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Advances in the Medical Treatment of Rheumatoid Arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory arthritis that affects nearly 1% of the world's adults. It is characterized by symmetric polyarticular inflammation of the synovium, typically of the small joints of the hands (MCP and PIP), wrists and feet. This inflammation results in pain and stiffness, and can lead to progressive joint damage resulting in deformities and loss of function. Associated organ damage also contributes to severe disability. Additionally, chronic inflammation secondary to RA can lead to an increased risk of cardiovascular disease and changes in bone metabolism.

Over the past two decades, the treatment of RA has been revolutionized by advances in the understanding of its pathologic mechanisms and the development of drugs which target them. These newer medications have shown great promise at improving disease outcomes, but they come with notable side effects which can pose long-term treatment challenges and difficulties in the perioperative arena. In this review, the major manifestations of RA and the current medical options for management are discussed. Complications from treatment are then reviewed and special consideration is given to perioperative medication recommendations.

ARTICULAR AND SYSTEMIC EFFECTS OF RA

Articular Manifestations

Inflammation and subsequent destruction of synovial joints is the hallmark of RA. Why the immune system is lured to attack and destroy still remains unknown, but great strides have been made in understanding how. Inflammation of the synovial tissue involves interactions between macrophages, T and B lymphocytes, synovial fibroblasts, and other cells of the inflamed synovium such as mast cells, dendritic cells and plasma cells. Neutrophils are rare in RA synovial tissue but abundant in RA synovial fluid. These cell-cell interactions occur both through direct cell-cell contact, as well as through the effects of secreted mediators. Proinflammatory cytokines, such as TNF α , IL-1 and IL-6, orchestrate synovial inflammation and stimulate cartilage degradation. This occurs through formation of a distinct tissue

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termed synovial pannus which invades cartilage with the assistance of proteolytic enzymes. Concurrently osteoclasts, which can form within the pannus through fusion of monocytic precursors, invade bone and cause periarticular erosions.

RA can involve most synovial joints, but rarely the DIPs or the thoracic, lumbar and sacral spine. The most commonly affected joints include the MCP and PIP joints of the hands, wrists and MTP joints of the feet. Joint destruction begins early in the disease with erosive changes often seen after only six months. The clinical exam can disclose synovial thickening and swelling, indicators of joint inflammation. At the time of presentation, nearly 70% of radiographs can be normal, but MRI and ultrasound with power Doppler have higher sensitivity to detect smaller erosions and synovial inflammation, and may reveal changes even when X-rays are normal⁴⁷. If RA is left untreated, progression to joint destruction, subluxation and severe disability are the likely outcomes.

Inflammation of tendon sheaths also contributes to RA pathology. Tenosynovitis of the flexor tendons can lead to trigger finger, and weakening of the extensor tendons of the hands from chronic inflammation can lead to tendon ruptures. Damage to supporting and tracking structures associated with tendons of the hand contribute to the formation of boutonniere and swan-neck deformities. Carpal tunnel syndrome secondary to median nerve compression by surrounding inflammation is also a common complication in RA patients.

Bone Manifestations

The bones of RA patients are affected in both a local and systemic manner. At a local level, factors that stimulate osteoclasts resulting in increased bone resorption are released from inflammatory and fibroblastic pannus cells¹⁶. Additionally, inflammatory cytokines prevent a compensatory increase in the rate of periarticular bone formation, resulting in net bone loss. This inhibition of osteoblastic activity is via a combination of impaired mineralization and impaired osteoblast differentiation⁴⁸. These processes combine to result in both periarticular osteopenia, one of the first radiographic signs of RA, and periarticular erosions, the hallmark of RA joint destruction⁴⁷. The use of disease modifying agents to induce clinical remission allows for restoration of normal function of osteoclasts and osteoblasts and may result in repair of erosive damage¹⁸.

