Newer Immunosuppressants for Rheumatologic Disease

Preoperative Considerations

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KEYWORDS

• Rheumatic diseases • Perioperative period • Biologic therapy
• Medication therapy management

KEY POINTS

- Many new targeted therapies are available for patients with rheumatic diseases.
- Knowledge of the mechanisms, risks, and pharmacokinetics of these agents is necessary for optimal perioperative management.
- Choosing how to manage these agents for each patient involves balancing infectious (and other) risks with the very real risk of disease flares.

INTRODUCTION

Preoperative stratification of risk factors and optimizing comorbidities can pose many challenges for anesthesiologists. Perioperative management of inflammatory rheumatic disease (IRD) requires further investigation due to lack of evidence and difficulties in conducting prospective trials in this context. IRDs affect soft tissues, muscles, joints, and bones and include rheumatoid arthritis (RA), psoriatic arthritis (PsA) ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and systemic lupus erythematosus (SLE).

With disease progression, joint replacement surgeries, including total hip arthroplasties (THA) and total knee arthroplasties (TKA), are often an inevitable course of treatment in patients with IRD and have been shown to be successful in treating and improving quality of life. Accordingly, over 30% of patients with rheumatic disease will require surgery within 30 years of diagnosis.[1] One key consideration in these patients is minimizing the risk of prosthetic joint infections (PJI) and delayed wound healing which are devastating complications that require long-term antibiotic therapy and eventually prosthetic joint removal. Inflammatory arthritis confers increased risk of

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infection following both THA and TKA.[2,3] PJIs have a mortality rate as high as 18% and therefore, prevention is of utmost importance.

This increased risk of complications is due to (1) the inflammatory nature of the disease, (2) associated cardiovascular comorbidities, and (3) the use of immunosuppressant medications. However, interruption in antirheumatic therapy has also been associated with increased risk of disease flare. Therefore, one of the biggest questions that arise for anesthesiologists, rheumatologists, and orthopedic surgeons is the perioperative management of antirheumatic medications.[4] Perioperative management of antirheumatic therapy is a careful balance between minimizing risk of PJI and delayed wound healing while also preventing disease flare. Although significant advancements in antirheumatic therapy have been made over the past few decades, many questions remain about the proper perioperative management of these patients.

Corticosteroids are widely used for a variety of diseases to suppress inflammation and regulate the body's immune system. However, steroids have significant long-term side effects. Due to concerns for its safety profile, nonsteroidal therapy began to garner attention. To minimize these effects, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, azathioprine, and sulfasalazine are used. They have been shown to be more effective but also have their own toxicities. More recently, better mechanistic understanding of disease processes led to the development of targeted immunotherapy such as small molecule modulators, monoclonal antibodies, and recombinant/fusion proteins. These agents are highly effective but carry their own risks as well.

This review will provide an overview of the variety of immunosuppressive therapies for IRD and perioperative recommendations based on recent evidence with emphasis some of the more novel medications. **Table 1** provides a list of drug classes and specific examples.

Traditional Agents

1. Corticosteroids

Table 1
Types of biologics

Class	Type of Molecule	Examples
CD20 antagonist	Chimeric antibody (30%–35% murine)	Rituximab
TNF-alpha inhibitor	Chimeric antibody (30%–35% murine)	Infliximab
	Chimeric antibody (<10% murine)	Certolizumab
	Human monoclonal antibody	Adalimumab
		Golimumab
	Fusion protein	Etanercept
IL-1 antagonist	Human monoclonal antibody	Canakinumab
	Fusion protein	Rilonacept
IL-2 antagonist	Chimeric antibody (<10% murine)	Daclizumab
IL-4 antagonist	Human monoclonal antibody	Dupilumab
IL-6 receptor antagonist	Chimeric antibody (<10% murine)	Tocilizumab
Immune checkpoint inhibitor	Human monoclonal antibody	Ipilimumab
		Nivolumab
	Chimeric antibody (<10% murine)	Pembrolizumab
BLyS inhibitor	Human monoclonal antibody	Belimumab
Costimulation inhibitor	Fusion protein	Abatacept

