Altering the natural history of rheumatoid arthritis: The role of immunotherapy and biologics in orthopaedic care

Steven J. Girdler^a, Ivan Ye^a, Ray Tang^a, Noah Kirschner^{b,*}

^a Department of Orthopedic Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA

^b Albert Einstein College of Medicine, Bronx, NY, 10461, USA

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ABSTRACT

Rheumatoid Arthritis (RA) is an idiopathic disease characterized by systemic inflammation, persistent synovitis, and the presence of autoantibodies. Because of the musculoskeletal deformity caused by RA, multiple orthopaedic procedures are regularly performed as part of the treatment. The changing rates of surgery and the rise in new efficacious medical therapy have improved the prognosis for patients with RA. This review will discuss the natural history of rheumatoid arthritis, common medications used to treat it, how disease progression has changed as a function of new biologic immunotherapy, and the role of orthopaedic intervention in this new landscape of advanced rheumatoid care.

1. Introduction

Rheumatoid Arthritis (RA) is an idiopathic disease characterized by systemic inflammation, persistent synovitis, and the presence of autoantibodies; often rheumatoid factor and citrullinated peptide. The disease is most prevalent in women and the elderly and most commonly affects multiple joints leading to damage of articular surfaces.¹ Traditional treatment of rheumatoid arthritis includes disease-modifying anti-rheumatic drugs (DMARDs), most commonly methotrexate, hydroxychloroquine and sulfasalazine. In recent years newer immunologic treatment options often called biologics have been developed to affect cytokine processing; deterring the immune response that causes the clinical sequelae seen in RA. Due to the efficacy of these new drugs, the incidence of orthopaedic surgery for patients with RA has decreased in recent years.¹ It is nonetheless imperative that orthopedic surgeons are aware of how this disease presents, progresses, and is treated in the modern era.

2. Natural history of rheumatoid arthritis

The natural history of rheumatoid arthritis begins before symptoms become clinically apparent. The insidious onset of RA has been previously described as 5 discrete phases that include genetic predisposition, asymptomatic inflammation, symptomatic inflammatory arthritis, well developed disease and a remitting and recurring course.

The first phase of the natural history begins with a genetic

predisposition for RA. Given the increased prevalence of RA seen within families, genetics is a major contributor to the development of RA. In fact, many studies have identified high risk genetic factors for RA. The shared epitope (SE) is a five amino acid sequence motif (residues 70–74) in the human leukocyte antigen (HLA) major histocompatibility (MHC) gene DRB1. SE has been strongly associated with high levels of autoantibodies such as anti-citrullinated protein antibody (ACPA), which is present in a majority of RA cases. The SE gene has been estimated to contribute almost 40% of the genetic risk for RA. Further genome-wide studies have lead to the discovery of over 100 genes associated with RA, which is estimated to explain an additional 5% of the genetic risk.² Various environmental factors have also been implicated in the development of RA such as coffee consumption, smoking history, and air pollution. A common hypothesis is that repeated activation of the innate immune system via environmental factors gradually increases autoimmunity, progressing towards RA. However, while genetic and environmental factors have been associated with RA, the linkage between these genes and the initial generation of autoantibodies has yet to be determined.

The second phase of RA is asymptomatic inflammation and the initial generation of autoimmunity. This phase is notable in that autoantibodies and inflammatory markers are first detectable, often prior to symptoms and a diagnosis of RA. Rheumatoid factor (RF) has been shown to be often present prior to the onset of RA. Later studies showed antibodies to citrullinated protein antigens (ACPAs) and anti-cyclic citrullinated peptide (anti-CCP) antibody increase the likelihood of future

* Corresponding author.

E-mail address: noah.kirschner@nyulangone.org (N. Kirschner).

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Table 1
Common biologic agents, their mechanism of action, and preoperative recommendations.²⁰