Bony changes in RA patients are not only seen in a periarticular distribution. RA is a known risk factor for osteoporosis, with up to 30% of patients affected by some estimates⁴¹. Most studies agree that, unlike postmenopausal osteoporosis, the risk of osteoporosis in RA patients is greater at the femoral neck than in the spine, but both areas can be involved. Disease duration and severity, sex, body mass and the use of corticosteroids all influence the risk of osteoporosis in RA patients^{10,41}.

An additional consideration is that many RA patients are on bisphosphonate therapy for osteoporosis or prevention of glucocorticoid-mediated bone loss. Research into the impact of bisphosphonate use in patients undergoing surgical procedures is ongoing. Osteonecrosis of the jaw in patients on bisphosphonates undergoing dental surgery has been a specific concern, but the consequences of manipulation of the peripheral skeleton in patients on these medications are still incompletely understood. Most research into this topic is in animal systems, and there are suggestions that while bone healing is not prevented, there are differences in bone quality after bisphosphonate exposure²⁷.

Airway Manifestations

The presence of airway disease in RA is estimated to affect 20–30% of patients. Manifestations can include cricoarytenoid arthritis, pulmonary fibrosis and small airway disease, typically seen as bronchiolitis obliterans on histopathology, with obstructive

abnormalities on lung function testing^{8,19}. Lung disease is more frequent in RA patients who are male, seropositive, smoke, and have longstanding disease¹⁹. Some types of RA-associated lung disease are steroid responsive, but some patients have a progressive course leading to end-stage fibrosis and death³⁰. In addition to lung disease secondary to RA, patients are also at risk for pulmonary toxicities from RA-related medications, including methotrexate, leflunomide and even anti-TNF medications¹⁹.

Cardiovascular Manifestations

RA patients have a 40% increased risk of mortality as compared to the general population after 20 years of disease. This increased risk of mortality is primarily attributed to an increased incidence of cardiovascular disease³⁷. A recent cohort study has suggested that the risk of cardiovascular events in RA patients is 2-fold higher than the general population, equivalent to the risk of patients with diabetes³⁴. The propensity for vascular changes is found even in newly diagnosed patients, indicating that common mechanisms may exist linking synovitis resulting in joint destruction with endothelial dysfunction resulting in atherosclerosis².

The risk of cardiovascular disease and death increases with more severe disease and elevated inflammatory markers^{24,37}. Despite improved treatments for the symptoms of RA, the mortality risk has not improved over the past two decades. Whether this continued risk of death reflects an inability to control cardiovascular risk factors with immunomodulatory treatment or a lack of long-term follow up in patients treated with newer medications remains to be determined. Additionally, the optimal management of traditional cardiovascular risk factors, such as elevated cholesterol, has not been determined for RA patients.

PHARMACEUTICAL OPTIONS FOR THE TREATMENT OF RA

DMARDs

Disease Modifying Anti-Rheumatic Drugs (DMARDs) became the mainstay of RA treatment in the 1970s. As a group, they have been shown to decrease inflammation and slow radiographic progression, but the degree to which this is accomplished is variable. The timing of DMARD initiation has been debated, but current consensus suggests that the earlier treatment can be initiated, the better the overall outcome for clinical improvement and prevention of erosive disease⁴⁶. The initial 15 months of RA are critical for initiation and escalation of DMARD therapy, in order to achieve acceptable outcomes long-term⁵⁰. A major difficulty in treating patients with RA is that it is currently impossible to predict which patients will respond to which medication regimen. Current research is ongoing to develop patient-specific disease signatures via genetic and proteomic approaches; however, the practical application of such advances has not been achieved. Thus, practice guidelines typically recommend starting with conventional DMARD treatment before addition or substitution of biologic DMARD medications. Importantly, the use of DMARDs in combination rather than monotherapy is more effective in achieving improved clinical outcomes as well as slowing radiographic progression²³. Conventional DMARDs can be combined with each other and/or with biologic DMARDs. Each DMARD has its own unique toxicities and required monitoring, which is summarized in Table 1.