Corticosteroids have been a major component of immunosuppressive therapy for a variety of autoimmune and inflammatory diseases. However, their use is limited by significant side effects with chronic use including surgical site infections, impaired wound healing, hemodynamic instability secondary to steroid induced adrenal insufficiency, Cushing syndrome, and gastrointestinal (GI) bleeding from ulcers. Steroids have a dose dependent increase in postoperative infections and readmission with prednisone doses greater than 10 mg/d[5] Compared to biologics, glucocorticoids had a higher risk of adverse events (including hospitalized infections, PJI, and 30 day readmission).

Stress dose steroids are often administered perioperatively but their efficacy is unclear due to lack of evidence demonstrating hemodynamic instability and the unknown dose threshold that induces suppression of the hypothalamic–pituitary–adrenal axis. The American College of Rheumatology/American Association of Hip and Knee Surgeons (ACR/AAHKS) guidelines recommended that patients take their daily dose of steroids rather than receiving a stress dose on the day of surgery.[6] Preferably, steroids should be tapered to less than 20 mg before surgery. If unable to taper to less than 15 mg due to disease flare, physicians should take extra precautions to avoid increasing risk of infections.

2. Methotrexate

Methotrexate (MTX) was first introduced in the 1940s for chemotherapy before it became commonly used to treat RA and psoriasis in the 1950s. It is continually used for a variety of autoimmune and inflammatory diseases including RA, psoriasis, JIA, SLE, inflammatory bowel disease (IBD), vasculitis, and many other connective tissue disorders.[7] MTX inhibits purine and pyrimidine synthesis resulting in reduced T-cell proliferation. It has the best efficacy-to-toxicity ratio among the DMARDs and is generally well tolerated. The most common side effect is GI upset and rarely can cause bone marrow suppression, pulmonary injury, and hepatotoxicity. Among the DMARDs, the perioperative recommendations for MTX are best established. It has been shown not to increase risk of infections[8] and continuation decreases the risk of disease flares.[9] Therefore, the ACR/AHHKS guidelines recommend MTX to be continued perioperatively.[6]

3. Leflunomide

Leflunomide (LEF) is a nonbiologic DMARD that prevents lymphocyte proliferation by inhibiting dihydroorotate dehydrogenase (DHODH) necessary for pyrimidine synthesis.[10] It is also used to treat PsA, JIA, dermatomyositis, and SLE. There have been conflicting results about the infectious risk from perioperative use of this drug.[11,12] At this time, the ACR/AAHKS guidelines state that perioperative continuation of LEF is safe in patients without risk factors (such as history of recurrent infections or prior PJIs).[6]

Common side effects of LEF include nausea, diarrhea, and liver injury. LEF has also rarely been associated with pancytopenia, interstitial lung disease and pneumonitis. For this reason, it is contraindicated in patients with hepatic and pulmonary diseases. Liver enzymes, complete blood counts (CBC), and blood pressure should be monitored in patients on LEF therapy. Due to teratogenic effects, LEF is also contraindicated during pregnancy.

4. Mercaptopurine

6-Mercaptopurine (6-MP) is an antimetabolite that prevents proliferation of T lymphocytes by inhibiting intracellular purine synthesis. Nausea, abdominal pain, aphthous ulcers, and bone marrow suppression are common side effects of 6-MP. It

has also been shown to cause hepatotoxicity and rarely liver cancers (including hepatocellular carcinoma and hepatosplenic T-cell lymphoma). For this reason, CBC and liver enzymes should be monitored in patients on therapy.

