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Comparison of the Therapeutic Efficacy of Rheumatoid Arthritis Treatments

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This is to certify that the doctoral dissertation by

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has been found to be complete and satisfactory in all respects,
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Walden University
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Abstract

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MA, Walden University, 2017

BS, Auburn University, 2011

Dissertation Submitted in Fulfillment

of the Requirements for the Degree of

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Abstract

Rheumatoid arthritis (RA) is an autoimmune condition that causes chronic joint pain and destruction. The current standard regimen of monotherapy disease modifying anti-rheumatic drug (DMARD) treatments may not be as effective as that of combination therapy of a DMARD and a biologic agent in treating RA. The purpose of this study was to answer the question, is there a difference in the therapeutic efficacy of combination DMARD treatments with a biologic, compared to monotherapy DMARDs without a biologic, in U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA? Guided by the theoretical framework of integrated theory from evidence-based practices, this study used a cross sectional study design and data from AR-PoWER Patient Powered Research Network. Having adjusted for age, logistic regression was used to examine the association between the therapeutic effectiveness and treatment modality (DMARDs without a biological agent versus DMARDs with a biologic agent; OR = 1.15, 95% CI = 0.57-2.33). The result indicated that there was no significant association between treatment effectiveness and treatment modality. A positive social change implication of this finding is that the assessment of the efficacy of DMARDs with or without a biologic agent may warrant further investigation in which studies with large sample sizes that include various populations are used. In this study, there was no difference between the monotherapy and combination therapy treatments for Caucasian women aged 30 to 60 years. However, a future study with a larger sample size that compares diverse populations may produce a different outcome.

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Dedication

I dedicate this study to my daughter and family. God has stood by us all to give us strength and blessings as we all had to struggle through the journey. When a person chooses to extend their education to a Ph.D., the entire family makes the decision. There were sacrifices made, but reasoned with, throughout the years. During my path of cognition and perception, I was diagnosed with inflammatory autoimmune. I had hoped that I would progress to remission, but over the past 2 years I realized it would be a battle that would lead to disablement. My strength came from God to push forward for the sake of my daughter. The process was so important because it communicated a message to her to never surrender yourself to fear. The only way I could send the message was by completing the mission. My husband was my anchor with his prodigious support and his zealous nature. My daughter was my drive and energy. My mother was my comfort because no matter the lengthy amount of time it took to complete my task, she assured me everything was going to be okay. God was my firm foundation of it all!

Acknowledgments

I would like to thank all of the faculty who have helped me reach this point in my academic career. I would like to express special gratitude towards my chair, Dr. Gudeta Fufaa, that has been a phenomenal mentor to me during this process. I would also like to show appreciation and gratitude to my committee, Dr. Howell Sasser. I am humbled by the academic support of the Dean of Sciences that contributed to this success. I would also like to acknowledge appreciation to the Global Healthy Living Foundation for their support in allowing me to use their AR-PoWER Database for this research. Thank you all and God Bless!

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Chapter 1: Introduction to the Study

Background

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that causes abnormal inflammation of the joints (Zengin et al., 2018). It can attack organs such as the heart and the lungs, tissues such as muscle and cartilage, and ligaments and bone (Shiel, 2018). RA causes chronic swelling that results in permanent joint destruction and severe pain (Shiel, 2018). The aggressiveness of this disease can cause permanent disability (Shiel, 2018). An estimated 23.5 million United States citizens have been affected by the autoimmune effects of RA (Alam et al., 2017). The disease is estimated to be 2-3 times more common in women than men (Bokarewa, 2014). RA can affect all ages and races (Shiel, 2018). RA is known to shorten the lifespan of patients and increase their risk of mortality (Kelly & Hamilton, 2007). One of the common treatment options for RA is the use of disease-modifying, anti-rheumatic drugs (DMARDs), but these treatments are still observed to be less effective than combination treatments with a biologic in reducing the risk of mortality due to their suppression of the immune system by targeting the entire system (Iliades, 2017). Researcher Chris Iliades (2017) observed Janus Kinases (JAK) pathways for a broad population that included all races and genders. His study showed that DMARDs were less effective than combination treatments. Because combination treatments have not been observed at specific population levels, this study observed Caucasian women from ages 30 to 60 years. Combination treatments can include other DMARDs or the use of biologics. Biologics, such as tumor necrosis factor (TNF) blockers, are different from DMARDs because these drugs target specific areas of the

inflammatory process (Iliades, 2017), whereas DMARDS inhibit the production of cellular immune response to antigens. There are biologics that target other immune pathways, such as interleukin pathways and JAK pathways, which was the pathway that Iliad studied.

Problem Statement

The therapeutic efficacy of combining DMARDs and biologics has never been comprehensively studied at population data levels of Caucasian Alabamian women aged 30 to 60 years who have been diagnosed with RA. Biologics may work well in combination with DMARDs, such as Plaquenil or methotrexate, that interfere with cell communication in autoimmune diseases by hindering the antigen processing (Goldman et al., 2000). These immunosuppressants can help prevent infection by reducing the frequency of producing antibodies to the biologic agent (Cunha, 2016). Adequate research has not been performed to provide data on the effectiveness of combination treatments with a DMARD and a biologic. Therefore, further research is needed on the comparative analysis of combination treatments with and without biologic agents (Gradual et al., 2014). The importance of this study was that it compared the results obtained in the target population when using a DMARD with and without a biologic. Methotrexate is the standard first choice treatment of physicians and insurance providers. Insurance companies may require patients to have a trial and failure on this drug before they can move to another DMARD treatment, such as Plaquenil, or a biologic. The observation and comparison of drug treatments was performed on a specific target

population of U.S. citizen women aged 30 to 60 years collected from a national database through statistical data analysis. The DMARDs work by stopping inflammatory cells from being produced, and the biologics work to stop the immune system from being overactive, and together the two may shorten the disease progression and allow the patient to feel pain relief in a timely manner (Levine, 2017).

Purpose of the Study

The purpose of the study was to compare the therapeutic efficacy of RA treatments, a DMARD, such as Plaquenil or methotrexate, which are the most commonly used DMARDs, with and without a biologic, in a specific population. This study used a cross sectional study design and data from Arthritis Partnership with Comparative Effectiveness Researchers (AR-PoWER), a Patient Powered Research Network. Having adjusted for age, logistic regression was used to examine the association between the therapeutic effectiveness and treatment modality (DMARD with and without a biologic.) The typical challenges of research on population data are time, expense, and clinical conditions. The plan to control for these challenges is the establishment of a target population and written approvals to access national databases. The target population for this research was specifically gender-based and population-based. It included Caucasian women that are United States Citizens, aged 30 to 60 years, because RA is most common in women between those ages (Arthritis Foundation, 2017). It is of high importance to control RA in these patients by suppressing the inflammation in a timely manner and

sustaining overall improvement and wellbeing of the patients (National Rheumatoid Arthritis Society [NRAS], 2019).