The mainstay of DMARD therapy is methotrexate, which is administered weekly, either orally or subcutaneously. Its use began for RA in the 1970s, and it has shown sustained benefits for at least 50% of RA patients who receive it. Known as an antagonist of folic acid metabolism, its effects in inflammatory diseases may actually be secondary to the induction of adenosine release and the inhibition of polyamines⁵. Typically, it is well-tolerated and most GI side effects can be mitigated by subcutaneous administration if needed. Folic acid is

co-administered to avoid toxicities secondary to inhibition of rapid cell turnover. Monitoring for liver toxicity is advised, but unless a patient has other risk factors for liver damage (hepatitis B or C infection, alcohol consumption), serious liver damage from methotrexate is rare. The use of methotrexate has been shown to slow radiographic progression and improve clinical outcomes of RA patients. DMARD monotherapy with methotrexate is sufficient for about 1/3 of RA patients; however, as mentioned above and below, its effect is more pronounced when used either in combination therapy with other DMARDs or in conjunction with a biologic agent^{14,23,36}

Leflunomide is a DMARD that acts specifically on lymphocytes by blocking pyrimidine synthesis. As a monotherapy, it generates similar improvements in clinical measures and radiographic scores as methotrexate^{36,43}. Often, it is used in the place of methotrexate in combination with other DMARDs or biologic DMARDs when side effects of methotrexate limit its use. As with methotrexate, pre-existing liver disease, alcohol abuse, pregnancy (or inadequate contraception) or active infection are contraindications to the use of leflunomide. Unlike methotrexate, leflunomide may be used in patients with mild-moderate renal insufficiency. A unique property of leflunomide is its prolonged half life secondary to binding of plasma proteins and enterohepatic circulation. Thus, an elimination protocol using cholestyramine is often needed when circumstances warrant rapid drug elimination such as during serious infections or pregnancy.

Hydroxychloroquine (HCQ) is a mild DMARD that is well tolerated and has minimal side effects. It has been shown to be effective in improving joint pain and function, but has not been shown to slow radiographic damage³⁶. Thus, the use of HCQ is recommended in conjunction with other DMARDs or for very mild RA that does not demonstrate ongoing joint damage. HCQ may protect RA patients from the subsequent development of diabetes, and it has been noted to have antithrombotic properties^{39,49}. Additionally, HCQ favorably alters lipid profiles, which may be of use in RA patients in view of their increased risk of cardiovascular disease⁴⁵. The primary toxicity of this medication is ophthalmologic, secondary to deposition of pigment in the retina, and routine monitoring by an ophthalmologist is required to detect this rare complication before permanent damage occurs. The dose of HCQ should never exceed 6.5 mg/kg/day to best avoid retinal toxicity.

Sulfasalazine is another, older DMARD that also has proven benefit for RA patients with relatively low toxicity. Similar to methotrexate, it enhances adenosine signaling and may also inhibit arachadonic acid pathways. Placebo-controlled studies have shown improvement in pain and function within four weeks of treatment with sulfasalazine. Additionally, sulfasalazine has been shown to slow radiographic progression after 1–3 years of therapy^{17,36}. However, it is generally considered a less potent DMARD and is typically used as part of a combination regimen. Gastrointestinal distress is the primary side effect of sulfasalazine, although allergic reactions and rashes may preclude its use. Leukopenia, which can be severe, occurs rarely during the first year of sulfasalazine treatment.

Other medications such as azathioprine, minocycline, doxycycline and cyclosporine have all been shown to have beneficial effects on disease activity in RA, but are typically used as adjunctive or substitute medications when the other DMARDs cannot be used secondary to adverse reactions. Injectable gold salts are an older form of treatment that can slow radiographic progression even without a full clinical response³⁶. However, with the advent of more reliable, less toxic medications, injectable gold has almost disappeared as an RA DMARD..

