA4-Ig with 2 amino acid substitutions, has shown considerable promise in clinical transplantation as part of a maintenance immunosuppression regimen. The authors review summarized the role of co-stimulation in T cell activation, detailed the development of co-stimulation antagonists and highlighted the pertinent clinical trials completed and ongoing utilizing belatacept as part of an immunosuppressive regimen in organ transplantation.

Riella and Sayegh (2013) stated that the concern about nephrotoxicity with calcineurin inhibitors led to the search of novel agents for immunosuppression. Based on the requirement of T-cell co-stimulatory signals to fully activated naïve T cells, it became clear that blocking these pathways could be an appealing therapeutic target. However, some unexpected findings were noticed in the recent clinical trials of belatacept, including a higher rate of rejection, which warranted further investigation

with some interesting concepts emerging from the bench. This review did not mention abatacept as an immunosuppressive agent in organ transplantation.

Polychondritis

Kemta et al (2012) evaluated the safety and effectiveness of biologics in patients with active relapsing polychondritis (RP). These investigators performed a systematic review of the literature using PubMed through December 2010. MeSH terms and keywords were used relating to RP and biologics. All papers reporting the efficacy and/or safety of biologics in RP were selected. Reference lists of included papers were also searched. All publications were related to case series or isolated case reports. No randomized controlled trial (RCT) has been performed. A total of 30 papers that included 62 patients were published. These patients were treated with TNF α blockers (n = 43), rituximab (n = 11), anakinra (n = 5), tocilizumab (n = 2), and abatacept (n = 1). The endpoint of treatment differs from 1 publication to the other and therefore made the comparison of efficacy among the various biologics difficult. Biologics were effective in 27 patients, partially effective in 5 patients, and not effective in 29 patients. Safety appeared to be good. However, 4 deaths were recorded (2 sepsis, 1 post-operatively after aortic aneurysm surgery, and 1 after accidental dislocation of the tracheostomy device). The authors concluded that the experience with biologics in RP is very limited and their real efficacy and indications need to be better defined. They stated that RCTs, although difficult to perform because of the rarity of RP, are needed to determine the place of biologics in the treatment strategy of this orphan disease.

Psoriasis

An UpToDate review on "Treatment of psoriasis" (Feldman, 2013) does not mention abatacept as a therapeutic option.

Reactive Arthritis

An UpToDate review on "Reactive arthritis (formerly Reiter syndrome)" (Yu, 2013) does not mention abatacept as a therapeutic option.

Rheumatoid Pleural Effusion

Fujita and colleagues (2018) noted that rheumatoid pleural effusion is generally responsive to corticosteroids, but refractory cases require consideration of 2nd-line therapy. These investigators reported the case of a 61-year old man with RA who developed a large right-sided pleural effusion and was successfully treated with abatacept. Thoracocentesis showed a sterile exudate and an elevated adenosine deaminase level.

The methotrexate and etanercept used to treat the RA were withheld initially while he underwent a trial of prednisolone 40 mg/day for the pleural effusion. However, the effusion did not respond to this therapy.

Thoracoscopic biopsy of the right pleura revealed fibrotic changes with lymphocyte infiltration mainly composed of CD4+ T cells and B cells, but no evidence of malignancy or infection. The patient was started on abatacept and resumed methotrexate. The treatment was effective in this case. The authors concluded that abatacept should be considered as a therapeutic option in patients with refractory rheumatoid pleural effusion.

This was a single-case study; this preliminary finding needs to be further investigated.

Furthermore, an UpToDate review on "Overview of lung disease associated with rheumatoid arthritis" (Lake, 2018) does not mention abatacept as a therapeutic option.