Many studies have shown that perioperative continuation of 6-MP for patients with inflammatory bowel disease undergoing elective surgery does not increase morbidity or infectious complications.[13,14] According to ACR/AAHKS guidelines, 6-MP should be continued perioperatively for patients with severe IRD but, due to its toxicities, should be held 1 week before surgery for nonsevere IRD.[6]

5. Sulfasalazine

Sulfasalazine is a DMARD that is used to treat RA, JIA, and ulcerative colitis. Other off label uses include AS, Crohn's disease, and PsA. Sulfasalazine can cause nausea, vomiting, dyspepsia, and skin rashes. Rarely it can also cause pancytopenia, liver, and renal injury. Therefore, CBC, serum creatinine, and liver enzymes should be monitored in patients on sulfasalazine therapy. Unlike other DMARDs, it is not teratogenic. Perioperative continuation of sulfasalazine is not associated with increased risk of infections[15] and the ACR/AHHKS guidelines recommend perioperative continuation of sulfasalazine in patients with no risk factors.[6]

6. Hydroxychloroquine

Well-known as an antimalarial drug, hydroxychloroquine has been shown to have immunomodulatory properties and is now used to treat a variety of rheumatic diseases including RA and SLE. However, its mechanism as an immunosuppressant is not well understood. Hydroxychloroquine has low immunosuppressive potency compared with other DMARDs and due its favorable toxicity profile, it has been thought to be safe to continue perioperatively.[8,16] Therefore, the ACR/AHHKS guidelines recommend perioperative continuation of sulfasalazine in patients with no risk factors.[6]

New Oral Disease-Modifying Antirheumatic Drugs

1. Phosphodiesterase type 4 inhibition

Apremilast is a novel oral DMARD that is FDA approved for treating PsA, plaque psoriasis, and oral ulcers in Behcet's disease. It is a selective PDE4 inhibitor that works in the innate immune system by increasing cAMP and decreasing inflammatory mediators including IL-2, TNF-alpha, and interferon (IFN)-gamma. The most common side effects include GI (primarily nausea, diarrhea, and rarely weight loss). For this reason, the patients' weight should be monitored carefully during therapy.[17] Rarely, apremilast has been shown to be associated with psychiatric conditions such as depression and suicidal ideations. Apremilast is relatively well tolerated with high safety profile and low risk of infections.[18] ACR/AHHKS guidelines recommend perioperative continuation of apremilast with the exception of patients with a history of recurrent/severe infections or prior PJI.[6] In high-risk patients, it can be held 3 days before surgery based on its half-life of 6 to 9 hours.[4]

2. Janus kinase inhibitors

Tofacitinib is the first oral Janus kinase (JAK) inhibitor developed to treat RA. Tofacitinib preferentially inhibits JAK3/JAK1 and downstream production of inflammatory cytokines including IL-2 that are essential for lymphocyte function.[19] It is currently approved for treatment of RA, PsA, ulcerative colitis (UC), and polyarticular JIA. Tofacitinib has a black box warning against serious infections, malignancies, and lymphoma. Due to the risk of opportunistic infections (with cytomegalovirus [CMV],

Epstein-Barr virus [EBV], BK virus, tuberculosis [TB]) patients should be tested for active/latent TB before initiating treatment and monitored for TB routinely while receiving therapy. JAK inhibitors are also known to increase the risk of thromboembolic disease and therefore should be used with caution in patients with increased cardiovascular risk. Some of the more common side effects include infections (urinary and respiratory tract), pancytopenia, hepatotoxicity, and hyperlipidemia. Blood counts, lipid panels, and liver enzymes should be monitored while on therapy. Concurrent use with strong immunosuppressants and biologic agents are not recommended. Patients should not receive live vaccinations before and during therapy as well. Tofacitinib was originally recommended to be held a week before surgery but, due to rapid offset of clinical effect, current guidelines recommend holding JAK inhibitors 3 days before surgery.[6]

