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Pharmacologic Management of Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune inflammatory disease of the joints, which can result in permanent cartilage and bone damage. Although the exact cause of RA is unknown, there are many risk factors that have been associated with RA. When RA occurs, the immune system mistakenly attacks healthy synovial and connective tissue. Available treatment options work to reduce inflammation or slow the disease progression. The American College of Rheumatology published guidelines for the treatment of rheumatoid arthritis in 2015, with an update expected in late 2019/early 2020. Nonpharmacologic therapy for patients with RA includes rest, occupational and physical therapy, and weight reduction and use of assistive devices, as necessary. Pharmacologic options include nonsteroidal anti-inflammatory drugs, corticosteroids, disease-modifying antirheumatic drugs, antitumor necrosis factor agents, and interleukin receptor antagonists.

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune inflammatory disease of the joints, which can result in permanent cartilage and bone damage. It may also have other systemic effects including ophthalmic, cardiopulmonary, neurologic, or lymphatic manifestations. Early diagnosis is imperative for optimal therapeutic success (Smolen, Aletaha, & McInnes, 2016; Wahl & Schuna, 2014). Rheumatoid arthritis affects more than 1.3 million Americans, 75% of whom are women (Duarte-Garcia, 2019). Treatment recommendations are based on several factors including duration of disease/symptoms.

Pathophysiology and Clinical Presentation

The exact cause of RA is unknown; however, studies have shown there are a number of genetic and environmental factors that may increase one's risk of developing RA. Specific risk factors include increased age, female sex, human leukocyte antigen-2 (HLA-2) genotype, smoking, obesity, and exposure to certain infectious pathogens such as Epstein-Barr virus or *Escherichia coli* (Centers for Disease Control and Prevention, 2019; Wahl & Schuna, 2014). When RA occurs, the immune system mistakenly attacks healthy synovial and connective tissue. This is a consequence of the dysregulation of humoral and cell-mediated immunity, often resulting in the production of antibodies called "rheumatoid factors." Seropositive patients typically have a more aggressive disease course as compared with seronegative patients. Proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 are substances also responsible for the initiation and continuance of the inflammation seen in RA. Vasoactive substance, including histamine, kinins, and prostaglandins, may also be released at sites of inflammation contributing to edema, erythema, and pain. Over time, the chronic inflammation of synovial tissue in the joint capsule results in proliferation of tissue. As a result of this tissue damage, chronic pain, unsteadiness, and deformity may occur. The most common joints affected include the hands, wrists, and knees. Patients with RA will typically present with symmetrical joint stiffness and pain. Other symptoms may include fatigue, weakness, low-grade fever, and loss of appetite (Duarte-Garcia, 2019; Wahl & Schuna, 2014). Available treatment options work to reduce inflammation or slow the disease progression. The options include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), anti-TNF agents, and IL receptor antagonists (Wahl & Schuna, 2014).

General Treatment Approach

The American College of Rheumatology (ACR) published guidelines for the treatment of RA in 2015, and it is anticipated that the ACR will release updated guidelines by the end of 2019/early 2020. Treatment recommendations are

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based on several factors including duration of disease/symptoms: early RA (<6 months) versus established RA (≥6 months) and disease activity (characterized by low, moderate, or high). Disease activity can be measured using a validated instrument including Patient Activity Scale, Soutine Assessment of Patient Index Data 3, Clinical Disease Activity Index, Disease Activity Score, or Simplified Disease Activity Index. In early and established RA, the treat-to-target strategy to achieve remission or low disease activity is strongly recommended. The ACR categorizes each recommendation as strong (ACR is confident that benefits outweigh risks in most patients) or conditional (benefits probably outweigh risks in most patients, but some may not want to follow recommendation).