Biologic DMARDs

The availability of medications targeted toward specific abnormalities of the immune system, the so-called biologic DMARDs, has revolutionized the treatment of RA. This expanding collection of drugs targets molecules which have been shown to play important roles in the pathology of RA. Because of their cost and side effect profile, the use of biologic DMARDs is typically recommended after patients have failed the use of single or combination conventional DMARD therapy. However, in patients who present with highly aggressive, erosive disease, they can be considered as a component of first line therapy. Typically, biologic DMARDs are not used in combination with each other, but trials are ongoing to evaluate the risks and benefits of combination therapy between different biologic DMARD classes.

The initial choice of a biologic DMARD is typically a tumor necrosis factor (TNF) blocking agent, which includes infliximab, adalimumab, etanercept, and the newer golimumab and certolizumab. These agents have varied effects on a molecular level including binding soluble TNF α and induction of apoptosis of TNF α expressing cells. Each of these drugs has a distinct dosing schedule or mode of administration. However, all appear to have similar benefits in RA⁴². They work more rapidly than non-biologic DMARDs with responses often seen within 4–8 weeks, occasionally earlier. These medications are effective as monotherapy, but have significantly more benefit on clinical response and prevention of radiographic progression if used in conjunction with a DMARD such as methotrexate⁴. However, the combination of anti-TNF therapy and methotrexate is not more effective for the clinical manifestations of RA than a combination of conventional DMARDs (MTX+SSZ+HCQ)²³. Prolonged follow-up to compare effectiveness at a structural level as monitored by serial radiographs is ongoing. Despite the success of anti-TNF medications, up to 30% of patients with RA may not have a clinical response to anti-TNF therapy¹⁵. However, these medications have been shown to slow and/or inhibit radiographic progression in RA patients, even without other evidence of clinical improvement^{14,42}. Some patients benefit from switching from one anti-TNF medication to another, but failure of multiple TNF inhibitors to improve symptoms often leads to the use of other biologic DMARD medications⁴².

The evidence for the role of B cells in the pathogenesis of RA is increasing rapidly. The recruitment of B cells to inflamed synovium and the production of inflammatory cytokines that stimulate osteoclasts suggest an important role for this cell type in the etiology of RA²⁶. Rituximab is a chimeric anti-CD20 monoclonal antibody which depletes immature and mature B cells, but not plasma cells, which lack CD20 expression. It is approved for moderate-to-severe RA in patients who do not have adequate response to conventional DMARDs and anti-TNF medications¹⁴. A recent randomized, placebo-controlled trial of rituximab showed that when used in conjunction with methotrexate, rituximab slows radiographic progression after a year of treatment²⁰. A sustained response appears possible with intermittent courses of treatment that consist of two intravenous infusions given two weeks apart, and repeated every six months before the return of symptoms²⁸. Serious infusion reactions can occur, that are often avoided by including intravenous methylprednisolone with the pre-infusion medications.

Abatacept is a fusion protein of Cytotoxic T lymphocyte-associated Antigen 4 (CTLA-4) and the Fc portion of IgG1. It interferes with the interaction of CD80/CD86 molecules on antigen-presenting cells with their receptor CD28, a molecule on the T cell surface that normally senses the “second signal” required for T cell activation. This results in decreased T-cell activation and ultimately decreased joint inflammation. It is currently recommended for treatment of RA after a trial of conventional DMARD therapy or an anti-TNF agent has failed to induce acceptable disease improvement¹⁴. Although the onset of efficacy is slower

than some of the other biologic medications, treatment with abatacept provides persistent improvement in disease activity and radiographic progression.^{15,22} Additionally, unlike other biologic DMARDs, some research suggests that abatacept may not increase serious infection risk over that seen with nonbiologic DMARDs, which may make it a more appealing option in patients more prone to infectious complications⁴⁰.