Rheumatoid Vasculitis

Al Attar and Shaver (2018) noted that abatacept is a fusion protein composed of the fragment crystallizable region (Fc region) of the immunoglobulin IgG1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4. These researchers described the case of a patient who presented with lower extremity purpura in the setting of RA and CVID. A biopsy of cutaneous lesions confirmed the etiology of rheumatoid vasculitis. Although rituximab is the recommended treatment, it has the potential to exacerbate immunodeficiency. The cutaneous lesions responded well to abatacept after the patient failed to respond to other therapeutic modalities. The authors concluded that, to their knowledge, this case was the first to be reported in North America; and these findings may encourage extensive clinical trials on abatacept as a therapeutic option.

Scleritis

In a retrospective study, Fabiani and colleagues (2020) examined the efficacy of biologic drugs, beyond TNF- α inhibitors, in the management of non-infectious refractory scleritis, either idiopathic or associated with systemic immune-mediated disorders. This trial evaluated the efficacy of several biologic agents (rituximab, anakinra, tocilizumab, and abatacept) and the small molecule tofacitinib in the treatment of scleritis through assessment of scleral inflammation and relapses, as well as treatment impact on best-corrected visual acuity (BCVA) and safety profile. A total of 14 patients (19 eyes) were enrolled in the study. Scleritis inflammatory grading significantly improved from baseline to 3 months ($p = 0.002$) and from baseline to the last follow-up visit ($p = 0.002$). Scleritis relapses significantly decreased between the 12 months preceding and following biologic therapy ($p = 0.007$). No differences regarding BCVA were observed ($p = 0.67$). Regarding AEs, only 1 patient developed pneumonia and septic shock under rituximab treatment. The authors concluded that these findings, although limited to a small number of patients, highlighted the effectiveness of different biologic therapies in the treatment of non-infectious refractory scleritis, showing to control scleral inflammation and allowing a significant reduction in the number of relapses. Moreover, these researchers stated that they are far from drawing firm conclusions, and their current limited knowledge warrants further prospectively designed studies with larger sample sizes to shed light on this topic. The authors noted that this study had several drawbacks, including its retrospective design, the small sample size ($n = 14$), and therapeutic heterogeneity with different biologic agents employed before study entry and within study period.

Scleroderma

Ong and Denton (2010) reviewed the evidence and recent developments leading to novel therapeutics in scleroderma. Recent advances have been made in understanding the key pathogenetic aspects of scleroderma, and these have led to potential targeted therapeutic agents for the management of these patients. Preliminary data from early clinical trials suggested that tyrosine kinase molecules may be potential candidates for therapy, especially in the fibrotic phase of the disease. On the basis of the new insights into the key role of effector T cells, in

particular Th-17 and T regulatory subsets, T-cell-directed therapies including halofuginone, basiliximab, alemtuzumab, abatacept and rapamycin have been proposed to be clinically beneficial. By analogy, recent clinical studies with rituximab in diffuse cutaneous systemic sclerosis lend support that B cells may be important in the pathogenesis of the disease. 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, endothelin receptor antagonists and phosphodiesterase type V inhibitor have been shown to be useful to treat the vascular manifestations associated with systemic sclerosis. Hematopoietic stem cell transplantation following immune ablation holds considerable promise in resetting of the immune system, and trial results are awaited. The authors concluded that although there is still no treatment that is unequivocally effective for scleroderma, there have been some promising developments over the past number of years with identification of novel candidate targets and innovative strategies, including targeted immunomodulatory therapies, tyrosine kinase inhibitors and agents that may promote vascular repair. These recent findings will need to be confirmed by larger, multi-center, randomized controlled trials.