Table 1. RA Dosing

Drug	Brand Name(s)	Route of Administration	Starting Dose	Usual Maintenance Dose
Methotrexate	Rasuvo Trexall Otrexup	Oral Subcutaneous Intramuscular	7.5 mg once weekly or 2.5 mg every 12 hours × 3 days once weekly	7.5–15 mg once weekly
Leflunomide	Arava	Oral	Loading dose: 100 mg daily for 3 days	20 mg once daily, may reduce dose to 10 mg once daily if not tolerated (Maximum dose: 20 mg/day)
Hydroxychloroquine	Plaquenil	Oral	400–600 mg given once daily or in two divided doses	May reduce dose after achieving adequate response to 200–400 mg once daily or in two divided doses (Maximum dose: 600 mg/day or 6.5 mg/kg/day)
Sulfasalazine	Azulfidine	Oral	500 mg once or twice daily	1 g BID (maximum dose: 3 g/day if inadequate response after 12 weeks of 2 g/day)
Etanercept	Enbrel	Subcutaneous	n/a	50 mg once weekly
Infliximab	Remicade Renflexis Inflectra	Intravenous	3 mg/kg at 0, 2, 6 weeks, then every 8 weeks	3–10 mg/kg every 4–8 weeks
Adalimumab	Humira	Subcutaneous	n/a	40 mg every other week (Patients not taking concomitant methotrexate may increase dose to 40 mg every week)
Golimumab	Simponi	Intravenous Subcutaneous	IV: 2 mg/kg at weeks 0 and 4 SubQ: n/a	IV: 2 mg/kg every 8 weeks SubQ: 50 mg once monthly
Certolizumab	Cimzia	Subcutaneous	400 mg initially and at weeks 2 and 4	200 mg every other week May consider maintenance dose of 400 mg every 4 weeks
Abatacept	Orencia	Intravenous Subcutaneous	IV: Infusion initially, and at weeks 2 and 4 <60 kg: 500 mg 60–100 kg: 750 mg >100 kg: 1,000 mg SubQ: May be initiated with or without IV loading dose	IV: Continue weight-based dosing every 4 weeks SubQ: 125 mg once weekly
Rituximab	Rituxan	Intravenous	1,000 mg on days 1 and 15	Subsequent courses (two-1000 mg infusions separated by 2 weeks) may be administered every 24 weeks, but not sooner than every 16 weeks
Tocilizumab	Actemra	Intravenous Subcutaneous	IV: Initial: 4 mg/kg once every 4 weeks SubQ: <100 kg: 162 mg once every other week ≥100 kg: 162 mg once weekly	IV: May be increased to 8 mg/kg once every 4 weeks based on clinical response (maximum dose: 800 mg) SubQ: <100 kg: May be increased to 162 mg once weekly based on clinical response ≥100 kg: 162 mg once weekly
Sarilumab	Kevzara	Subcutaneous	n/a	200 mg every 2 weeks
Tofacitinib	Xeljanz	Oral	n/a	IR: 5 mg BID XR: 11 mg once daily
Baricitinib	Olumiant	Oral	n/a	2 mg once daily

Note. BID = twice a day; IR = immediate release; IV = intravenous; n/a = not available; SubQ = subcutaneous; XR = extended release.

Nonpharmacologic therapy for patients with RA includes rest, occupational and physical therapy, and weight reduction and use of assistive devices, as necessary. It is essential that, although rest is key to relieve stress on inflamed joints and alleviate pain, too much immobility can be destructive. Therefore, a collaborative approach to care is essential, including interprofessional care with the patient at the center. Considering the impact of RA on quality of life and the multiple facets to care, discussion with the patient on options, recommendations, risks, benefits, and expectations is essential.

When choosing medications to treat RA, important considerations include laboratory monitoring, tuberculosis (TB) screening, comorbidities, especially congestive heart failure, hepatitis B or C, malignancy and previous serious infection(s), and immunization history. Disease-modifying antirheumatic drugs are central in RA treatment and are classified as traditional/conventional, which include methotrexate (MTX), hydroxychloroquine (HCQ), leflunomide (LEF), and sulfasalazine (SSZ). The other treatment modalities include tumor necrosis factor inhibitor (TNFi)—adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; non-tumor necrosis factor (non-TNF) biologics—abatacept, rituximab, tocilizumab, and sarilumab; or janus kinase (JAK) inhibitors—tofacitinib and baricitinib (Singh et al., 2016). Table 1 includes information about the medications used to treat RA.

The treatment algorithm for early RA starts with classifying disease activity and initiating DMARD monotherapy ± glucocorticoids (short-term, <3 months) for RA flare-ups. If disease activity continues or worsens, the following should be recommended: combination traditional DMARDs *or* TNF inhibitor ± MTX *or* non-TNF biologic ± MTX. Similarly, in DMARD-naïve established RA, DMARD monotherapy should be initiated, progressing to the aforementioned combinations as well as tofacitinib ± MTX as an option. If disease activity continues, if it was a single TNFi failure, change to non-TNF biologic +/1 MTX or TNFi ± MTX. If it was a single non-TNF biologic failure, change to another non-TNF biologic ± MTX. If the failure to therapies continues, then another non-TNF biologic ± MTX or tofacitinib ± MTX is recommended. In terms of duration of treatment, in patients where low disease activity continues, RA treatment should continue. If in remission, tapering RA treatments should be considered by reducing doses or dosing frequency. As any recommendations are being considered, shared decision-making should be employed (Singh et al., 2016).