Anakinra, an IL-1 receptor antagonist has been approved as a second-line treatment for RA after failure of another biologic DMARD, typically an anti-TNF medication. In Europe, its use is recommended in conjunction with methotrexate¹⁴. Daily injections have been shown to improve patient function and radiographic progression; however, this effect is less than the improvements seen with anti-TNF therapy²⁹. Anakinra has at most a limited role in the treatment of RA, although it has important benefits in rare systemic febrile inflammatory syndromes such as pediatric and adult Still's disease (for which it is not currently FDA-approved).

Tocilizumab is a recently approved biologic therapy for moderate to severe RA. It is a recombinant humanized monoclonal antibody that binds to the IL-6 receptor. IL-6 is a proinflammatory cytokine which is increased in the serum of RA patients. Monthly infusions of tocilizumab improve function and quality of life, and slow radiographic progression in patients who have failed management with traditional DMARDs or anti-TNF therapy^{11,33}. This effect is greater when it is used in conjunction with methotrexate³³. Its unique mechanism of action is associated with an increased risk of elevated liver enzymes and a reversible elevation in total cholesterol and triglycerides, thus appropriate selection of patients is important for this medication³³. Transient neutropenia and thrombocytopenia can be seen in 1–3% of patients post-infusion and intestinal perforations have also been noted³³.

COMPLICATIONS OF MEDICAL TREATMENT OF RA

RA itself confers an elevated risk of infection, and DMARD and biologic therapies suppress the immune system through various targets, also increasing this risk³¹. Bacterial infections, particularly pneumonia and soft-tissue infections, are increased with the use of methotrexate, and this is increased 2–4-fold with the addition of an anti-TNF medication⁷. Similar infectious risks have been found with other biologic DMARDs as well^{11,15}. A significant risk of reactivation of tuberculosis has also been noted with anti-TNF medication⁹. Thus, screening for TB exposure and treatment of latent TB prior to initiation of anti-TNF agents is recommended. Similar precautions are in place for other RA biologics, although the actual risk of TB due to these medications is less well understood. TNF blockers also increase the risk for severe and systemic fungal infections such as histoplasmosis and coccidioidomycosis, which may be a significant issue in specific geographic locales. An increased risk of viral infections with traditional or biologic DMARDs, including varicella-zoster virus, Epstein-Barr virus and cytomegalovirus has been documented²¹. Hepatitis B and C reactivation have also occurred with biologic DMARDs, so screening prior to treatment and vaccination when possible is recommended^{21,38}. Progressive multifocal leukoencephalopathy, an infection caused by reactivation of the JC virus, has also been reported in RA patients treated with Rituximab¹³.

Immunosuppression also can lead to a theoretical risk of malignancy, as tumor surveillance by the immune system may be affected. Since RA patients have an increased risk of lymphoma secondary to the disease itself, the extent of the increased risk of developing a cancer such as lymphoma while taking immunosuppressive medications remains debatable¹. A recent analysis of a German RA registry did not find an increased risk of malignancy, either hematologic or solid tumor, with the use of anti-TNF agents or anakinra, however, this included only four years of exposure data⁴⁴. Contrarily, an analysis of French

patients on anti-TNF medications has shown an increased incidence of lymphoma in patients on adalimumab or infliximab²⁵. The coexistence of other autoimmune diseases, such as Sjögren's syndrome, may also increase the likelihood of developing lymphoma, thus making it more difficult to determine the contribution from immunosuppressive medications²⁵.

PERIOPERATIVE MANAGEMENT

Because of the nature of their disease, patients with RA have many features that can impact perioperative management. Thus, consultation with a patient's rheumatologist prior to surgery may help to identify unique risks for that patient and prevent perioperative morbidity and mortality.

Given their elevated cardiac risk factors, a thorough cardiovascular history and physical should be completed in all RA patients prior to surgery. Depending on their risk profile and activity level, either an exercise or pharmacologic stress test could be considered to stratify their risk for cardiovascular complications. Additionally, patients with risk factors for interstitial lung disease, such as seropositivity (positive rheumatoid factor and/or positive titer of antibodies to citrulline-containing proteins), smoking, chronic cough or complaints of shortness of breath should have pulmonary function testing completed prior to surgery. This will allow for maximization of lung function prior to anesthesia.