Biologic Drug	Mechanism	Preoperative Hold
Etanercept (Enbrel)	TNF alpha receptor fusion protein	2 weeks
Infliximab (Remicade)	Chimeric monoclonal antibody directed to TNF alpha	5, 7, or 9 weeks (depending on dosing)
Adalimumab (Humira)	Human monoclonal antibody targeting TNF alpha	3 weeks
Golimumab (Simponi)	Human monoclonal antibody kappa chain against TNF alpha	SC 5 weeks IV 9 weeks
Certolizumab (Cimzia)	Humanized Fab segment of monoclonal antibody for TNF alpha bound to polyethylene glycol	3 or 5 weeks (depending on dosing)
Anakinra (Kineret)	Human interleukin-1 receptor antagonist	2 days
Tocilizumab (Actemra)	Humanized monoclonal antibody directed for interleukin-6 receptor	SC 2 weeks IV 5 weeks
Rituximab (Rituxan)	Chimeric monoclonal antibody targeting CD20 antigen of B cell lymphocytes	7 months
Abatacept (Orencia)	Fusion protein with CTLA-4 domain binds CD80 and CD86 preventing T cell activation	SC 2 weeks IV 4 weeks
Tofacitinib (Xeljanz)	Molecular inhibitor of JAK enzymes	7 days

RA diagnosis. In fact, a combination of anti-CCP and any RF isotype was highly specific (99%) for future RA development.³ While no causal relationship has been identified between these autoantibodies and RA, one hypothesis is that the autoantibodies might lead to the formation of immune complexes that engage the innate immune system, leading to the initial synovitis. This may stimulate the innate system to activate the complement system, recruit immune cells, and promote inflammation, further progressing towards the third phase of RA.

The third phase of RA is characterized by the initial symptoms of inflammatory arthritis. During this phase, inflammatory cells such as lymphocytes and macrophages invade the synovial membrane, leading to inflammation that causes pain and swelling in the joint. This may result in reduced range of motion and functional impairment. Early inflammatory arthritis can occur at multiple joints without satisfying classification criteria for diseases such as RA, and thus is classified as undifferentiated arthritis (UA). An undifferentiated arthritis diagnosis typically lasts between 6 weeks and 1 year before remission or a defined disease could be diagnosed. About 30% of patients with UA progress to RA.

This period of time may serve as a key turning point in the progression of RA. Since inflammation is generally reversible, treatment during this phase may prevent irreversible joint damage and disability caused by the inflammation. However, if left untreated, chronic inflammation may result in irreversible joint destruction via cartilage and bone erosion, leading to more severe form of RA.

The fourth phase begins when RA can first be diagnosed. According to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria, four criteria are graded on a point system and score above a threshold classifies the disease as RA. The first criteria is the number and size of joints affected by inflammatory arthritis. The second criteria is a positive test for RF or anti-citrullinated peptide antibody (anti-CCP). The third criteria is elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which are indicative of inflammation. The fourth criteria is that symptoms be present for at least 6 weeks. Finally, diseases with similar clinical manifestations must be ruled out, such as psoriatic arthritis, polyarticular gout, and systemic lupus erythematosus (SLE). The onset of RA is a gradual process that often starts with arthritis of a single joint (monoarthritis) before spreading to multiple joints (polyarthritis). The classic presentation of RA is morning stiffness of joints that improves with movement. The inflammation causes synovial hypertrophy and effusions that contribute to the swelling around joints. In the early course of RA, the MCP and PIP joints of the hand, wrist, and joints of the foot are affected, resulting in restricted range of motion, reduced muscle strength, and swelling.

The fifth phase includes the late course of RA that features exacerbations and remissions. During this period, the chronic inflammation of RA causes more severe damage to the affected joints as well as including more joints, such as shoulder and hip joints. For example, when

RA affects the knee, the synovial membrane thickens via fibroblast-like synoviocytes that also trigger catabolic cascades that initiate cartilage and bone damage. Immune cells can infiltrate the subchondral bone, leading to inflammatory cysts and bone erosion. These structural damages to the joint and underlying bone are irreversible and can lead to mechanical and degenerative changes to the joint. Furthermore, RA can fluctuate in severity of symptoms, characterized by flares of increased symptoms that subside after weeks to months. During these flares, bone erosion can be exacerbated. RA can also go into remission, during which time there is minimal RA activity. Remission from RA is classified by ACR/EULAR using the number of tender and swollen joints and the patient global assessment (PGA) that captures patient's perspective on RA. Despite remission, pain and swelling can still result from prior structural damage without active inflammation being present. RA is lifelong chronic condition that can't be cured but can be managed with treatment to achieve RA remission.