Medication Classes

Disease-Modifying Antirheumatic Drugs

Disease-modifying antirheumatic drugs, or DMARDs, are recommended first-line for RA because of their proven safety and clinical efficacy. They are termed as such because they work to slow RA progression resulting in more favorable outcomes. These therapies work by inhibiting cytokine production and nucleotide biosynthesis, which ultimately decreases inflammation. Nonbiologic medications in this class include MTX, LEF, HCQ, and SSZ.

Methotrexate is the preferred initial DMARD of choice. It is recommended for initial use because data suggest superior outcomes over other DMARDs. Methotrexate works by inhibiting purine biosynthesis and it can improve articular swelling in as little as 3–6 weeks. It is available as an oral, intramuscular, and subcutaneous formulation and is usually dosed once weekly. Common side effects associated with MTX include nausea, vomiting, diarrhea, stomatitis, elevated liver enzymes, and folic acid deficiency. Complete blood count (CBC) with differentials and liver function tests should be monitored in patients taking this agent. Due to the teratogenicity, MTX is contraindicated in pregnant and nursing women. Women of child-bearing potential should use contraception or discontinue this agent if conception is planned. Additional contraindications include chronic liver disease, alcoholism, immunodeficiency, and preexisting blood dyscrasias (Methotrexate Package Insert, 2016; Singh et al., 2016).

Leflunomide works by inhibiting pyrimidine synthesis, which leads to decreased lymphocyte production. It is available in an oral formulation and is given as a loading dose, followed by a once daily maintenance dose. Common adverse effects include diarrhea, headache, alopecia, and rash. Leflunomide is contraindicated in severe hepatic impairment, pregnancy, and concomitant use with teriflunomide. Monitoring parameters include CBC and liver function tests at least monthly for the first 6 months of treatment, then every 6–8 weeks thereafter (Arava Package Insert, 2016).

Hydroxychloroquine is another DMARD that impairs antigen–antibody reactions. It has a slow onset of action that may take up to 6 weeks to demonstrate benefits in RA. It is available as an oral formulation that can be dosed once or twice daily. The most prominent adverse effect is retinal toxicity, which is associated with high daily doses and use beyond 5 years. For this reason, ophthalmologic examinations should be monitored at baseline and annually after 5 years of use. Hydroxychloroquine lacks the myelosuppressive, hepatic, and renal toxicities that may be seen with other DMARDs, which simplifies monitoring (Fox, 1993; Plaquenil Package Insert, 2017).

Sulfasalazine's mechanism of action in RA is largely unknown; however, it is thought to modulate the inflammatory response and inhibit TNF. Antirheumatic effects are seen after up to 2 months of therapy. It is available as an oral formulation and dosed once or twice daily. Patients should be counseled that SSZ may cause the urine or skin to turn a yellow–orange color. Adverse effects include rash, gastrointestinal side effects, hematologic abnormalities, and abnormal liver function tests. Complete blood counts with differential and liver function tests should be monitored in these patients. Contraindications include use in patients with intestinal or urinary obstruction or porphyria (Azulfidine Package Insert, 2012).

Within the treatment algorithm, typically DMARD monotherapy is initiated with MTX. Disease-modifying antirheumatic drug combination therapy known as double or triple DMARD therapy may be considered depending on disease activity. Double DMARD therapy combinations include MTX + SSZ, MTX + HCQ,

SSZ+ HCQ, or combinations with LEF; triple DMARD therapy is MTX + SSZ + HCQ.

TNF-α Inhibitors

Tumor necrosis factor-alpha (TNF-α) inhibitors also have disease-modifying activity. They are biologic agents, which are large protein molecules, used to block proinflammatory cytokines to slow disease progression. Tumor necrosis factor-α inhibitors work by inhibiting TNF-α—a multifunctional cytokine responsible for systemic inflammation and immunoregulatory activities. These medications are indicated in moderate to high disease activity after failure of non-TNF-α biologic agents (Roy, 2017). This class of biologic agents includes etanercept, infliximab, adalimumab, golimumab, and certolizumab. Each drug works via a unique mechanism to inhibit TNF-α.