Sjogren's Syndrome

In a pilot study, Adler et al (2013) prospectively evaluated histopathologic, blood cellular, serologic, and clinical changes in response to abatacept treatment in patients with primary Sjogren's syndrome (pSS). Blood, saliva, and minor salivary gland biopsy samples were obtained before and after the last of 8 doses of abatacept in 11 pSS patients. The histologic data evaluated the numbers of lymphocytic foci and B and T cell subtypes (CD20+, CD3+, CD4+, and CD8+). The numbers of FoxP3+ regulatory T cells were measured and the FoxP3:CD3 ratio was calculated. Histologic data were compared with results from peripheral blood and with changes in saliva secretion. The numbers of lymphocytic foci decreased significantly ($p = 0.041$). Numbers of local FoxP3+ T cells decreased significantly in percentage of total lymphocytic infiltrates ($p = 0.037$). In the peripheral blood, B cells increased ($p = 0.038$). This was due to an expansion of the naive B cell pool ($p = 0.034$). When adjusting for disease duration, an increase was also noted for total lymphocytes ($p = 0.044$) and for CD4 cells ($p = 0.009$). Gamma globulins decreased significantly ($p = 0.005$), but IgG reduction did not reach significance. Adjusted for disease duration, saliva production increased significantly (p

= 0.029). The authors concluded that CTLA-4Ig treatment significantly reduced glandular inflammation in pSS, induced several cellular changes, and increased saliva production. Remarkably, this increase in saliva production was significantly influenced by disease duration.

The authors noted that a drawback of this study was the small number of patients (n = 11). This was primarily due to the invasive character of the study protocol, with biopsy samples taken before and after treatment. Furthermore, the primary focus of this pilot study was the characterization of histologic and cellular changes and not the detailed measurement of clinical effects. A 2nd issue to be considered was the measurement of stimulated salivary flow by the Saxon test; more sensitive tests and the characterization of saliva composition might have depicted more pronounced differences before and after treatment.

In a pilot, open-label, proof of concept study, Meiners et al (2014) evaluated the safety and effectiveness of abatacept in patients with early and active primary Sjogren's syndrome (pSS). All 15 patients (12 women, 3 men) included in the study met the revised American-European Consensus Group criteria for pSS and were biological DMARD-naïve. Patients were treated with 8 intravenous abatacept infusions on days 1, 15 and 29 and every 4 weeks thereafter. Follow-up was conducted at 4, 12, 24 (on treatment), 36 and 48 weeks (off treatment). Disease activity was assessed with EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI). Several other functional, laboratory and subjective variables were analyzed. Generalized estimating equations were used to analyze parameters over time. ESSDAI, ESSPRI, rheumatoid factor and IgG levels decreased significantly during abatacept treatment and increased post-treatment. Salivary and lacrimal gland function did not change during treatment. Fatigue and health-related quality of life (HR-QoL) improved significantly during treatment. No serious side effects or infections were seen. The authors concluded that in this open-label study, abatacept treatment is effective, safe and well-tolerated, and results in improved disease activity, laboratory parameters, fatigue and HR-QoL in patients with early and active pSS. These preliminary findings from a pilot, proof of concept study need to be validated by well-designed studies.

Haacke et al (2017) evaluated the histopathological changes in parotid gland tissue of pSS patients treated with abatacept. In all 15 pSS patients included in the open-label Active Sjogren Abatacept Pilot (ASAP, 8 abatacept infusions) study parotid gland biopsies were taken before treatment and at 24 weeks of follow-up. Biopsies were analyzed for pSS-related histopathological features and placed in context of clinical responsiveness as assessed with ESSDAI. Abatacept treatment resulted in a decrease of germinal centers (GCs)/ mm² ($p = 0.173$). Number of GCs/mm² at baseline was associated with response in the glandular domain of ESSDAI (Spearman $p = 0.644$, $p = 0.009$). Abatacept treatment did not reduce focus score, lympho-epithelial lesions, area of lymphocytic infiltrate, amount of CD21+ networks of follicular dendritic cells, and numbers of CD3+ T-cells or CD20+ B- cells. Number of IgM plasma cells/mm² increased ($p = 0.041$), while numbers of IgA and IgG plasma cells/mm² were unaffected during abatacept treatment. The authors concluded that abatacept affected formation of GCs of pSS patients in parotid glands, which was dependent on co-stimulation of activated follicular-helper-T-cells. Herewith, local formation of (auto-reactive) memory B-cells was inhibited. These researchers stated that presence of GCs at baseline predicted responsiveness to abatacept in the ESSDAI glandular domain.