Biologics/recombinant Proteins

1. Emapalumab

Macrophage activation syndrome-hemophagocytic lymphohistiocytosis (MAS-HLH) is a life-threatening dysregulation of the immune system seen in patients with rheumatic disease due to uncontrolled activation and exaggerated responses of cytotoxic T cells producing massive amounts of interferon gamma. It is most frequently associated with systemic JIA and adult onset Still disease. Emapalumab is a monoclonal antibody that inhibits interferon gamma and the first targeted therapy that was approved for the treatment of HLH in rheumatic disease. Clinically presents with fever, hepatosplenomegaly, cytopenia, liver dysfunction, coagulation abnormalities, and eventually progresses to multiorgan failure. In the past, MAS has been treated with high-dose glucocorticoids and cyclosporin. Emapalumab is extremely effective for treating MAS, especially in patients who fail standard therapy.[20,21] The 2 most common side effects are infections and hypertension. Infusion-related reactions and fever are other frequent side effects that have been reported as well.[22]

2. Immune checkpoint inhibitors

Immune checkpoints are T-cell surface proteins involved in downregulating T-cell activity and regulating the immune system. Examples include cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed death protein 1 (PD1), and PD1 ligand (PDL1). Immune checkpoints may be overexpressed on the surface of tumor cells to downregulate and evade the immune system.[23] Targeted therapy against these immune checkpoints has shown great promise in treating cancer. Ipilimumab is a CTLA4 inhibitor that is administered every 3 weeks for a total of 4 doses. Therapy with PD-1/PDL1 inhibitors can vary between 1 week and every 2 to 3 weeks.

Nivolumab is a monoclonal antibody against PD1 that is FDA approved for a variety of cancers including melanoma, esophageal cancer, urethral cancer, and non-small cell lung cancer. Pembrolizumab is another monoclonal antibody against PD1 that is indicated for various cancers including melanoma, non-small cell lung cancer, and advanced breast and uterine cancers.

However, immune checkpoint inhibitors are also associated with significant side effects. The incidence of immune-related side effects is greater with anti-CTLA4 therapy compared with anti-PD1 therapy. The GI tract, skin, and endocrine system are affected most but less commonly these agents can also affect the pulmonary, cardiac, and neurologic system.[24] The GI system is the most affected and can present with diarrhea, enterocolitis, and hepatitis.[25] Immune-related endocrine dysfunction can present with pituitary dysfunction, adrenal insufficiency, and hypothyroidism. Therefore,

anesthesiologists should check electrolyte levels and assess thyroid and adrenal function.[26] Immune-related cardiac toxicity is rare with an incidence of less than 1%. Myocarditis is the most common cardiac complication but heart failure, cardiomyopathy, and conduction abnormalities may also be seen.[27,28] Anesthesiologists should make sure to assess for cardiac symptoms and review appropriate testing (such as electrocardiography, echocardiography, and possibly biomarkers) before surgery. Pneumonitis is the most common pulmonary complication and therefore respiratory symptoms should be assessed preoperatively to evaluate the need for steroid therapy.[29,30]

3. TNF alpha inhibitors

TNF alpha inhibitors (infliximab, adalimumab, certolizumab, and golimumab) are monoclonal antibodies that decrease inflammation by binding and inhibiting TNF alpha, a proinflammatory molecule involved in activating host cell responses leading to neutrophil recruitment and initiating inflammatory responses. TNF alpha inhibitors are used to treat a variety of inflammatory and autoimmune diseases including psoriasis, RA, PsA, and IBD.[31] Etanercept is a recombinant fusion protein combining the TNF receptor with the Fc portion of the IgG1 antibody. Like the previously mentioned antibodies, it also inhibits the activity of TNF alpha but does so by acting as a "decoy" receptor, binding TNF alpha and preventing its biological activity.

Infliximab was the first anti-TNF antibody that was used to treat chronic inflammatory and autoimmune diseases. The side effects of infliximab are well known, the most common being infection. Other adverse reactions include hypersensitivity reactions, infections (hepatitis B virus [HBV], opportunistic infection, and TB reactivation), malignancies, lupus like syndrome, pancytopenia, demyelinating disorders, congestive heart failure, and hepatotoxicity.[32] There are contradictory results regarding the association between perioperative continuation of tumor necrosis factor (TNF) alpha inhibitors with postoperative complications. Results range from increased infectious risk to decreased risk and improved wound healing.