Significance of the Study

This study enhanced the knowledge on how DMARD treatments could be used in conjunction with a biologic to control for the inflammatory responses to prevent pain, severe bone erosion, joint deformity, and organ damage (Guo et al., 2018). Combination treatments can be effective for some RA patients but are not necessarily effective for all RA patients, because the prescribed treatments for the autoimmune disease will respond to each individual's cellular structure differently. There was a knowledge gap between the use of DMARD monotherapy versus combination biologic-DMARD therapy for the therapeutic efficacy of RA treatments, but this study provided knowledge that helped close the gap for Caucasian women aged 30 to 60 years that have been diagnosed with RA. The statistical findings were that a DMARD and biologic work together to provide relief to the patient with RA, but not necessarily better than DMARDs alone. In some patients, an early diagnosis together with a combination therapy could provide relief by suppressing the inflammation and blocking the inflammatory pathway in a shorter time frame than monotherapy treatments because biologics cause cells to respond quicker than DMARDs (Rein & Mueller, 2017). A combination drug treatment, such as a Plaquenil DMARD and a Remicade biologic, may seem to be an effective therapy, considering DMARDs work by stopping inflammatory cells from being produced, and the biologics work to stop the immune system from being overactive (Levine, 2017). However, the

findings of this study did not support the therapeutic efficacy of the two treatments taken in conjunction. This research was performed to fill the gap in the literature as to whether combination therapy consisting of a DMARD and a biologic should be the initial standard drug treatment for U.S. Caucasian women between the ages of 30 to 60 years that have been diagnosed with RA. Public health practitioners, insurance providers and physicians are the ones that design the policies of standard regimen for the disease. This research can possibly make an impact on their policies of treatments for patients being diagnosed with RA.

This study did not find that combination therapy is better than the current standard monotherapy, but it may continue to cause social change through statistical evidence that a combination treatment could be used to decrease the severity of joint pain for some patients, but is not statistically therapeutic for all patients to control the pain ailments and disability that occur with RA. This study may help bring social change by providing evidence related to the efficacy of combination therapy for RA, compared to the standard monotherapy treatment, which would be valuable in developing more effective clinical and/or public health practices for healthcare policy regulations to ensure regulatory standards are being met. A social change implication of this study's findings is that the assessment of the efficacy of DMARDs with a biologic agent and DMARDs without a biologic agent may warrant further investigation in studies with large sample sizes that include various populations.

Rationale of Theoretical Framework

The use of integrated theory from evidence-based practices uses data from patients that details their effectiveness of the drug treatments that would allow for more accurate decision making to be made in comparing monotherapy and combination therapy for RA patients. Integrated theories are based on evidence in research (Gopalakrishnan & Ganeshkumar, 2013). Integrated theories make connections through knowledge and practice. Integrated theory from evidence-based practice is customarily used to examine intervention efficacy and safety (Pipe, 2017) and is adopted as an appropriate framework for guiding the comparison of therapeutic efficacy of RA treatments. There are particular areas of interest for the use of integrated research, such as epidemiology, health promotions, health risk factors, clinical pathology, preclinical biology and disease mechanisms, and models in medicine and biosciences (National Research Council, 2018). Stakeholders that would be interested in using the integrated research model would be clinicians, scientists, health providers, pharmaceuticals, and bio-tech industries (National Research Council, 2018). The research model targets tailored care, better quality of life, and healthcare maintenance and promotion (National Research Council, 2018). The end users of the research model are the patients that benefit from the therapeutics (National Research Council, 2018). This proposed research framework has the potential to inspire questions and challenge method assumptions (Din & Paskevich, 2013).

Quantitative Research Question

Is there a difference in the therapeutic efficacy of combination DMARD treatments with a biologic, compared to monotherapy DMARDs without a biologic, in U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA?

This study was conducted as quantitative research. It consisted of secondary data for comparative analysis. The possible differences in the variables were the focus of the exploration. The goal was to reveal a variation of differences in the forms of treatments as the basic formation of statistical analysis. It was beneficial to determine the statistical impact of the variables: DMARD therapy without a biologic, in comparison to the DMARD with a biologic.

Null Hypothesis: There is no difference in the therapeutic efficacy between combination therapy and monotherapy in treating U.S. Caucasian women between the ages 30 and 60 that have been diagnosed with RA.

Alternative Hypothesis: There is a difference in the therapeutic efficacy between combination therapy and monotherapy in treating U.S. Caucasian women between the ages 30 and 60 that have been diagnosed with RA.

Definition of Terms

Antigen: A molecule in the body that triggers an adaptive immune response. (Arduengo, 2020). In reference to autoimmunity, the antigen is a self-antigen that triggers an immune response on itself.

Articular: The synovial joints (Bhosale & Richardson, 2008).

Autoimmune: A self-damaging condition in which the cells mistakenly attack the body in response to a malfunction of the immune system (Zengin et al., 2018).

Biologic Agents: Drugs that are complex medicinal products from living organisms. This class of drugs is used to treat a variety of diseases, including autoimmune diseases, cancer, growth disorders, and rare genetic conditions (Cunha, 2016).

Clinical Conditions: The identification of a patient's diagnosis that is associated with one specific health condition or more than one health condition (Tilea et al., 2018).

Disease-modifying antirheumatic drugs: A class of drugs made of monoclonal antibodies that are used to treat RA, as well as other autoimmune diseases, to suppress joint damage, induce or maintain remission, reduce flare-ups, and sustain disease control (Guo et al., 2018).

Immunogenicity: The ability of an antigen to trigger a cell-mediated immune response (Sauna, 2020).

Immunosuppressants: A class of drugs used for autoimmune diseases to weaken the immune system to suppress the damaging reaction that is being induced on the body by its own cellular activity (Cunha, 2016).

Methotrexate: A folic acid analogue drug that is used as a chemotherapeutic agent in the treatment of RA and other autoimmune diseases as well as cancer (Teja & Damodharan, 2018).

Plaquenil: An anti-inflammatory, hydroxychloroquine (HCQ) drug that is used as a suppressive treatment for RA and lupus, and it is also used against malaria (American College of Rheumatology, 2018). It interrupts cellular communication of the immune system to prevent joint damage and reduce the risk of long-term disability (American College of Rheumatology, 2018).

Population Data: Information gathered from a specific group or population identified by characteristics for data. In this research it is women with RA (Taylor et al., 2019).

Rheumatoid Arthritis: A chronic autoimmune disorder that causes abnormal inflammation of the joints (Zengin et al., 2018).

Suppress: The reduction or inhibition of a

reaction of the immune system (Cunha, 2016).

Synovial: A secreted membrane fluid that lubricates the joints (Bhosale & Richardson, 2008).

Therapeutic Efficacy: The maximum response of a drug to achieve beneficial therapy/treatment (Mandal, 2018).

Tumor Necrosis Factor: A protein that is capable of inducing apoptosis, cell death, of a tumor cell through pro-inflammatory actions (Shiel, 2019). Cytokines are the small proteins that are released to signal the process that causes inflammation (Shiel, 2019).

Tumor Necrosis Factor-IR (TNF-IR): Patients who exhibit inadequate response to TNF (Shiel, 2019).