3. History of immunotherapy

There are multiple treatments available for RA with the goal of clinical remission and pain relief (Table 1). The primary treatment option for RA is disease-modifying antirheumatic drugs (DMARD), which are a collection of drugs that have been shown to improve symptoms, decrease structural damage, and improve function and range of motion.⁴ Approximately 50% of patients have been shown to enter RA remission when DMARDs are started early in the disease progression.⁴

One of the DMARDs, methotrexate (MTX) was first used to treat RA in 1962 and has since become one of most common treatments for RA. MTX is a competitive inhibitor of dihydrofolate reductase, which is required for tetrahydrofolate synthesis and ultimately DNA synthesis. This is effective against not only active cancer cells, but also lymphocyte proliferation, thus having an anti-inflammatory effect. Studies have shown that 46–65% of patients using MTX achieve 20% improvement as judged by the standard American College of Rheumatology 20 (ACR20) criteria.⁵ Further studies have shown that MTX improves physical function, decreases radiographic progression scores, reduces joint pain and swelling, as well as limits further joint destruction, deformity, and disability.⁶ However, MTX is ineffective for approximately 33% of patients. Furthermore, MTX has been associated with adverse events such as nausea, headaches, and hair loss, which contribute to the high 16% treatment discontinuation rate.⁶

If MTX and other DMARDs are not effective after 3 months, current recommendations suggest immunotherapy initiation.⁴ These treatments are biologic agents that target various components of the immune system contributing to RA symptomatology. Currently, there are 5 main classes of immunotherapies approved for use in the United States for RA: TNF inhibitors, interleukin inhibitors, B cell inhibitors, T cell activation inhibitors, and kinase inhibitors.

Tumor-necrosis factor (TNF) inhibitors are class of drugs that suppress TNF, which is an important protein in the activation of immune and inflammatory responses. There are five total anti-TNF drugs approved by the FDA for RA. Etanercept was the first approved TNF inhibitor to treat RA in 1998. Etanercept is a recombinant human fusion protein that functions as a decoy receptor, preventing TNF- α from binding the normal receptor. In 1999, the second approved TNF inhibitor was infliximab, a chimeric murine-human monoclonal antibody against TNF- α . In 2003, adalimumab was the first human monoclonal antibody against TNF- α approved by the FDA.

TNF-inhibitors have been presented as an effective option for RA. Studies have shown that more than 50% of patients using anti-TNF medications achieve 20% improvement (ACR20) in 30 weeks. A meta-analysis of the five TNF inhibitors found that combinations of TNF-inhibitors with MTX were more likely to reach ACR 20, 50, and 70 at 12 months than MTX-only or TNF inhibitor monotherapy.⁷ Thus, TNF inhibitors are now recommended with MTX rather than as a monotherapy. The interclass differences between the five TNF inhibitors is less clear. The meta-analysis also found no statistical difference in ACR 20, 50, or 70 (measured as % improvement) between monotherapy of etanercept, adalimumab, golimumab, and certolizumab pegol.⁷ Since anti-TNF treatments block a major activator of the immune system, infections are a major side effect, particularly tuberculosis. Etanercept stands out from the other TNF-inhibitors as having the lowest risk for serious adverse reaction and lowest incidence of tuberculosis compared with the other anti-TNF treatments.⁷

The second class of immunotherapy options for RA are interleukin (IL) inhibitors. Anakinra was first FDA approved in 2001, notable for being the first biologic that didn't target TNF- α . Instead, anakinra is a recombinant human antagonist that targets the IL-1 receptor. IL-1 is a proinflammatory cytokine with elevated levels in patients with RA. However, recent meta-analyses have shown that anakinra is less likely to reach ACR 20 and 50 at 6 months than TNF inhibitors.⁸ In 2010, the FDA approved tocilizumab, a humanized recombinant monoclonal antibody that can bind to soluble and membrane-bound IL-6 receptors. Tocilizumab is recommended for patients who fail DMARD or anti-TNF α treatments. One phase IV study found that tocilizumab achieved better disease activity improvement than adalimumab monotherapy.⁹ However, more data is needed to assess the effectiveness of tocilizumab compared to combination therapy.

The third class of biologics for RA are B cell inhibitors. In 2006, combination treatment of MTX and rituximab was approved to treat RA only if anti-TNF treatment failed. Rituximab is a chimeric monoclonal antibody against CD20 that causes B cell depletion, and thus decreases the production of autoantibodies. The REFLEX trial compared MTX with two IV infusions of rituximab vs. MTX with a placebo. After 24 weeks, ACR20 was 51% in the rituximab and MTX group and 18% for the MTX only group, ACR50 was 27% vs. 5%, and ACR70 was 12% vs. 1%, respectively.¹⁰ Mean disease activity was lower for patients receiving rituximab and MTX, as well as greater improvement in patient reported outcomes such as pain and functional disability. A recent meta-analysis found that 29% of patients taking rituximab and MTX achieved ACR 50 compared to 9% of patients taking MTX at 24 weeks.¹¹ Furthermore, after 52 weeks, clinical remission was achieved in 22% of patients in the rituximab and MTX group compared to 11% in the MTX only group.¹¹ These results are promising, and more studies are needed to compare the efficacy of rituximab to other available treatment options.