Etanercept is a fusion protein that binds to TNF rendering it inactive. It is available as a subcutaneous injection that may be administered once or twice weekly. No clinical monitoring is required. Infliximab is a chimeric antibody that binds TNF and prevents it from binding inflammatory cells. It is available as an intravenous (IV) infusion that is administered at 0, 2, and 6 weeks, then every 8 weeks. Infusion reactions may occur. Methotrexate must be given concomitantly with infliximab to prevent the development of antibodies against this drug (Enbrel Package Insert, 2017; Inflectra Package Insert, 2016).

Adalimumab, golimumab, and certolizumab are all human antibodies against TNF, which makes them less antigenic than infliximab. Adalimumab is available as a premixed syringe or injection pen, which is administered subcutaneously every 2 weeks. Local injection site reactions may occur. Golimumab is available as a monthly subcutaneous injection. Certolizumab is also available as a subcutaneous injection administered at 0, 2, and 4 weeks, followed by every 2 weeks (Cimizia Package Insert, 2017; Humira Package Insert, 2019; Simponi Package Insert, 2011).

Tumor necrosis factor-α inhibitors have black box warnings associated with increased risk of infection, malignancies, and TB. They have also demonstrated increased risk of cardiac toxicities and worsening heart failure. Biologic DMARDs may be used in combination with other nonbiologic agents; however, two biologics may never be used in combination with one another, as this may potentiate toxicities.

Non-TNF Biologics

Non-TNF-α biologics include IL receptor antagonists and other large protein immunomodulators. All of these agents work via various mechanisms to help blunt the immune response in RA. The choice of biologic agent should be individualized based on patient factors such as dosing consideration, economic factors, and/or side effect profiles.

Abatacept is a selective costimulation modulator that binds CD80/CD86 receptors. This prevents T-cell activation, which decreases the inflammatory response. It is available as an IV infusion that may be administered every 2 weeks for the first two doses, followed by every 4 weeks. It also is available as a subcutaneous injection administered every 7 days. Adverse effects include infusion-related reactions, increased risk of infection, nasopharyngitis, headache, and possible antibody development. Patients should be monitored for signs and symptoms of infection while using this drug (Orencia Package Insert, 2017).

Rituximab is an anti-CD20 monoclonal antibody that binds and depletes β-cells. It is administered as an IV infusion every 2 weeks for two doses, followed by every 24 weeks depending on clinical evaluation. Steroids should be administered prior to the infusion to reduce incidence of infusion reactions. Adverse effects include fatigue, chills, weight gain, hematologic disturbances, pain, hypertension, and cardiac and pulmonary toxicities. Monitoring includes CBCs with differential, cardiac status, and signs and symptoms of infection (Rituxan Package Insert, 2019).

Tocilizumab and sarilumab are IL-6 receptor antagonists. Tocilizumab is available as an IV infusion administered every 4 weeks and a subcutaneous injection administered every 1–2 weeks. Sarilumab is available as a subcutaneous injection to be administered every 2 weeks. Both agents may elevate liver enzymes, and tocilizumab may increase serum cholesterol levels. For this reason, liver function tests and lipid panels should be monitored (Actemra Package Insert, 2018; Kevzara Package Insert, 2017). Anakinra is also an IL receptor antagonist; however, it works on IL-1. Data suggest this agent may be less effective than other biologic agents (Mertens & Singh, 2009).

JAK Inhibitors

Janus kinase inhibitors are new to the RA market. Janus kinase is a tyrosine kinase that mediates cytokine signaling responsible for leukocyte function. Inhibition of JAK results in immunosuppression, which gives this class of medication utility in RA. Tofacitinib is a JAK inhibitor that was Food and Drug Administration (FDA) approved in 2012 as monotherapy or in combination with other nonbiologic DMARDs. Studies have shown use of tofacitinib plus MTX further reduced RA progression of structural damage compared with MTX alone. Additionally, use of tofacitinib alone versus MTX has been shown to inhibit the progression of structural damage in RA. This agent is available in an oral formulation that is dosed once daily. Black box warnings for this agent include increased risk of serious infections and malignancies. Adverse effects include elevated low-density lipoprotein and high-density lipoprotein cholesterol. Complete blood counts, liver function tests, and lipid panels should be monitored for patients using this drug (FDA 2018; Tofacitinib Package Insert, 2018; O'Shea, Kontzias, Yamaoka, Tanaka, & Laurence, 2013).