Chapter 2: Literature Review

Introduction

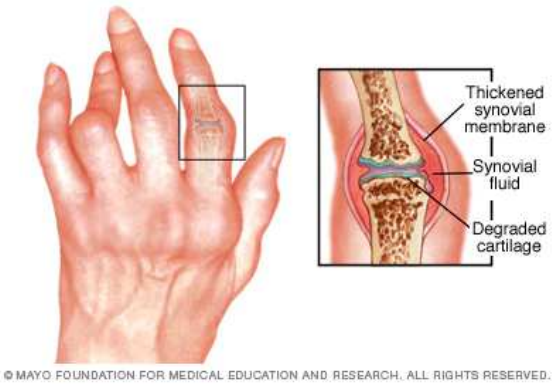
RA is a common chronic autoimmune disease with disabling joint inflammation. The inflammatory disease causes chronic pain, stiffness, and swelling of the joints. It affects approximately 1% of the United States population and has an annual mortality rate of 26 per 1000 persons (95% CI, 25.87-27.97; Dellabella, 2018). The disease is twice as prevalent in women compared to men (Cherascu, 2011). The general range of affected ages are 40 to 70 years (Cherascu, 2011). However, all ages can be affected by RA.

Patients suffering from RA endure chronic pain that can be localized to select body parts such as the knees or can be all over the body. The inflammation caused by the disease affects the tissues that surround the joints as well as other organs in the body (Kerkar, 2018). A person's immune system attacks the healthy tissues of the body as if it were using antibodies to destroy invaders like pathogens that cause infections (Kerkar, 2018). Therefore, patients diagnosed with this autoimmunity have antibodies in their blood that target the tissues of the body resulting in inflammation of the joints (Kerkar, 2018). The chronic inflammation of the disease may result in damage to the bones, ligaments, and cartilage that leaves the joints deformed (Kerkar, 2018). The symmetrical arthritis of the smaller joints refers to the arthritis that attacks hands and feet (Cherascu, 2011). However, bilateral arthritis attacks bilateral hand joints, which consist of interphalangeal joints (phalanges), metacarpophalangeal joints (knuckles), carpometacarpal joints, and wrist joints and/or bilateral foot joints, which consist of

interphalangeal joints (phalanges), metatarsophalangeal joints (base of phalanges), tarsometatarsal joints (mid-foot), talonavicular joint (talus side of foot), and tibio-talar joint (ankle) (Arthritis Foundation, 2017). The larger joints that may be affected by the inflammatory processes are the shoulders, knees, hips, and axial skeleton (Cherascu, 2011). The functional impairments of the disease result in the loss of productivity and an increase in disability (Cherascu, 2011). The disease can be so severe that it causes unrelenting joint destruction that can lead to amputation if not treated before the joint becomes deformed (Cherascu, 2011).

Figure 1

Rheumatoid Arthritis Deformity Example



(Mayo Clinic, 2018)

Risk Factors of RA

RA causes chronic inflammation of the synovial membrane which lines the joints and connects the bone and cartilage (Jimenez-Boj et al., 2005). Thus, the joints are not the only part being injured as neighboring structures are also damaged (Jimenez-Boj et al., 2005). In fact, RA is capable of attacking all parts of the body, including the organs, bones, blood, and bone marrow. Specific organs and areas that may be affected by RA are the skin, lungs, heart, blood, eyes, mouth/gums, kidneys, liver, spleen, nervous system, bones, and bone marrow (Dunkin, 2015).

Parts of the Body Affected by RA:

1. **Skin:** Half of the patients with RA may develop rheumatoid nodules under the skin in bony areas that are exposed to pressure, the feet being a good example (Dunkin, 2015). These nodules are sensitive and can diminish or recede with DMARD treatment (Dunkin, 2015). Rashes and skin ulcers are capable of forming due to the underlying inflammation of the skin itself or the blood vessels (Dunkin, 2015).
2. **Lung:** About 80% of the patients with RA experience lung inflammation that may cause interstitial lung disease and consequently shortness of breath (Dunkin, 2015). If persistent inflammation occurs, pulmonary fibrosis can develop, which is scarring of the lungs (Dunkin, 2015). The result is the thickening of the pulmonary wall and decreased oxygen. Rheumatoid nodules are also capable of forming inside the lungs (Dunkin, 2015).

3. **Heart:** About 50% of the patients with RA experience inflammation of the heart lining known as pericarditis that results in chest pain (Dunkin, 2015). However, treatment with DMARD therapy and biologics can control the inflammation of the pericardium (Dunkin, 2015). Plaque from damaged blood vessels (atherosclerosis) can cause heart attack and strokes in patients with RA (Dunkin, 2015). DMARDs and biologics can reduce cardiovascular risks (Dunkin, 2015).
4. **Blood:** Persistent inflammation can lead to a reduction of red blood cells thus causing anemia, which results in low-iron or low serum ferritin (Dunkin, 2015). Inflammation of the blood and blood vessels can potentially cause blood clots by increasing the platelet counts (Dunkin, 2015).
5. **Eyes:** RA patients are at risk of developing scleritis, which is an inflammation of the sclera of the eyes resulting in pain, redness, blurred vision, and light sensitivity (Dunkin, 2015). Another type of inflammation of the eyes is uveitis. The inflammation targets the area between the sclera and the retina and is capable of causing blindness without treatment (Dunkin, 2015). Inflammation can cause Sjogren's syndrome, which damages the tear-producing glands, resulting in severe dry and gritty eyes (Dunkin, 2015).
6. **Mouth/Gums:** Inflammation of the moisture-producing glands in the mouth can lead to dry mouth and gum disease; bacteria can develop and cause tooth decay (Dunkin, 2015).

7. **Kidneys:** If a patient does not pursue a therapeutic regimen of DMARDs and/or biologics and chooses to treat RA with only non-steroidal anti-inflammatory drugs (NSAIDS) to alleviate pain and swelling, damage to the kidneys may occur (Dunkin, 2015).
8. **Liver:** Overuse of Tylenol and methotrexate therapy can result in liver damage (Dunkin, 2015).
9. **Spleen:** Longstanding untreated RA can lead to Felty syndrome, which results in an enlarged spleen and low white blood cell counts (Dunkin, 2015). The condition increases the patient's risks of bacterial infections, cancers, and lymphoma (Dunkin, 2015).
10. **Nervous System:** Inflammation flares of tissues can lead to compression of nerves resulting in numbness and tingling (Dunkin, 2015). Carpal tunnel syndrome is a common concern with RA due to compressing of nerves by inflamed tissues of the wrist (Dunkin, 2015). The nervous system normally detects inflammation in the tissues, but RA can cause an imbalance in the nervous system (Koopman et al., 2016). RA reduces the activity of the parasympathetic nervous system and causes the sympathetic nervous system to become overactive (Koopman et al., 2016).
11. **Bones:** RA causes chronic inflammation of the bones resulting in the loss of bone density and vitamin D (Dunkin, 2015). The bones and the joints become

thin and brittle (Dunkin, 2015). DMARD therapy and biologic treatments can improve the bone condition.

12. **Bone Marrow:** RA can infiltrate the bone marrow and disrupt the production of red blood cells (Bouchnita et al., 2016). This is consistent with the cause of anemia and lack of oxygen-binding proteins in the red blood cells.
13. **Cancer:** RA is known to be associated with a number of cancers, including lymphoma, lung cancer, and non-melanoma skin cancer, and possibly cervical, prostate, and melanoma skin cancers, but a decreased risk of colorectal and breast cancers (Lange et al., 2016).