Verstappen et al (2017) examined the effect of abatacept (CTLA-4Ig), which limits T cell activation, on homeostasis of CD4+ T cell subsets and T cell-dependent B cell hyperactivity in patients with pSS. A total of 15 patients with pSS treated with abatacept were included. Circulating CD4+ T cell and B cell subsets were analyzed by flow cytometry at baseline, during the treatment course, and after treatment was completed. CD4+ effector T cell subsets and Treg cells were identified based on expression of CD45RA, CXCR3, CCR6, CCR4, CXCR5, programmed death 1, inducible co-stimulator (ICOS), and FoxP3. Serum levels of anti-SSA/anti-SSB and several T cell-related cytokines were measured. Expression of ICOS and interleukin-21 (IL-21) protein was examined in parotid gland tissue at baseline and after treatment. Changes in laboratory parameters and associations with systemic disease activity (ESSDAI) over time were analyzed using generalized estimating equations. Abatacept selectively reduced percentages and numbers of circulating follicular helper T (Tfh) cells and Treg cells. Other CD4+ effector T cell subsets were unaffected. Furthermore, expression

of the activation marker ICOS by circulating CD4+ T cells and expression of ICOS protein in parotid gland tissue declined. Reduced ICOS expression on circulating Tfh cells correlated significantly with lower ESSDAI scores during treatment. Serum levels of IL-21, CXCL13, anti-SSA, and anti-SSB decreased. Among circulating B cells, plasmablasts were decreased by treatment. After cessation of treatment, all parameters gradually returned to baseline. The authors concluded that abatacept treatment in patients with pSS reduced circulating Tfh cell numbers and expression of the activation marker ICOS on T cells. These investigators stated that lower numbers of activated circulating Tfh cells contributed to attenuated Tfh cell-dependent B cell hyperactivity and may underlie the efficacy of abatacept.

Thompson et al (2018) noted that interstitial lung disease (ILD) is a significant complication of SS associated with increased morbidity and mortality. The mainstay of treatment remains corticosteroid administration, with or without additional immunosuppressive therapies. Preliminary studies in SS have shown benefit in glandular and serologic parameters following treatment with the CTLA4 immunoglobulin fusion protein abatacept. Topical tacrolimus has been effective for ocular symptoms in SS, but systemic therapy has not been reported. These researchers described the first case, to their knowledge, of the successful use of a combination of systemic tacrolimus and abatacept in severe refractory SS and related ILD.

An UpToDate review on "Treatment of Sjogren's syndrome: Constitutional and non-sicca organ-based manifestations" (Baer and Vivino, 2019a) states that "Abatacept -- An open-label, pilot study of 11 patients has shown improvement in salivary gland biopsy and extraglandular manifestations, and a good safety profile. Another open-label study of 15 SS patients showed improvement in biomarkers but no change in tear flow or subjective symptoms".

Moreover, UpToDate reviews on "Overview of the management and prognosis of Sjogren's syndrome" (Baer and Vivino, 2019b), "Treatment of dry mouth and other non-ocular sicca symptoms in Sjogren's syndrome" (Baer and Sankar, 2019), and "Treatment of dry eye in Sjogren's syndrome: General principles and initial therapy (Baer and Akpek, 2019) do not mention abatacept as a therapeutic option.