Guidelines vary for the perioperative management for TNF alpha inhibitors and treatment should be individualized. The optimal individualized strategy is based on a combination of anti-TNF half-life and bioavailability. In general, the effects of anti-TNF alpha inhibitors disappear approximately after 4 to 5 half-lives and the timing of preoperative interruption of therapy depends on each medication's half-life and dosing regimen.[33,34] Witrand and colleagues[35] demonstrated that discontinuing treatment 5 half-lives before surgery does not increase the risk of complications. Postoperative complications increased by 13% with infliximab if given within 2 to 5 half-lives before orthopedic surgeries. Therefore, majority guidelines recommend stopping infliximab 4 to 5 weeks before elective surgery. The half-life of infliximab is 9.5 days, adalimumab 10 to 20 days, etanercept 3.5 to 5.5 days, golimumab 14 days, and certolizumab 14 days.[36] Based on these data, one group recommends that infliximab should be discontinued 21 to 39 days before surgery.[34] Because of its long half-life, this is equivalent to less than 1 dose of infliximab that should be held. Etanercept should be held 7 to 14 days, adalimumab 56 days, and golimumab 4 weeks before surgery.

Similarly, the ACR/AHHKS guidelines recommend scheduling surgery after the end of the dosing cycle to ensure that there is minimal drug left in the system.[6] For infliximab, hold medication 5 weeks before surgery if the patient is taking it every 4 weeks. For adalimumab, hold 3 weeks prior and for etanercept, hold 2 weeks before surgery.

To prevent a disease flare postoperatively, therapy should be resumed as soon as it is deemed safe from the surgical standpoint. The process of wound healing is often completed 2 weeks postoperatively and some use this as a general guideline as to

when to restart therapy. However, for specific medications a combination of the half-life and mechanism of action can be used to provide guidance. In general, infliximab is recommended to be restarted 3 to 4 weeks, etanercept 12 days, and adalimumab 56 days postoperatively.[34]

4. IL-1 inhibitors

Interleukin-1 (IL-1) and its receptor are strong inflammatory activators that can induce fever and acute phase reactions by stimulating production of IL-6 at higher doses. For this reason, IL-1 receptor antagonists are used to treat diseases mediated by excessive IL-1 such as hereditary autoinflammatory disease, cryopyrin associated periodic syndromes (CAS), and monogenic period fever syndrome that often present with recurrent febrile episodes. Rilonacept is a fusion protein incorporating the IL-1 receptor bound to the Fc region of human IgG1. This binds to IL-1, preventing its biologic effects. It is the first and only FDA approved medication for recurrent pericarditis and CAS. In addition to immunosuppression and risk of infections, other common side effects include injection reactions, upper respiratory tract infections, and joint and muscle aches.[37]

IL-1 is also a major cartilage destructive cytokine. Anakinara, which is a recombinant IL-1 receptor antagonist, has been used to decrease cartilage destruction in RA. Other off label use of anakinra includes idiopathic juvenile arthritis and other autoimmune arthritic diseases (adult onset still disease and macrophage activation syndrome). Common side effects of anakinra include local skin reactions, GI upset, headache, arthralgias, and increased risk of infections. More severe side effects include TB reactivation, neutropenia, and hypersensitivity reactions.[38] Therefore, blood counts should be monitored regularly while on therapy. Anakinara is taken daily and has a half-life of 4 to 6 hours. According to ACR/AHHKS guidelines, anakinra should be held 2 days before surgery.

5. IL-6 inhibitors

IL-6 is a proinflammatory cytokine released in response to infection and injuries. It is also a key mediator of chronic inflammation. IL-6 is highly expressed during the active phases of RA and has been shown to induce osteoclast differentiation, explaining its destructive effects on cartilage.[39,40] Tocilizumab is a human monoclonal antibody against the IL-6 receptor.[41] It has been shown to successfully treat a variety of inflammatory diseases including COVID-19 and cancer patients with cytokine release syndrome.[42,43] As other biologics, the ACR/AHHKS guidelines recommend scheduling surgery the week after the end of the dosing cycle: Hold tocilizumab 2 weeks before surgery in patients who take it subcutaneously every week and hold it 5 weeks before surgery in patients who receive tocilizumab therapy intravenously every 4 weeks. Side effects of tocilizumab include bowel perforation,[44] neutropenia/thrombocytopenia,[45] hepatotoxicity,[46] hypersensitivity reactions,[47] and reactivation of latent TB and opportunistic infections.[48]