The fourth class of immunotherapies for RA are T cell inhibitors (Fig. 1). Abatacept was first approved by the FDA in 2005 for moderate to severe RA. Abatacept is a recombinant human fusion protein featuring the Fc region of an IgG antibody and the extracellular domain of CTLA-4, which inactivates CD80 or CD86 when bound. T cells require two signals for activation, one of which is provided by CD80 and CD86, abatacept inhibits T cell activation by blocking that signal. One study found that 65% of patients taking abatacept achieved ACR20 compared

to 63% with adalimumab after 1 year.¹² Thus, abatacept can be considered another option for patients who had failed MTX treatment.

The fifth class are kinase inhibitors. Protein kinases are part of the signal transduction process that is responsible for a wide range of intracellular reactions. The reactions include modification of enzyme activity, regulating ion channels, and inflammatory cytokines. Approved by the FDA in 2012 for RA as a secondary option after MTX, tofacitinib inhibits JAK1 and JAK3. One study reported that tofacitinib decreased expression of matrix metalloproteinase, which are enzymes that degrade collagen and the extracellular matrix, a major component of RA. Another study found that patients taking tofacitinib had significantly less radiographic progression and erosion after 6, 12, and 24 months compared to patients taking only MTX.¹³ Tofacitinib also had higher rates of remission and low disease activity than MTX.¹³ Tofacitinib is a promising treatment option for RA.

4. Common orthopaedic conditions in rheumatoid arthritis

Rheumatoid arthritis (RA) is a common, chronic autoimmune disorder affecting about 1% of the global population. It is characterized by polyarticular inflammatory processes affecting the synovium leading to the progressive destruction of both bony and cartilaginous elements of the joint. If left untreated, RA may result in painful, disabling, and deforming orthopedic conditions requiring surgical intervention. Symptoms of RA can be found in the joints of the neck, hands, elbows, hips, knees, and feet. Total joint arthroplasty (TJA) is a procedure with up to 31.7% 30-year cumulative incidence in patients with RA. The most frequently affected joint is the knee followed by hip, MCP joints, wrist, shoulder and elbow. Small joints seem to be affected earlier than large joints and lower extremities are affected earlier than upper extremities. Additionally, foot and ankle problems have been reported to affect up to half of RA patients with a lifetime incidence of up to 90%.¹⁴ Atlantoaxial instability is found in up to 80% of patients with RA. This requires preoperative evaluation with flexion and extension imaging to assess the safety of endotracheal intubation in these patients.

The most common orthopaedic surgeries in patients with RA are TJA, joint fusions, and soft tissue procedures. Patients with RA have inferior bone and soft tissue quality, requiring special consideration particularly in TJAs. The prosthesis used for patients with RA may require increased constraint to prevent premature failure. Additionally, a total synovectomy may be necessary when operating on patient with RA, as they are at increased risk for recurrent synovitis following a TJA. Outcomes following TKA in patients with RA have been reported to have a joint survival rate between 81% and 95%.¹⁵ However, complications occur at higher rates due to the poor quality of the soft tissue, worse preoperative joint deformity, and the polyarticular disease preventing proper rehabilitation.

5. Sequelae for orthopaedic surgeons

The increasing use of DMARDs and biologics since the late 1980s has changed rate of orthopedic surgery in patients diagnosed with RA. The newer treatments have been used to inhibit and prevent the autoimmune processes that drive rheumatic disorders. As a result, the number of orthopedic operations has fluctuated. A single-institution observational study in Japan looked at rates of biologic use and RA-associated operations from 2001–2012.¹⁶ It was found that the number of operations decreased from 2002 to 2007 (31.8/1000 to 15.4/1000) with a slight increase from 2007 to 2012 (21.2/1000). This decrease coincided with increased use of biologics and decreased use of steroids and NSAIDs from 2001 to 2012. The gradual increase in operations after 2007 was partially attributed to new TER and TAR techniques made available to Japanese patients at that time. Patients with long-term RA experience improved symptoms as a result of DMARD and biologic treatments.