Patients with RA have a shorter life expectancy than the general population mostly due to the significant increase in comorbidities such as heart attacks and strokes (Emrich, 2009). RA is commonly referred to as a systemic illness or rheumatoid disease since chronic inflammation affects multiple organs of the body (Kerkar, 2018). Vasculitis is one of the serious complications that results from RA (Cleveland Clinic, 2019). The comorbidity occurs when the blood vessels become inflamed. The arteries and veins may become weakened causing little or no blood flow to the skin, nerves, and internal organs (Cleveland Clinic, 2019). Vasculitis of the larger arteries that decreases or stops the blood flow to tissue sites can ultimately result in a stroke or heart attack (Cleveland Clinic, 2019). Rheumatoid vasculitis occurs in the more severe RA cases. Patients who have suffered from RA for many years are likely to experience the illness (Cleveland Clinic, 2019). The condition occurs in less than 5% of RA patients (Cleveland Clinic, 2019).

Inflammation and swelling of the heart's outer wall or heart muscle itself is another serious complication among RA comorbidities. The swelling causes patients to experience chest pain and decreased cardiac output, which can lead to congestive heart failure (Emrich, 2009). The inflammation and swelling of the heart's outer wall are called pericarditis (Emrich, 2009). Inflammation of the heart muscle is called myocarditis (Emrich, 2009). The two conditions weaken the functionality of the heart leading to congestive heart failure, which is a decrease in the pumping of the blood in and out of the heart. Although RA has high morbidity and mortality rates, it is often not the immediate cause of death but rather predisposes the patients to comorbidities that may directly cause death (Molina et al., 2015).

Diagnosis of Rheumatoid Arthritis

Through rheumatoid factor (RF) and anti-citrullinated protein antibody (tested as anti-cyclic citrullinated peptide [anti-CCP]), physicians, specifically rheumatologists, are able to establish the presence of the autoimmune disease (Cubero et al., 2016). Anti-CCP and RF are immunoglobulin M (IgM) antibodies produced by the immune system in response to foreign cells that produce inflammatory symptoms (Freeman, 2018). RF intensifies the inflammatory response of macrophages induced by the specific immune complexes of RA (Laurent et al., 2015). Citrullinated proteins are found in the synovial tissue, and they diminish amino acids such as arginine that change the charge of the protein which could potentially be a cause for the autoimmune disease because of its inability to interact with neighboring proteins (Van Venrooij and Pruijn, 2000). Proteins

must interact with other proteins to function and communicate. Anti-CCPs are present in 60- 70% of RA patients, and RF is present in 70- 90% of RA patients (Freeman, 2018). These markers can be found in early or late-stage disease (Freeman, 2018). The more aggressive the units of the lab results are for these tests, meaning the results exceed the normal range, can determine the aggression of the disease as well as a more aggressive treatment option (Freeman, 2018). These are specific biologic markers in the DNA that are associated with the pathogenesis of RA (Liao et al., 2009). The U.S. National Institutes of Health defined biomarkers as characteristic diagnostic indicators to measure the activity of the disease (Taylor, 2019). To fully diagnose a patient with RA, a positive anti-CCP blood test in conjunction with a positive RF along with physical examinations, imaging, and other blood tests that measure inflammation levels are required (Freeman, 2018). However, x-rays may not show any signs of disease activity in early RA. On the other hand, inflammation and swelling are typically present on physical examination. Anti-CCP is used in conjunction with RF because RF alone can be present in other illnesses, such as hepatitis (Freeman, 2018). Therefore, the two biomarkers must be positive for a more accurate seropositive diagnosis of RA (Freeman, 2018).

Autoimmune conditions like RA are mostly identified by autoantibodies. Autoantibodies are just like normal antibodies that are immune proteins created by the immune system, except autoantibodies mistakenly target the wrong cells or proteins as the antigen. RA patients might have a positive antinuclear antibody test result. The test is of prognostic importance among juvenile RA cases (Ravelli et al., 2005). C-reactive

protein (CRP) and fibrinogen are immunological proteins produced by the liver (Babikir et al., 2017). They are used as biomarkers to monitor the status of inflammation in the body (Babikir et al., 2017). Erythrocyte sedimentation rate (ESR) is another blood test performed to check the inflammation in the body (Babikir et al., 2017). CRP and ESR levels mostly rise in RA, but they can also increase in other inflammatory diseases. The acute phase reactants formulate part of the RA classification process by serving as inflammatory markers (Aletaha et al., 2010). CRP and ESR levels help to measure RA disease activity and elicit medication response as well.

Autoimmunity can cause disruptions and complications throughout the entire immune system. A decrease in the inflammatory articular disease reduces the autoantibodies being released that are attacking healthy cells. Besides, some ways have been used in differentiating RA from other arthritic disorders. Structural changes are seen using conventional radiography or the imaging methods used to distinguish RA from other arthritic disorders in their early stages. RA is less destructive in the early stages, but it accumulates over time by damaging bone, cartilage, and tissue. The longer RA is left untreated, the more damage it causes, which increases pain, deformity, and potential infections, and decreases lifespan.

In the last 10 years, the process of fighting arthritic disorders has been done using DMARDs (Chatzidionysiou et al., 2017). The most commonly used DMARDs include methotrexate and Plaquenil. However, the development of new biological agents has made it possible to manage the signs and symptoms associated with RA. Early treatment

of RA improves the likelihood of suppressing the disorder. In fact, early treatment of RA has saved patients from the severe effects of the disease. Current RA clinical treatment trials have been hindered by inadequate numbers of patients in the early stage of disease. Consequently, researchers have failed to establish the effectiveness of an early intervention therapy to prevent the progression of the disorder to later stages.

Classification criterion is the standardized way of defining the presence of RA disorder in an individual. Taking the appropriate steps of diagnosing the disease by observing the specific markers doctors use to diagnose RA is classification criterion. However, careful clarification is involved because some markers can represent another autoimmune disease. For example, CRP and ESR are inflammatory markers for RA but can also be seen in Lupus. However, adequate elevation levels of RF and anti-CCP with ESR can represent autoimmunity for RA. Through the use of the classification method, healthcare personnel can group individuals by whether or not they have RA. Further, the grouping has helped in clinical trials on individuals who might be genetically receptive or who are already suffering from the disorder symptoms and being diagnosed. Again, the classification criteria have helped investigators to conduct various studies that relate to RA (Ajeganova et al., 2017). Through the research, scientists have managed to develop stringent measures of managing the disease. Doctors have applied the criteria in many parts of the world to address the effect and treatment of the disease. The American College of Rheumatology (ACR) came up with the classification criteria used commonly by doctors in many parts of the world (Ajeganova et al., 2017). However, the criteria

developed by the ACR are used in diagnosis to provide the benchmark for defining the presence of the condition. The classification criteria established by ACR distinguishes the afflictions of RA from other known rheumatology disorders, such as psoriatic arthritis.

Etiology and Classification of RA

Modern therapies aim to make sure RA patients do not go through the chronic stages of the disease as indicated in the 1987 criteria for RA disorder. However, experts from both ACR and the European League against Rheumatism (EULAR) came together to develop a more simplified way of approaching the diagnosis and treatment of RA disorder (Shiboski et al., 2017). The main aim of the ACR and EULAR experts was to devise classification criteria that would address methods of handling early cases of RA. The approach led to the development of the 2010 ACR/ EULAR classification criteria for RA.