Cervical spine involvement is common in RA and it parallels the progression of peripheral joint erosions, especially of the hands and feet³². Thus, patients considering hand surgery for RA complications should be screened for cervical disease. In RA, the alignment of the cervical spine can be compromised secondary to joint erosions or ligamentous laxity from synovial inflammation. This leads to anterior, posterior or vertical subluxation, and if severe can result in spinal cord and/or brain stem injury or even death with neck manipulation, such as during intubation. Symptoms of cervical instability include neck pain which radiates to the occiput, painless sensory loss in the hands, changes in consciousness with head motion, difficulty walking that is unexplained by RA involvement of the lower extremity joints, or paresthesias of the shoulders or arms with head motion. However, subluxation can be asymptomatic in as many as 31% of patients, so a screening cervical spine series that includes additional lateral views in both flexion and extension should be considered in all patients who will require intubation³². Significant abnormalities noted on plain radiographs should prompt a neurosurgical consult as well as a preoperative MRI with contrast to assess the existence or threat of injury to the spinal cord.

The medications used to treat RA also provide for challenges in the perioperative period. Many patients with RA use chronic, low dose steroids to improve their daily function. As a result, these patients must be assumed to have a suppressed hypothalamic-pituitary-adrenal (HPA) axis and thus be prone to adrenal insufficiency in times of stress, such as surgery or infection. Current guidelines suggest that any patient receiving more than 5 mg of prednisone per day should receive higher dose replacement during the perioperative period⁶. Minor non-invasive procedures, such as outpatient hand surgery, may not require steroid supplementation¹². However, any procedure which requires general anesthesia should be considered more invasive and these patients should be given 50–100 mg IV hydrocortisone preoperatively and possibly additional iv steroid doses over the subsequent 24 hour period before resuming their usual oral steroid dose. Severely ill patients or those who undergo extreme procedures such as cardiothoracic surgery should have their stress dose of hydrocortisone tapered by half every day post-operatively until they reach their maintenance dose^{6,12}. For patients who have recently been on steroid treatment in whom the status of their HPA axis is unclear, an ACTH stimulation test may highlight patients whose

endogenous steroid production would be suppressed under stress and thus would benefit from steroid supplementation perioperatively.

RA patients have an increased risk of infection after orthopedic surgery³. The use of DMARDs and biologic DMARDs can increase the risk of infection and theoretically may impair wound healing. There is ongoing debate regarding which medications to interrupt perioperatively. Current recommendations for perioperative use of these medications are summarized in Table 2. While some studies suggest that methotrexate is safe to continue through surgery, a prudent recommendation is to hold the doses prior to and immediately after surgery³⁵. Plaquenil has a long half life and does not confer an increased risk of infection, thus its use is typically continued in the perioperative period. Sulfasalazine may be continued without interruption other than on the day of surgery. Leflunomide should be held at least one week prior to surgery, although more data are needed to guide recommendations regarding this medication in view of its especially long half-life.

Anti-TNF agents have been sparsely studied with regards to their perioperative use. There is a theoretical risk of increased susceptibility to gram positive infections but there is no definitive data for this. In fact, most studies, including those which examined surgical procedures on small joints, have not found an increased risk of wound infections with concomitant use of anti-TNF agents³¹. No data exists as to their effects on wound healing. Because of the paucity of data, a reasonable approach is to hold anti-TNF medications for one dosage cycle perioperatively. Postoperative complications such as wound infection should delay resumption of anti-TNF agents, methotrexate, leflunomide or other cytotoxic/immunosuppressive agents.