Baricitinib is also a JAK inhibitor that was FDA approved in 2018 for patients with moderate to severe RA who have had an inadequate response to one or more TNF-α inhibitors. Use with other JAK inhibitors, biologic DMARDs, or potent immunosuppressants is not recommended. It is also not recommended for use in patients with hepatic or renal impairment. Adverse effects include upper respiratory tract infections, nausea, herpes simplex, and herpes zoster. Warnings associated with baricitinib use include serious infections, malignancy, and thrombosis and patients should be monitored for signs and symptoms of infection. It is

available as a once daily oral formulation (Olumiant Package Insert, 2018; Singh et al., 2016; Wahl & Schuna, 2014).

Biosimilars

The World Health Organization (WHO) defines a biosimilar as a "biotherapeutic product which is similar [defined as: absence of a relevant difference in the parameter of interest] in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product" (WHO, 2009). The ACR has published a white paper and a position statement on biosimilars in rheumatology. They outline several considerations for the use of biosimilar products, including the decision to substitute for biosimilar product should be made by the prescribing physician, the importance postmarketing surveillance studies, and maintaining cautiousness when extrapolating information from one biologic to another. Biosimilar agents are developed to offer more medication options at potentially a lower cost. Biosimilar agents FDA-approved for use in RA include infliximab-dyyb, etanercept-szzs, and adalimumab-atto. Both of these agents are not interchangeable with the original compound and require a written prescription (ACR, 2018; Bridges et al., 2018; FDA 2018; WHO 2009).

Adjunctive Therapy

Glucocorticoids

Glucocorticoids work in RA via their anti-inflammatory and immunosuppressive properties. Mechanistically, it interferes with the immune response via inhibition of prostaglandin and leukotriene synthesis, inhibition of neutrophil and monocyte radical generation, and antigen presentation to T lymphocytes (Wahl & Schuna, 2014). Within RA, corticosteroids can be used in various ways such as a bridge to other therapies, short term for flare control, or continuously for disease control. In general, glucocorticoids should be used short term (defined as <3 months) and at the lowest dose possible. The ACR guidelines differentiate low dose as 10 mg/day or less of prednisone or equivalence and high dose as more than 10 mg/day up to 60 mg/day (Singh et al., 2016). Corticosteroids should be avoided as monotherapy, as they do not prevent RA progression. There are several adverse effects associated with corticosteroid including increased cardiovascular risks, adrenal insufficiency, gastrointestinal complications, and increased risk of infection. Due to the lack of disease-modifying activity and other risks, long-term use of corticosteroids should be avoided (Prednisone Package Insert, 2012).

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs, or NSAIDs, work in RA by reducing joint pain and inflammation. Their mechanism of action is via reversible inhibition of COX-1 and COX-2 enzymes, which inhibits prostaglandin synthesis. Nonsteroidal anti-inflammatory drugs may be associated with cardiovascular, gastrointestinal, and renal toxicities, and therefore, caution should be used in patients who are high risk for these conditions (Motrin Package Insert, 2007). This class of medications is used primarily for symptom management and does not limit disease progression like other medications used in RA. Because of this, NSAIDs should seldom be used as monotherapy and instead be used in combination with other disease-modifying agents.[2]

Conclusion

Rheumatoid arthritis is a lifelong autoimmune disease that has significant negative impact on the quality of life, ability to perform daily activities, and mortality. Early diagnosis and treatment with appropriate DMARDs is essential. Rheumatoid arthritis is a complex disease where the treatment options also require a multitude of considerations, including benefit, risk, and cost. The key principles to treating RA center around the patient and the treat to target approach. The goal of the treatment is to induce remission or at the least, low disease activity. Additional consideration prior, during, and after treatment includes use of vaccines due to the immunosuppression that may occur from the medications used to treat RA, screening for TB due to the use of biologics, and laboratory monitoring to assess for adverse effects from the DMARDS. A holistic, team-based approach with discussions about the disease, treatment options, role of treatments, outcomes and expectations, and nonpharmacologic modalities is optimal when caring for a patient with RA (Singh et al., 2016).

References

Actemra [package insert]. (2018). South San Francisco, CA: Genentech Inc.

American College of Rheumatology. (2018). *Position statement: Biosimilars*. Retrieved from https://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf

Arava [package insert]. (2016). Bridgewater, NJ: Sanofi-Aventis.

Azulfidine EN-tabs [package insert]. (2012). Kalamazoo, MI: Pharmacia & Upjohn.