RA's etiology remains multifactorial just like other autoimmune conditions; meaning it has various causes and influences. Familial clustering alongside monozygotic twin studies revealed genetic susceptibility with about half of RA risk being traceable to genetic factors (Chung et al., 2007). Genetic RA associations include human leukocyte antigen-DR45 and DRB1 among other alleles referred to as shared epitope (Chung et al., 2007). Genome-wide studies pointed to other genetic signatures that raise the chances of acquiring RA and other autoimmune conditions, like cluster-of-differentiation-40 (CD40) and *STAT4* gene (Chung et al., 2007). A cluster-of-differentiation (CD) surface protein acts as a marker protein on an antigen-presenting cell, such as macrophages, dendritic

cells, and B-cells. There is oxidative damage implicated in the pathogenesis of RA which causes an imbalance between the reactive oxygen and the biological system's reaction to antioxidants (Karlson et al., 2008). Free radicals have been found within the rheumatoid synovium and in the plasma (Karlson et al., 2008). RA can be caused by environmental factors, such as long-term smoking and various infectious diseases, or it can be caused by genetic predisposition (Edwards & Cooper, 2006). Potential infectious candidates that could trigger this autoimmune response are retroviruses, Epstein-Barr Virus, Fifth Disease, *Escherichia coli, Mycobacterium tuberculosis,* and *Proteus mirabilis* (Edwards & Cooper, 2006). These infections can increase the antibody titers found in RA patients (Edwards & Cooper, 2006). Genetic factors are responsible for at least 50% of the risk, while environmental factors potentially make-up the rest (Edwards & Cooper, 2006).

Individuals from families with genetic history of the disease, the elderly, and women are at a higher risk of the disease than those that are not of these categories. Gender and age differentials directly contribute to the disease prominence (Firestein & Kelley, 2009). Current and previous cigarette smokers have higher chances of contracting RA (Costenbader et al., 2006). Pregnancy is known to cause RA remission due to immunologic tolerance (Kaaja & Greer, 2005). Parity exhibits a long-lasting impact, and it is notable that RA is less likely to occur among pregnant women compared to nulliparous women (Guthrie et al., 2010). However, during pregnancy there is a spike of estrogen and progesterone. Hormones can play a huge role in woman in various ways. Estrogen imbalances have been thought to make an impact as a potential risk factor of the

disease. Recently, researchers Grant Hughes and Divaker Choubey studied the hormonal effect on RA (Lunardo, 2016). They found that at high levels, these two hormones suppress RA, such as during pregnancy, but at lower levels, such as during menopause, hormone replacement and oral contraceptives are associated with a greater risk of RA (Lunardo, 2016). More research is required on the hormonal effect of RA, but researchers have confirmed that estrogen and progesterone are "dominant risk modulators" for a similar autoimmune disease called Lupus (Lunardo, 2016). A risk of disease production through breastfeeding was a concern until a recent study was performed and found that long-term breastfeeding of greater than 13 months was associated with a significant reduction of RA (Liao et al., 2009). Therefore, breastfeeding reduces the chances of advancing to RA among women who breastfeed. High birthweight is a potential risk factor for RA. A recent study focused on this risk and found that babies weighing greater than 9.9lbs at birth had at least a two-fold risk of developing RA compared with babies who were 7.0 - 8.5lbs at birth (Liao et al., 2009). The disease is high during menstrual cycles and intermittent menstrual periods; increasing the woman's risk of advancing to RA (Karlson et al., 2004). The hormone changes that occur during menstrual cycles disrupt the inflammatory markers in the body causing flare-ups of RA.

RA creates inflammatory pathways that result in synovial cell proliferation within the joints. Over secretion of proinflammatory cytokines like TNF, JAK and interleukin-6 (IL-6) makes the destruction process take place quickly (Scott et al., 2010). TNF is a protein that is capable of inducing apoptosis, cell death, of a tumor cell through pro-

inflammatory actions (Shiel, 2019). Elevated levels of IL□6 have been reported in the serum and synovial fluid of RA patients and found to correlate with inflammation and disease activity (Genovese, Fleischmann & Kivitz, 2015). A humanized inhibitor of IL□6 activity has been shown to be elevated in RA, but an administered combination of therapeutics with a DMARD and a biologic may reduce the pro-inflammatory cytokine (Genovese et al., 2015). Cytokines are expressed at high levels in the joint tissues resulting in inflammation and articular destruction (Taylor & Feldman, 2009). "TNF was the first cytokine to be fully validated as a therapeutic target for RA" (Taylor & Feldman, 2009). Although TNF is the preferred target for biologic therapy, interleukins have also been validated for target therapy (Taylor & Feldman, 2009).

Patients diagnosed with RA mostly exhibit pain and stiffness across various joints of the body. The most affected joints are proximal interphalangeal joints, wrists, and metatarsophalangeal joints. Morning stiffness that lasts beyond an hour could be a form of inflammatory etiology. Dreadful swelling from synovitis becomes visible at any stage. The subtle synovial thickening might be palpable when examined. Before the onset of clinically diagnosable swelling, the patient might develop indolent arthralgias. Systemic symptoms like fatigue, low-grade fever, and weight loss might occur once the disease fully develops or matures.

ACR and EULAR worked together in 2010 to establish newly distinct classification measures for RA (Aletaha et al., 2010). The newer techniques express efforts towards early RA diagnosis among patients that never met the 1987 ACR

classification criteria through observation of specific protein markers and magnetic resonance imaging (MRI) of bone erosion. Moreover, a group of Dutch researchers developed clinical prediction rules for RA (Van der Helm-van Mil et al., 2007; Mochan & Ebell, 2008) whose purpose was to identify patients with undifferentiated arthritis that could potentially develop RA. As a result, this standard involves follow-up and referral processes. After doctors diagnosed a patient with RA there were standards for follow-up appointments to re-evaluate the progress of the disease and the effectiveness of the medications. If a doctor was not able to make an accurate diagnosis, then a referral was performed. It is best to see an actual rheumatologist for evaluation of RA opposed to general physicians because the rheumatologists are more knowledgeable of the biomarkers to evaluate.

Immunology Alongside RA

The understanding of the pathophysiological aspects of RA is difficult. There is evidence that RA plays a pivotal role on the immune response, but researchers understanding of the disease is far from complete (Kavanaugh & Lipsky, 2012). The immune system responds when it is activated by antigens that may include proteins being seen as antigens. For people with RA, their immune system is activated consistently due to an immune response of releasing cytokines, interleukins, and TNF in response to healthy cells that are foreseen as antigens. As a result of the autoimmunity activating an immune response, the body becomes weak and exhausted. There have been vigorous experimentations for defining the immunopathological basis of disease to create