A Spanish nation-wide retrospective study of patients with RA also

Fig. 1. Abatacept mechanism of action.

found a significant reduction in rates of orthopedic surgery.¹⁷ In the 2013 study cohort, only 7.4% of patients underwent any orthopedic surgery compared to 25.9% in a previous similar cohort from a 2000 study. This reduction in rates of surgery can be attributed to improved management of RA in the years following the 2000 study. Early and aggressive treatment of RA with biologics became more widespread. It is hypothesized that as biologic management of RA continues to become the standard of care, the number of orthopedic surgeries is likely to further decline.

A 2013 nation-wide Finnish study looked at changes in rates of RA-related orthopedic surgery during the evolution of biologic therapies from 1995 to 2010. The register-based analysis found that while the total number joint replacement procedures increased, the number of RA-associated surgeries decreased by 42%. This downward trend was greater for upper-extremity procedures than lower-extremity procedures. Over the same period, there was a rise in overall use of DMARD's to treat RA patients with a particular rise in use of biologics which became available in 2001.

These studies did not involve randomized treatments and thus cannot prove a causative effect. Additionally, though there is substantial coincidence in the decline of orthopedic surgery rates and the popularization of biologic treatments and drug combinations, there has been some research contradicting the general impact of biologics on orthopedic surgery rates. A multicenter, nation-wide observational study in Japan examined the prevalence of orthopedic surgeries to treat RA after the introduction of biologic treatments.¹⁸ The 2010 study looked at patient data from 2004 to 2007. There was no substantial change in the proportion of patients utilizing traditional DMARD's during this time period (81.7%–86.1%), whereas the use of biologic agents steadily increased (1.8%–10.0%). Against expectation, there was no significant difference in the proportion patients who underwent RA-associated surgeries, from 6.2% in 2004 to 5.2% in 2007. Also, the proportion of patients treated with biologics that underwent RA-associated surgery was about double the proportion of patients not treated with biologics. However, patients treated with biologics tended to have significantly higher disease activity and lower physical function, which may somewhat account for the contrary results.

With increasing the prevalence of biologic agents in the management of RA symptoms, the percentage of patients receiving biologic therapy who present for surgery will likely increase as well. Thus, it is important to review considerations for perioperative management of biologics in order to ensure safety. In 2017, the American College of Rheumatology (ACR) in coordination with the American Association of Hip and Knee Surgeons (AAHKS) put forth some guidelines for such cases. The first recommendation involving biologics is to restrict biologics for patients undergoing elective THA or TKA, and to schedule the surgery at the end of the dosing cycle. The risk of serious infection was found to be increased with the use of biologic treatments, with no significant difference in risk between different types of biologics. Risk of infection was also found to be highly associated with high-dose treatments and not with low-dose. The second biologic-specific

recommendation was to restart biologic therapy for patients once there is evidence of wound healing, after the removal of sutures, and as long as there are no signs of significant swelling, erythema, drainage, or non-surgical site infections. This recommendation is based on general precautions regarding wound management, as there is no direct evidence concerning the optimal time to restart biologic therapy. The guidelines laid forth by the ACR and AAHKS are similar to recommendations of other societies regarding perioperative biologic treatments. A 2017 study by the British Society of Rheumatology (BSR) recommends that anti-TNF therapy be paused 3–5x the half-life of the drug prior to surgery.¹⁹ For tocilizumab, a pause 4 weeks prior to surgery is recommended. These recommendations are based on studies which reported higher risk of post-operative infection and poor wound healing in patients receiving biologic therapy. However, there have been studies showing no significant difference in risk of post-operative complications rendering these recommendations general precautions.

6. Conclusion

RA is a common inflammatory disease affecting 1% of the global population. It is an idiopathic disease causing systemic inflammation, synovitis, production of autoantibodies. Orthopaedic complications are frequent, due to chondrocyte destruction, joint damage, and deformity found in RA. RA is currently treated with DMARDs, biologic agents that deter immune response, or combination therapy. Biologic treatments have been popularized since FDA starting approving these innovative drugs in the late 1990's and early 2000's. There has been a significant decrease in orthopaedic surgical interventions since the advent of the biologic treatments. The rate of operations in patients with RA should continue to decrease as the use of biologics become more common. Due to increase risk of infection when taking biologics there is concern about perioperative dosing of these medications. Current literature supports a short hiatus, or surgical scheduling around dosing cycles depending on which biologic the patient is prescribed. However, this is still a lot of data being collected to produce the ideal guidelines for this growing population.

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