Other biologic medications with longer half-lives make the timing of surgery even more uncertain. Rituximab can result in B-cell depletion for up to six months, albeit without profound hypogammaglobulinemia. Elective surgery is probably safest when B cell counts have rebounded. The half-life of abatacept is 15 days, so holding this medication for one month prior to surgery is reasonable³¹. Data regarding the use of tocilizumab in the perioperative period is minimal, but it has been shown to suppress post-operative fever and rise in inflammatory markers³¹. Thus, holding it in the perioperative period would also be a reasonable approach.

CONCLUSIONS

RA is common disease with widespread focal joint destruction and complications secondary to systemic inflammation. Recent treatment options based on better understanding of disease pathology have led to immense changes in the management of this disease. The aggressive use of DMARD and biologic DMARD therapy has allowed patients to achieve improved function and decreased joint destruction. These medications are not without side effects or long-term risks, however. An understanding of these pitfalls will allow for the optimal patient care in both the medical and surgical settings.

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Table 1
Common treatments for RA and their targets and toxicities

Abbreviations: CBC: complete blood count, Cr: creatinine, LFTs: liver function tests, PML: progressive multifocal leukoencephalopathy, TB: tuberculosis, TLR: toll-like receptor, TNF: tumor necrosis factor.

Conventional DMARDs	Target	Testing Prior to Starting Medication	Toxicities	Monitoring
Methotrexate	Enhances adenosine release; inhibits polyamines; folic acid antagonist	Cr, CBC, LFTs, Hepatitis B and C screening	Nausea, Diarrhea, Liver Toxicity, Pneumonitis, Cytopenias, Infections, Lymphoma	LFTs, Cr, CBC every 4–8 weeks
Leflunomide	Pyrimidine synthesis	Cr, CBC, LFTs, Hepatitis B and C screening	Nausea, Diarrhea, Liver Toxicity, Pneumonitis(rare), Infections	LFTs, Cr, CBC every 4–8 weeks
Hydroxychloroquine	TLR signaling; Stabilization of lysosomal membranes	Retinal screen	Retinal Toxicity, Nausea	Yearly ophthalmologic exam
Sulfasalazine	Enhances adenosine pathways and inhibits arachadonic acid	CBC	Nausea, Diarrhea, Allergic Reactions, Neutropenia (rare)	CBC every 4–8 weeks during first year of treatment
Biologic DMARDs				
Anti-TNF drugs	TNF- α	TB screen, Hepatitis B and C screen, fungal screens (depending on geography)	Infusion and injection site reactions, Rash, Infections, Lymphoma	None
Rituximab	CD-20	Hepatitis B screen, TB screen	Infusion reaction (can be severe), PML (rare)	None
Abatacept	CTLA-4 CD 80/86 interaction	TB screen, Hepatitis B and C screen, fungal screens (depending on geography)	Possible infusion reaction, Infections	None
Anakinra	IL-1 receptor antagonist	TB screen, CBC	Injection site reactions, Neutropenia, Infections	Monthly CBC
Tocilizumab	IL-6 receptor antagonist	Lipid profile, CBC, TB screen, hepatitis B and C screen, fungal screens (depending on geography)	Neutropenia, Thrombocytopenia, Elevated total cholesterol and triglycerides, Bowel perforations (rare), Infections	Monthly CBC, Cr, cholesterol profile.

Table 2
Perioperative management of medications used to treat RA

Medication	Perioperative Management
Steroids	Continue at lowest dose possible; consider stress dose steroids as indicated.
Methotrexate	Hold doses immediately before and after surgery.
Leflunomide	Hold at least one week prior to surgery*
HCQ	Continue perioperatively.
Sulfasalazine	Hold only on day of surgery.
Anti-TNF drugs	Hold for one dose perioperatively.
Rituximab	Optimal timing of surgery when CD20 counts have rebounded (3–6 months after last dose).
Abatacept	Hold one month prior to surgery.
Anakinra	Hold one week before and after surgery* .
Tocilizumab	Hold dose prior to surgery* .

* More evidence is needed to affirm recommendation.