therapeutic agents and improved therapies (Kavanaugh & Lipsky, 2012). The molecular design to treat the damaging immunological responses caused by RA is to target specific parts of the immune system that are responsible for the reaction without causing further damage to the filtering organs (Kavanaugh & Lipsky, 2012). The primary complete blood count alongside the differential and assessment of the hepatic and renal functions fundamentally assists in determining the treatment options. For instance, patients that suffer from insufficient renal function or significant thrombocytopenia would not be prescribed a NSAID due to an increase in renal toxicity. Of those RA patients that experienced problems or difficulty with their hemoglobin levels or hepatic functions, 33-60% incurred chronic mild anemia (Wilson et al., 2004). This is due to a drop in red blood cells and the reduction of oxygen needed to be transferred to functioning organs that make proteins important for fighting infection and inflammation (Wilson et al., 2004). Gastrointestinal blood loss should be prevented among patients on NSAIDs or corticosteroids. Methotrexate is not recommended for patients with hepatitis C or severe renal impairment (Saag et al., 2008) because methotrexate can elevate liver enzymes which can leak chemicals into the blood stream and cause toxicity to the blood (Kassas et al., 2018). Biological agent therapies deserve negative tuberculin tests that tests for latent tuberculosis (TB) because TNF inhibitors interfere with immune system allowing for infections to occur, and TB is still active today. The TNF inhibitors are used for autoimmunity, but the potency of the medication can interfere with immune responses. However, when taken as a combination with a DMARD, the risk of infection is reduced

because the DMARDS suppress the immune system to reduce the frequency of producing antibodies to the biologic (Cunha, 2016). Hepatitis B reactivation is a possible occurrence with TNF inhibitor use. Patients whose symptoms are of less than six weeks duration might experience viral processes like parvovirus (Saag et al., 2008). Recurrent self-limited episodes of acute joint swelling predict crystal arthropathy, which means arthrocentesis ought to be performed to assess calcium pyrophosphate dehydrate or monosodium urate monohydrate crystals (Saag et al., 2008). To assist in conducting diagnosis and possible choice of a given treatment strategy, patients with inflammatory arthritis may get a prompt referral to rheumatology subspecialists to check characteristics of given erosive changes. Hands and feet radiography should be performed to assess patients who exhibit inflammatory back symptoms, inflammatory eye disease, or inflammatory bowel disease that might depict spondyloarthropathy (Saag et al., 2008). Skin findings, such as rashes that suggest systemic lupus erythematosus, systemic sclerosis, or psoriatic arthritis, may be the cause of the rashes from an autoimmune reaction (Wilson et al., 2004). Polymyalgia rheumatic are typically considered among older patients incurring symptoms within their hips and shoulder; and these patients should be asked questions based on temporal arteritis. Various myofascial trigger points and somatic symptoms predict possible fibromyalgia that may exist alongside RA. There may be multiple immune-mediated conditions that seem to follow the autoimmune disease, RA (Zerbo et al., 2016).

Efficacy-Based Treatment Guidelines for Rheumatoid Arthritis

The main treatment guidelines for RA suggest the use of DMARDs as the mainstay therapeutic intervention for the disease. DMARDs should be administered immediately after diagnosis to treat the condition. Early diagnosis and drug therapy using DMARDs may help prevent structural damage, and may lead to possible remission (Cherascu, 2011). The sooner the diagnosis, the sooner the treatments begin. Once the treatments become active, the desirable outcome will entail reduced pain and inflammation as well as the prevention of further destruction of the body by the disease.

Medical practitioners should begin administering the therapy to patients with RA, who are at risk of erosive and persistent arthritis, even if they do not meet the prescribed benchmarks for initiating the treatment. It is not absurd to start the treatment with DMARDs before confirmation of diagnosis. Because RA takes time to diagnose, there are outcomes of good quality randomized controlled trials (RCT) that give evidence of a possible role of therapeutic drugs in undistinguished arthritis (Wilson et al., 2004). These RCTs may prevent progression of radiographic damage of joint destruction and anemia through trial and error of research (Wilson et al., 2004). The mission of the treatment is to aim for a target. The target may be remission or low disease activity (Craven, 2017). The disease activity may be monitored every 1-3 months (Craven, 2017). If there is not any improvement by the 3rd month of treatment, then the physician may adjust the treatment option (Craven, 2017). If the target trial time of the medication has been reached by the 6th month after diagnosis, the treatment options may be adjusted if there is no

improvement. Methotrexate is the first treatment strategy (Craven, 2017). If methotrexate cannot be tolerated, HCQ, leflunomide or sulfasalazine are the next DMARD treatment options of choice. ACR/ EULAR classification criteria for RA are based on the efficacy of evidential management of RA by a large international task force (Craven, 2017). The international task force included several departments of rheumatology all around the world that based their decisions, principles, and recommendations on systemic literature reviews for therapeutic strategies of RA (Smolen et al., 2017).

Monotherapy and Combination Therapy in RA

RA is an autoimmune disease that has a significant negative impact on the ability to perform daily activities, work, and household tasks (Singh et al., 2016). The disease symptoms need to be treated to prevent further damage to the body. Anti-RA drugs consist of DMARDs and/or Biologics. DMARDs can slow the progression of the disease by suppressing the body's overactive immune and inflammatory systems (Cohen et al., 2019). DMARDs work to decrease the pain severity, reduce the inflammation, prevent joint damage, or reduce joint damage, and preserve the structure and function of the joints (Cohen et al., 2019). These medications are not designed to provide immediate relief of symptoms (Cohen et al., 2019). DMARDs are for long- term use and take weeks to months to become active in the body. There are a variety of types of DMARDs. The choice of which DMARD to take depends on the following: the stage and severity of the condition, the side effects, and the patient's personal preference which can be driven by insurance coverage plans (Cohen et al., 2019). In combination therapy, combining

DMARDs is frequently used as a first-line strategy that can provide a greater therapeutic efficacy than monotherapy in some patients, but it has higher toxicity (Wilsdon & Hill, 2017). Optimal combination of a DMARD with a biologic, and the timing of the combination therapy, has been demonstrated to have a superior outcome for some RA patients with an inadequate response to methotrexate alone (Wilsdon & Hill, 2017).

The most used DMARD treatments are methotrexate, sulfasalazine, HCQ, leflunomide, and azathioprine (Cohen et al., 2019). Methotrexate was originally designed for cancer patients but was found to reduce inflammation and decrease joint damage in RA patients (Cohen et al., 2019). It may be combined with other DMARDs or a biologic agent if it does not adequately control the disease alone (Cohen et al., 2019). It is the recommended first choice of treatment in the guidelines of the ACR and EULAR (Wilsdon & Hill, 2017). Sulfasalazine (Azulfidine) is used to treat RA as well as other rheumatic autoimmune diseases. It may be combined with other DMARDs or a biologic agent if it does not adequately control the disease alone (Cohen et al., 2019). HCQ (Plaquenil) was originally developed to treat malaria but was found to improve symptoms of arthritis and lupus. It can be used in combination with other DMARDs or a biologic (Cohen et al., 2019). Leflunomide (Arava) inhibits production of inflammatory cells to reduce inflammation and prevent joint damage from the inflammation (Cohen et al., 2019). It may be used in combination with DMARDs or with a biologic agent (Cohen et al., 2019). Azathioprine (Imuran) was also developed for the treatment of cancer, RA, lupus, and a variety of other inflammatory illnesses, and has been used in organ

transplantation to prevent rejection of the transplanted organ (Cohen et al., 2019). This DMARD is only taken as a combination treatment with methotrexate (Arthritis Foundation, 2019). A systematic review using meta-analysis found that DMARDs may reduce radiographic erosions, but their long-term use has undesirable effects on the body (Wilsdon & Hill, 2017).