Spondyloarthritis

De La Mata et al (2011) examined the effectiveness of available drugs in undifferentiated spondyloarthritis (u-SpA). Systematic review of studies retrieved from Medline (1961 to July 2009), Embase (1961 to July 2009), and Cochrane Library (up to July 2009) was carried out. A complementary hand-search was also performed. The selection criteria were as follows: (population) u-SpA patients; (intervention) non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), anti-tumor necrosis factor- α , anakinra, abatacept, bisphosphonates, or thalidomide; (outcome) pain, function, structural damage and quality of life; (study design) randomized controlled trials (RCTs), cohort studies, and case reports; (level of evidence) according to The Oxford Centre for Evidence-based Medicine (update 2009). An additional narrative review was performed to analyze the effects of drug therapies in patients with spondyloarthritis according new Assessment of Spondyloarthritis International Society criteria. The following 7 studies were included: 2 RCT, 1 cohort study, and 4 case reports, which included 117 patients with u-SpA (mostly young men). No evidence related to the effect of NSAIDs or DMARDs on u-SpA patients was found. Infliximab and etanercept showed some benefit regarding clinical outcomes, function, and quality of life. Two RCTs reported important benefit of infliximab and adalimumab also in patients with predominantly axial spondyloarthritis. Rifampicin plus doxycycline improved some clinical outcomes but ciprofloxacin had no benefit. Anecdotal positive evidence was reported with pamidronate. No serious adverse events were reported in the retrieved studies. The authors concluded that low-quality evidence suggested a benefit of tumor necrosis factor α blockers in u-SpA and good-quality evidence in predominantly axial spondyloarthritis. The use of antibiotics remained controversial. Moreover, the authors stated that high-quality trials are needed to definitively assess the effect of available drugs in these patients.

Lekpa et al (2012) evaluated the effectiveness of abatacept in patients with axial spondyloarthropathies who had failed TNF- α antagonist therapy. Consecutive patients fulfilling criteria for active axial spondyloarthritis, despite at least 2 previous TNF- α antagonists, were treated with abatacept (10 mg/kg) given on days 1, 15, and 29, then every 28 days until week 24. Clinical and laboratory outcome criteria

were assessed monthly for 6 months. A total of 7 patients were treated and followed, all women (median age of 39 years; median disease duration of 12 years), 5 with ankylosing spondylitis and 2 with undifferentiated spondyloarthropathy. After 6 months of abatacept therapy, no patient had an at least 50 % decrease in the BASDAI; a single patient had an at least 2 cm decrease in the BASDAI (-3.8 cm; -49.3 %). No significant changes were observed in pain or patient global assessment scores. Inflammatory back pain persisted in all 7 patients. When present, enthesitis improved in most patients. Improvements in spinal mobility measures occurred in 2 patients. There were no clinically significant adverse events. The authors concluded that a 6-month regimen of abatacept did not meaningfully improve disease activity, function, or other disease parameters in 7 patients with axial spondyloarthropathies. They noted that these preliminary results did not suggest a strong efficacy of abatacept in axial forms of spondyloarthropathies.

Systemic Sclerosis

Elhai et al (2013) evaluated the safety and effectiveness of tocilizumab and abatacept in systemic sclerosis (SSc)-polyarthritis or SSc-myopathy. A total of 20 patients with SSc with refractory polyarthritis and 7 with refractory myopathy from the EUSTAR (EULAR Scleroderma Trials and Research) network were included: 15 patients received tocilizumab, and 12 patients received abatacept. All patients with SSc-myopathy received abatacept. Clinical and biological assessments were made at the start of treatment and at the last infusion. After 5 months, tocilizumab induced a significant improvement in the 28-joint count Disease Activity Score and its components, with 10/15 patients achieving a European League Against Rheumatism (EULAR) good response. Treatment was stopped in 2 patients because of inefficacy. After 11 months' treatment of patients with abatacept, joint parameters improved significantly, with 6/11 patients fulfilling EULAR good-response criteria. Abatacept did not improve muscle outcome measures in SSc-myopathy. No significant change was seen for skin or lung fibrosis in the different groups. Both treatments were well-tolerated. The authors concluded that in this observational study, tocilizumab and abatacept appeared to be safe and effective on joints, in patients with refractory SSc. No trend for any change of fibrotic lesions was seen but this may relate to the exposure time and inclusion

criteria. Moreover, they stated that larger studies with longer follow-up are needed to further determine the safety and effectiveness of these drugs in SSc.