6. CD-20 inhibitors

Rituximab (RTX) is a monoclonal antibody against CD20 on B lymphocytes. B lymphocytes play a large role in the pathogenesis of a variety of autoimmune diseases such as RA by secreting proinflammatory cytokines, activating T lymphocytes, and acting as antigen-presenting cells (APCs).[34] CD20 is expressed by 95% of B lymphocytes in non-Hodgkin's lymphoma and was first monoclonal antibody that was approved for treating that disease. It is now used for patients with RA who are intolerant or had inadequate response to anti-TNF therapy.[49] RTX is FDA approved for

treating hematologic cancers (including non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, B-cell acute lymphocytic leukemia, and chronic lymphocytic leukemia) and a variety of autoimmune diseases (including RA, SLE, idiopathic thrombocytopenic purpura, vasculitis and chronic autoinflammatory polyneuropathy).[50] There is growing evidence that it could be effective in treating vasculitis and connective tissue diseases.[51]

Hypogammaglobulinemia is a well-known side effect of RTX therapy, and clinical trials have demonstrated that the rate of serious infections increases with RTX therapy.[52,53] However, there is little evidence about the risk of postoperative infections when continuing RTX therapy as the effects of RTX therapy can last up to 1 year after discontinuing treatment.[51] However, the risk of postoperative complications including surgical site infection (SSI) following orthopedic surgery in patients receiving rituximab has been shown to be similar to those receiving anti-TNF therapy.[15]

For IRD patients undergoing elective orthopedic surgeries, surgery should be scheduled after the end of the dosing interval; for instance, surgery should be scheduled on the fifth month for patients taking RTX every 4 months. Therapy should be resumed 14 days following surgery at which point wound healing has been completed. For severe SLE, surgery should be scheduled in the last month of the dosing cycle; for instance, if the patient is taking RTX every 4 months, then surgery should be scheduled in the fourth month to avoid skipping doses.

7. Alpha4beta7 integrin antibodies

Vedolizumab is an antibody against alpha4beta7 integrin that is currently FDA approved for the treatment for UC and Crohn's disease. Its efficacy in treating IBD is due to better safety profile and gut selectivity. Although biologic therapy has played a role in controlling the disease process, surgical intervention continues to be a part of the treatment plan for a majority of patients with IBD. Perioperative management of vedolizumab is not well established, and there are conflicting studies regarding the association of perioperative continuation of vedolizumab and postoperative infections.[54,55] It has been difficult to study vedolizumab's association with postoperative infections in patients with Crohn's disease because the majority of patients are already on multiple therapies, making it difficult to isolate the effects of vedolizumab from other agents. Common side effects include nasopharyngitis, headaches, arthralgias, nausea, and fatigue. Vedolizumab has been associated with more severe side effects such as infusion-related reactions, hypersensitivity reactions, infections, rarely progressive multifocal leukoencephalopathy (PML), and hepatotoxicity. As other with biologics, the ACR/AAHKS guidelines recommend elective surgeries to be scheduled at the end of the dosing cycle and restarted 14 days after surgery.[6]

8. B-cell activating factor

Belimumab is the first targeted therapy and only biologic agent that is FDA approved for the treatment of SLE and lupus nephritis. It is a human monoclonal antibody against B lymphocyte stimulator (BLyS) and mostly used as adjunct therapy for patients with SLE who are already receiving standard therapy. BlyS is essential for B-cell maturation and survival. Overexpression of BlyS can cause production of autoreactive B lymphocytes that can lead to variety of autoimmune diseases including SLE. Therefore, targeted therapy against BlyS such as belimumab can be used to control the disease process in autoimmune disorders.[56]