Biologic response modifiers, such as abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olumiant), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), upadacitinib (Rinvoq), tocilizumab (Actemra) and tofacitinib (Xeljanz) all work to target specific pathways of the immune system that trigger inflammation (Mayo Clinic, 2019). Etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab, are all part of the TNF inhibitor class of biologics; and abatacept, rituximab, anakinra, and tocilizumab are part of the interleukin kinase inhibitor class of biologics (Cohen et al., 2019). Baricitinib, tofacitinib, and upadacitinib all target the JAK pathway. Biologics target specific cells that contribute to the manifestation of the disease (Spriggs & Boynes-Shuck, 2016). Monotherapy biologic medications can increase the risks of infections because they work as blocking agents to cytokine activity (Mayo Clinic, 2019). Cytokines are used to alert that antigens are present in the body. However, when biologic agents are taken as a combination with a DMARD, the risk of infection is reduced, because the DMARDS suppress the immune system to reduce the frequency of producing antibodies to the biologic (Cunha, 2016). Before any treatment begins, the physician

discusses benefits, risks, dosing schedule, monitoring frequency and expected results of all considered medications for each type of therapy (Cohen et al., 2019). Ongoing monitoring is required to identify any potential adverse effects for each patient for safety and effectiveness of the treatment (Wilsdon & Hill, 2017). Routine assessments of disease activity are essential for the determination of flares that occur with RA (Wilsdon & Hill, 2017). Flares are associated with inflammation and pain. Some flares may occur from environmental factors that cannot be controlled. Some flares may occur from certain foods that cause an inflamed flare-up in the joints. However, constant flares may be due to an increased activity of the disease that causes functional deterioration and radiographic progression (Wilsdon & Hill, 2017). In this situation, medications may need to be increased or potentially changed. To achieve the optimal goal of treatment, the best outcomes will come from understanding the therapeutic options available, pre-treatment evaluations, follow-up evaluations, and ongoing monitoring for any potential complications of the disease or its treatment (Wilsdon & Hill, 2017).

The development of targeted monoclonal antibodies and small-molecule kinase inhibitors has expanded the effective therapeutic options in RA (Wilsdon & Hill, 2017). Each of the medications listed in the paragraph above has the ability to modify the diseases process to varying extents depending on the individual's immune response (Wilsdon & Hill, 2017). Combination therapy may be used to achieve the optimal results for RA relief in some patients, but not all. Combination therapy consists of a DMARD and a biologic inhibitor. Conventional DMARDs combined with TNF, JAK or interleukin

biologics can enhance treatment outcomes more than the conventional monotherapy approach for some patients that require multiple treatment options. One of the main transformations in the way RA is treated is the adoption of an approach whereby the activity index of a disease is utilized as a score, a mark to aim at with the therapies. Therefore, the approach not only focuses on the reduction score, but also remission or low activity of the disease. Setting a treatment target, following the treatment recommendations and principles, and applying a sequence of drug strategies, may maximize the optimal results. Head-to-head trials comparing the efficacy and safety of DMARDs and TNF inhibitors in patients with active RA, despite a trial and/failure of methotrexate therapy, are inadequate due to the need for research (Smolen, et al., 2016).

An expert in RA can only prescribe therapeutic agents for RA. Therefore, it may not seem relevant to the primary care, but the rheumatologist and primary care work together for the better health of someone with RA. However, general practitioners ought to understand the implication of using the drugs and their adverse effects, since they form part of the multidisciplinary team that reviews the progress of the disease and its treatment options. IL-23 anti-interleukin antibody treatment never reduces the activity of the disease by a great margin among RA patients with an inadequate response to methotrexate (ACR response 53.6% and 41.3% vs. 40.0% in placebo; Smolen et al., 2017). The data for the compounds secukinumab and brodalumab (human anti-IL-17 RA monoclonal antibodies) that block IL-17 and IL-23 are not effective for some patients in a previous study (Genovese et al., 2014). Some clinical patients that had an inadequate

response to the TNF inhibitors improved their immune response using ixekizumab (Taltz) because it targeted the interleukin pathway (Genovese et al., 2014). Interestingly, it remains contentious whether IL-17 and IL-23 blocking agents might be competitive among the already approved and available compounds to treat RA (Genovese et al., 2014).

It is important to be evaluated and treated by a rheumatologist to be placed on the right treatment regimens. The patient may try several different types of treatment before finding the appropriate therapy that provides relief for a better wellbeing. There are several factors that contribute to the appropriate treatment plan. The duration and severity of the disease, previous treatment restrictions, comorbidities, family planning, preferences, and financial and social circumstances are some of the major issues to consider when deciding on the appropriate treatment plan (Wilsdon & Hill, 2017). During the pre-treatment evaluation, the patient should have baseline blood tests performed that include a full blood examination, serum creatinine levels, liver enzyme levels, hepatitis screening and TB screening, because abnormalities may alter the choice of therapy and dosing (Wilsdon & Hill, 2017).

EULAR reiterates that biosimilars, which are generic drug therapies, either approved by the U.S. Food and Drug Administration (FDA) or the European Medical Agency (EMA), report the same safety and efficacy outcomes as the respective biological originator, which is the brand name drug therapy (Smolen et al., 2017). Biosimilars infliximab (Remicade), etanercept (Enbrel), and rituximab (Rituxan) are FDA approved

biologics that were also approved by the EMA in 2017 (Generics and Biosimilars Initiative Online, 2017). A significant series of biosimilars is still under development.

For patients who incur persistent remissions following tapered steroids, tapering DMARDs might be a good alternative (Smolen et al., 2017). Injecting patients with 25 mg etanercept, down from 50 mg per week, or increasing the etanercept or adalimumab injection intervals is consistent with tapering medications for the preservation of clinical remission or low disease activity, amidst clinically relevant flare rates (Smolen et al., 2013). Alternatively, abrupt DMARD therapy cessation results in flares among most patients, if not all patients. However, not each of those DMARD therapies attain their initial remission states or low disease activity. In a recent epidemiological study, 50% of the patients involved in an ACT-Ray study stopped using tocilizumab (Actemra) a year after sustained clinical remission (Huizinga et al., 2015). However, later in the study, 84% of the patients suffered recurrent flare-ups and were reintroduced to the tocilizumab treatments (Huizinga et al., 2015). Within that double-blind randomized trial, the patients under remission with certolizumab pegol (Cimzia) and a DMARD ceased getting treatment (Huizinga et al., 2015). Three out of the seventeen patients taking certolizumab pegol maintained remission until the 52nd week (Smolen et al., 2015). In accordance with EULAR recommendations, when there was particularly persistent remission, tapering the DMARDs became a good alternative. However, the recommendation is still under investigation because most of the rheumatologists might not cease DMARDs in remission by letting the patient go without a disease-modifying therapy (Smolen et al.,

2017). The anti-CCP antibodies should continue being measured in patients with RA or suspected RA while taking a combination therapeutic treatment to potentially taper medications (Deighton et al., 2009).

Remission may be achieved through medical interventions and therapeutics because bone erosion can be detected in 25% of RA patients within the first 3 months of onset of symptoms (Wilsdon & Hill, 2017). In 70% of the RA patients that have not been diagnosed with RA, bone erosion may be detected by the third year of painful symptoms (Wilsdon & Hill, 2017). Therefore, patients whose RA is detected early and treated immediately are less likely to have excessive bone erosion than patients that wait years after the symptoms have begun. Delaying treatment beyond 3 months increases joint destruction and leads to a higher chance of requiring a more persistent therapy (Wilsdon & Hill, 2017).