Systemic Vasculitis

In a systematic review, Silva-Fernandez and colleagues (2014) analyzed the current evidence on the therapeutic use of biological agents for the treatment of systemic vasculitis (SV). Medline, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials were searched up to the end of April 2013. Systematic reviews and meta-analysis, clinical trials, cohort studies, and case series with more than 3 patients were included. Independent article review and study quality assessment was done by 2 investigators with consensus resolution of discrepancies. Of 3,447 citations, abstracts, and hand-searched studies screened, 90 were included. Most of the studies included ANCA-associated vasculitis (AAV) patients and only a few included large vessel vasculitis (LVV) patients. Rituximab was the most used agent, having demonstrated effectiveness for remission induction in patients with AAV. A number of studies used different anti-TNF α agents with contrasting results. A few uncontrolled studies on the use of abatacept, alemtuzumab, mepolizumab, and tocilizumab were found. The authors concluded that current evidence on the use of biological therapies for SV is mainly based on uncontrolled, observational data. Rituximab is not inferior to cyclophosphamide for remission induction in AAV and might be superior in relapsing disease. Infliximab and adalimumab are effective as steroid-sparing agents. Etanercept is not effective to maintain remission in patients with granulomatosis with polyangiitis, and serious adverse events have been reported. For LVV, both infliximab and etanercept had a role as steroid-sparing agents, and tocilizumab might be effective also for remission induction in LVV.

Takayasu Arteritis

In a randomized, double-blind, multi-center trial, Langford and associates (2017b) compared the effectiveness of abatacept to that of placebo for the treatment of TAK. Patients with newly diagnosed or relapsing TAK were treated with abatacept 10 mg/kg intravenously on days 1, 15, and 29 and week 8, together with prednisone administered daily. At week 12,

patients in remission underwent a double-blinded randomization to continue to receive abatacept monthly or switch to placebo. Patients in both study arms received a standardized prednisone taper, reaching a dosage of 20 mg daily at week 12, with discontinuation of prednisone at week 28. All patients remained on their randomized assignment until meeting criteria for early termination or until 12 months after enrollment of the last patient. The primary end-point was duration of remission (relapse-free survival). A total of 34 eligible patients with TAK were enrolled and treated with prednisone and abatacept; of these, 26 reached the week 12 randomization and underwent a blinded randomization to receive either abatacept or placebo. The relapse-free survival rate at 12 months was 22 % for those receiving abatacept and 40 % for those receiving placebo ($p = 0.853$). Treatment with abatacept in patients with TAK enrolled in this study was not associated with a longer median duration of remission (median duration 5.5 months for abatacept versus 5.7 months for placebo). There was no difference in the frequency or severity of AEs, including infection, between the treatment arms. The authors concluded that in patients with TAK, the addition of abatacept to a treatment regimen with prednisone did not reduce the risk of relapse.

Furthermore, an UpToDate review on "Treatment of Takayasu arteritis" (Hunder, 2017b) does not mention abatacept as a therapeutic option.

Appendix

Appendix A: Examples of Clinical Reasons to Avoid Pharmacologic Treatment with Methotrexate, Hydroxychloroquine, or Leflunomide

1. Clinical diagnosis of alcohol use disorder, alcoholic liver disease or other chronic liver disease
2. Drug interaction
3. Risk of treatment-related toxicity
4. Pregnancy or currently planning pregnancy
5. Breastfeeding

6. Significant comorbidity prohibits use of systemic agents (e.g., liver or kidney disease, blood dyscrasias, uncontrolled hypertension)
7. History of intolerance or adverse event
8. Hypersensitivity

Appendix B: Risk Factors for Articular Juvenile Idiopathic Arthritis

1. Positive rheumatoid factor
2. Positive anti-cyclic citrullinated peptide antibodies
3. Pre-existing joint damage

Table: Brands of Targeted Immune Modulators and FDA-approved Indications (not an all-inclusive list):