Bridges, S. L. Jr., White, D. W., Worthing, A. B., Gravallese, E. M., O'Dell, J. R., Nola, K., … American College of Rheumatology. (2018). The science behind biosimilars: Entering a new era of biologic therapy. *Arthritis & Rheumatology*, *70*(3), 334–344. https://doi-org.ezproxy.rosalindfranklin.edu/10.1002/art.40388

Centers for Disease Control and Prevention. (2019). *Rheumatoid arthritis*. Retrieved from https://www.cdc.gov/arthritis/basics/rheumatoid-arthritis.html

Cimizia [package insert]. (2017). Smyrna, GA: UCB, Inc.

Duarte-Garcia, A. (2019). *Rheumatoid arthritis*. Retrieved from https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Rheumatoid-Arthritis

Enbrel [package insert]. (2017). Thousand Oaks: CA: Immunex Corporation.

Food and Drug Administration. (2018). *Biosimilar product information: FDA-approved biosimilar products*. Retrieved from https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm

Fox, R. I. (1993). Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Seminars in Arthritis and Rheumatism*, *23*(2, Suppl. 1), 82–91. Retrieved

from https://search-ebscohost-com.ezproxy.rosalindfranklin.edu/login.aspx?direct=true&db=cmedm&AN=8278823&site=eds-live&scope=site
Humira [package insert]. (2019). North Chicago, IL: Abbott Laboratories.
Inflectra [package insert]. (2016). New York, NY: Division of Pfizer Inc.
Kevzara [package insert]. (2017). Bridgewater, NJ: Sanofi Biotechnology.
Mertens, M., & Singh, J. A. (2009). Anakinra for rheumatoid arthritis. *Cochrane Database of Systematic Reviews*, (1):CD005121. Retrieved from https://search-ebscohost-com.ezproxy.rosalindfranklin.edu/login.aspx?direct=true&db=edschh&AN=edschh.CD005121&site=eds-live&scope=site
Methotrexate [package insert]. (2016). Huntsville, AL. DAVA Pharmaceuticals, Inc.
Motrin [package insert]. (2007). New York, NY: Division of Pfizer, Inc.
O'Shea, J. J., Kontzias, A., Yamaoka, K., Tanaka, Y., & Laurence, A. (2013). Janus kinase inhibitors in autoimmune diseases. *Annals of the Rheumatic Diseases*, *72*(Suppl. 2), ii111–ii115. https://doi-org.ezproxy.rosalindfranklin.edu/10.1136/annrheumdis-2012-202576
Olumiant [package insert]. (2018). Indianapolis, IN: Eli Lilly and Company.
Orencia [package insert]. (2017). Princeton, NJ: Bristol-Myers Squibb Company.
Plaquenil [package insert]. (2017). St. Michael, Barbados: Concordia Pharmaceuticals Inc.
Prednisone [package insert]. (2012). Columbus, OH: Roxane Laboratories, Inc.
Rituxan [package insert]. (2019). South San Francisco, CA: Biogen and Genentech Inc.
Roy, U. (2017). Structural modeling of tumor necrosis factor: A protein of immunological importance. *Biotechnology and Applied Biochemistry*, *64*(4), 454–463. https://doi-org.ezproxy.rosalindfranklin.edu/10.1002/bab.1523
Simponi [package insert]. (2011). Horsham, PA: Janssen Biotech Inc.
Singh, J. A., Saag, K. G., Bridges, S. L. Jr., Akl, E. A., Bannuru, R. R., Sullivan, M. C., ... McAlindon, T. (2016). 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care & Research (Hoboken)*, *68*(1), 1–25. https://doi-org.ezproxy.rosalindfranklin.edu/10.1002/acr.22783
Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016). Rheumatoid arthritis. *Lancet*, *388*(10055), 2023–2038. https://doi org.ezproxy.rosalindfranklin.edu/10.1016/S0140-6736(16)30173-8
Tofacitinib [package insert]. (2018). New York, NY: Division of Pfizer Inc.
Wahl, K., & Schuna, A. A. (2014). Chapter 72. Rheumatoid arthritis. In J. T. DiPiro, R. L. Talbert, G. C. Yee, G. R. Matzke, B. G. Wells, & L. Posey (Eds.), *Pharmacotherapy: A pathophysiologic approach (9th ed.)* New York, NY: McGraw-Hill.
World Health Organization. (2009). *Expert Committee on Biological Standardization. Guidelines on evaluation of similar biotherapeutic products*. Retrieved from https://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

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