Side effects of belimumab include infections, infusion reactions, hypersensitivity reactions, headache, nausea, and fatigue. Psychiatric complications including suicidal tendency, PML, and malignancies have also been reported. Belimumab is generally

well tolerated and as other biologics, recommended to undergo surgery at the end of the dosing cycle. ACR/AHHKS guidelines recommend continuing belimumab perioperatively for severe SLE in patients taking it subcutaneously weekly and taking it on the fourth week for those taking it intravenously every month. For nonsevere SLE, surgery should be scheduled the week after the end of the dosing cycle.[6] For instance, surgery should be scheduled on the fifth week following the last dose for those taking it every month.

9. Costimulation blockade

Abatacept (CTLA4-Ig) is a dimeric fusion protein that targets the interaction between T lymphocytes (CD28) and receptors (CD80/CD86) on APCs to modulate the costimulatory signal required for T-cell activation involved in joint swelling and damage. It is currently approved for patients with moderate-severe RA refractory to DMARDs and TNF-alpha inhibitors.[57] It is also used for treating JIA, PsA, and prophylaxis for graft-versus-host disease. One study by Nishida and colleagues[58] found no increase in SSI or delayed wound healing when abatacept was discontinued an average of 16 days before surgery (ranging between 8 and 21 days before the surgery depending on the patients' condition). There was also no difference in adverse outcomes when intravenous abatacept therapy was held 2 weeks before surgery versus 1 month (1 dosing interval) before surgery.[59] Therapy is recommended to be resumed a week after the process of wound healing is complete (approximately 3 weeks postoperatively).

The half-life of abatacept is 14 days and recommended to be held 2 to 3 weeks before surgery to prevent risk of flare. Abatacept can be administered intravenously every month or subcutaneously every week. The ACR/AHHKS guidelines recommend scheduling surgery on the fifth week following last dose (for monthly IV dosing) or the 2nd week following the last dose (for weekly subcutaneous dosing).

SUMMARY

Therapeutic options for patients with IRDs have greatly expanded in recent years. In addition to traditional medications like corticosteroids and the early DMARDs, today's armamentarium includes small-molecule immune modulators, recombinant fusion proteins, and monoclonal antibodies. Although very effective, these agents carry significant risks that affect perioperative care. Although there are published guidelines for the perioperative management of most of these agents, an individualized approach to each patient, balancing known risks and benefits, remains the most prudent course.

CLINICS CARE POINTS

- The optimal perioperative management of therapies for IRDs is a challenge for clinicians. Joint replacement surgeries are an inevitable course of treatment with disease progression and have been shown to be successful in treating and improving quality of life. However, patients with IRD are already at increased risk for serious postoperative complications (especially prosthetic joint infections and delayed wound healing) which have a high mortality rate in that population. Perioperative management of antirheumatic therapy requires careful balance between the risk of infections and the risk of prompting disease flares.
- Because of their extensive effects on various organ systems, corticosteroid use has decreased. Because of risk of adrenal suppression from exogenous steroid administration, perioperative stress dose steroids have been administered but there continues to be conflicting data regarding the dose and efficacy of giving supraphysiologic doses of steroids.

- The introduction of DMARDs including methotrexate, sulfasalazine, mercaptopurine, hydroxychloroquine leflunomide, and aprelimast revolutionized the treatment of rheumatic disease. These agents successfully delay disease progression while avoiding the side effects resulting from steroids. Generally, these steroid-sparing DMARDs are safe and recommended to continue throughout the perioperative period to avoid disease flares. JAK inhibitors are recommended to be held 3 days before surgery.
- As knowledge of these diseases' pathophysiology improved, direct targeted immunotherapy against specific parts of the inflammatory pathways such as small molecule modulators, monoclonal antibodies, and recombinant/fusion proteins were developed. Biologics are recommended to be held preoperatively and elective surgeries are recommended to be scheduled the week after the end of the last dosing cycle.

DISCLOSURE

The authors have no financial relationships to disclose.

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