Brand Name	Generic Name	FDA Labeled Indications
Actemra	tocilizumab	COVID-19 in hospitalized adults Cytokine release syndrome (CRS) Giant cell arteritis Juvenile idiopathic arthritis Rheumatoid arthritis Systemic juvenile idiopathic arthritis Systemic sclerosis-associated interstitial lung disease (SSc-ILD)
Arcalyst	rilonacept	Cryopyrin-associated periodic syndromes Deficiency of interleukin-1 receptor antagonist (DIRA) Recurrent pericarditis
Cimzia	certolizumab	Ankylosing spondylitis or axial spondyloarthritis Crohn's disease Plaque psoriasis Psoriatic arthritis Rheumatoid arthritis

Cosentyx	secukinumab	Ankylosing spondylitis or axial spondyloarthritis Enthesitis-related arthritis Plaque psoriasis Psoriatic arthritis
Enbrel	etanercept	Ankylosing spondylitis Juvenile idiopathic arthritis Plaque psoriasis Psoriatic arthritis Rheumatoid arthritis
Entyvio	vedolizumab	Crohn's disease Ulcerative colitis
Humira (for Humira biosimilars, see CPB 0655 - Adalimumab (..//600_699/0655.html))	adalimumab	Ankylosing spondylitis Crohn's disease Hidradenitis suppurativa Juvenile idiopathic arthritis Plaque psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis Uveitis
Ilaris	canakinumab	Adult-onset Still's disease Periodic fever syndromes Systemic juvenile idiopathic arthritis
Ilumya	tildekrizumab-asmn	Plaque psoriasis
Kevzara	sarilumab	Polymyalgia rheumatica Rheumatoid arthritis
Kineret	anakinra	Cryopyrin-associated periodic syndromes Deficiency of interleukin-1 receptor antagonist (DIRA) Rheumatoid arthritis

Olumiant	baricitinib	Alopecia areata COVID-19 in hospitalized adults Rheumatoid arthritis
Orencia	abatacept	Acute graft versus host disease Juvenile idiopathic arthritis Psoriatic arthritis Rheumatoid arthritis
Otezla	apremilast	Oral ulcers associated with Behcet's Disease Plaque psoriasis Psoriatic arthritis
Remicade (for Remicade biosimilars, see CPB 0341 - Infliximab (..../300_399/0341.html))	infliximab	Ankylosing spondylitis Crohn's disease Plaque psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis
Rinvoq	upadacitinib	Ankylosing spondylitis or axial spondyloarthritis Atopic dermatitis Crohn's disease Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis
Rituxan (for Rituxan biosimilars, see CPB 0314 - Rituximab (..../300_399/0314.html))	rituximab	Chronic lymphocytic leukemia Granulomatosis with polyangiitis Microscopic polyangiitis Pemphigus vulgaris Rheumatoid arthritis Various subtypes of non-Hodgkin's lymphoma
Siliq	brodalumab	Plaque psoriasis

Simponi	golimumab	Ankylosing spondylitis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis
Simponi Aria	golimumab intravenous	Ankylosing spondylitis Juvenile idiopathic arthritis Psoriatic arthritis Rheumatoid arthritis
Skyrizi	risankizumab- rzaa	Crohn's disease Plaque psoriasis Psoriatic arthritis
Stelara	ustekinumab	Crohn's disease Plaque psoriasis Psoriatic arthritis Ulcerative colitis
Taltz	ixekinumab	Ankylosing spondylitis or axial spondyloarthritis Plaque psoriasis Psoriatic arthritis
Tremfya	guselkumab	Plaque psoriasis Psoriatic arthritis
Tysabri and Tyruko	natalizumab	Crohn's disease Multiple sclerosis
Xeljanz	tofacitinib	Ankylosing Spondylitis Polyarticular Course Juvenile Idiopathic Arthritis Psoriatic arthritis Rheumatoid arthritis Ulcerative Colitis
Xeljanz XR	tofacitinib, extended release	Ankylosing Spondylitis Polyarticular Course Juvenile Idiopathic Arthritis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis

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