RA biological drugs causing infections are on the rise. An estimated 6 out of 1,000 patients annually are being treated for infections due to biological agents, unlike the case of DMARDs (Singh et al., 2015). Future infection prevalence depends on glucocorticoid use, comorbidity, age, and history of severe infections as identified in the AR-PoWER database. The rise in risks depends on the baseline risks among different patient categories (Strangfeld et al., 2011). Therefore, public health surveillances are deployed for daily practices to reduce the cases (Lahiri & Dixon, 2015). RCTs associated serious inflictions among the biologic augur with the infection rates identified in anti-TNF surveys among follow-up patients (Lahiri & Dixon, 2015). RA treatment guidelines

were presented and addressed for safety concerns (Singh, Saag, & Bridges, 2016). ACR suggests and recommends the use of DMARDs alongside TNF inhibitors, especially among patients that have suffered severe infections in the past, despite insufficient supporting evidence, because the DMARDs can reduce the infections of TNF biologics by reducing the antibodies that respond to the biologic (Lahiri & Dixon, 2015). Therefore, biologics may have less risk of infections when taken with a DMARD. RCTs have revealed that combination therapy elicits fewer hospitalizations and less severe infections (Schiff et al., 2008; Yun et al., 2005). The recommendations do not necessarily apply to all patients, as some patients might not want the particular therapy. Therapy cannot be forced on patients, but it can be recommended.

Following TNF inhibitors approval, heart failure cases have lessened when infliximab (Remicade) is given to a patient at a dose of 10 mg/kg (Chung et al., 2003). Infliximab is a monoclonal antibody that binds to the TNF, so the TNF cannot bind to a receptor to trigger immune response. Similarly, the latest studies reveal that heart failure never occurs among patients using TNF inhibitors. In fact, symptomatic congestive heart failure risk never increases among high-risk patients that endure heart failure, while being treated with TNF inhibitors (Emrich, 2009). In a large-scale international study, Bykerk and associates reported that subjects using the biologic agent, tocilizumab, while remaining on DMARD therapy demonstrated a rapid onset of effect and continued to improve over a 6-month period (Bykerk et al., 2012).

The risk of opportunistic infections in patients being treated with a biological DMARD requires these patients to be tested for underlying latent TB (Salliot et al., 2009). TB reactivation is more prevalent among patients receiving anti-TNF monoclonal antibodies, relative to those on etanercept (Enbrel). The membrane-bound TNF plays a crucial role in safeguarding a patient against acquiring TB. The TNF antibody neutralizes TB, thereby reducing the infection risk (Plessner et al., 2007; Tubach et al., 2009). TNF biologics, such as abatacept and rituximab, did not interfere with *Mycobacterium tuberculosis* controls in mice studies (Bigbee et al., 2007). Minor cases of TB occur during tofacitinib therapy, and the cases that arise are speculated as new infections the patients acquire during clinical trials. The new TB infections manifest among some patients because clinical trials take place in a high prevalence zone for the condition (Winthrop et al., 2016). Tocilizumab exhibits no TB risk factors in RCTs (Singh et al., 2016). Before enacting a treatment methodology, determining which DMARDs would be best for results, a relevant screening methodology with a TNF inhibitor may be of better use (Hua et al., 2004).

Methotrexate monotherapy results in vaccine impairment. Discontinuing the methotrexate for a given period of time perfects the immunogenicity of the influenza vaccine among patients suffering from RA (Campbell et al., 2011; Park et al., 2017). Tofacitinib elicits little impact regarding vaccine response (Winthrop et al., 2016). TNF inhibitors taken with tocilizumab do not lessen the vaccine response (Mori et al., 2013). A safety issue related to tocilizumab during therapy involves large intestinal perforation

risk. Data obtained from a European study illustrated that perforation in the large intestine occurs in tocilizumab patients relative to those who undergo combination treatment with DMARDs (Strangled et al., 2017). Large intestinal perforation risk does not get resolved despite an improved concomitant glucocorticoid use within Cox regression analysis (Strangled et al., 2017). A positive medical history regarding diverticulitis contradicts tocilizumab use, meaning that various large intestinal perforation issues lack diverticulitis history. Patients need to be aware of large intestinal perforation risks and elevated inflammation markers, which may not get interpreted during the tocilizumab therapy.

Lymphoma, non-melanoma and melanoma skin cancers, and other cancers occur less frequently among patients using TNF inhibitors relative to patients on the standard monotherapy DMARDs (Mercer et al., 2017). A previous study was performed to investigate the safety of biologics and DMARDs and found that patients on TNF compared to patients on conventional DMARDs did not have an increased risk for malignancies in general (Ramiro et al., 2016). Rituximab (Rituxan) is more predominant in comorbidities like lymphoproliferative disorders and concomitant multiple sclerosis than other biological agents (Mercer et al., 2017). Between 30-40% of the patients with RA have poor response to DMARDs (Liu et al., 2017). Therefore, a combination of DMARDs together with various action modes of biologics is preferred by some patients. Biologics have various roles that target specific areas of the body. TNF, JAK and interleukins are the common targets of biologics. Interleukin-1 receptor antagonist with

TNF inhibitors reveals the absence of additional benefits, with a minimum of two combinations that raise the adverse events like severe infections (Weinblatt et al., 2006; Genovese et al., 2004).

Challenges in RA Management

There are various challenges regarding the management of RA patients, coupled with inefficient responses to the initial standard monotherapy treatment. The increasing modes of actions and consequent DMARDs remain core issues still not addressed.

Observational data reveals advantages regarding altering the action mode within TNF-IR inhibitors by switching to a biologic of a non-TNF. (Greenwald et al., 2011; Emery et al., 2015). ACR suggests the application of a non-TNF biological in the event of an inadequate response to the initial TNF inhibitor (Singh et al., 2016). In randomized control trials and other observational studies, the non-responders to the first DMARD therapy gave little clinical response following the conversion to a second trial using a TNF inhibitor in co-therapy (Bombardieri et al., 2004; Remy et al., 2011; Schiff et al., 2014). Cytokines, other than TNFs, might perform disease mediation among primary non-responders; and then the patients might experience additional benefits based on compounded use of various action modes instead of just TNF blocking (Bombardieri et al., 2004; Remy et al., 2011; Schiff et al., 2014). A previous study recommended a second TNF inhibitor, or the deployment of agents with different action modes that have no hierarchical ranks, was recommended in a case if a TNF inhibitor fails (Rubbert-Roth & Finckh, 2009). Combination therapy is recommended for therapy non-responders.

Nearly 60% of patients that switch to a second TNF inhibitor following primary failure of the first TNF inhibitor attain a reduction in their disease activity score (DAS)-28 by a minimum of 1.2 points (Mease et al., 2010). DAS-28 is the 28th version that measures disease activity in the 28 joints being examined (NRAS, 2019). The examination includes swelling, pain, tenderness, RA specific inflammation markers, x-rays, and questionnaires (NRAS, 2019). The DAS-28 score is calculated using a unique formula. The scores > 5.1 is high disease activity, < 5.1 is moderate disease activity, < 3.2 is low disease activity, and < 2.6 is remission (NRAS, 2019).

Patients who do not respond to TNF inhibitors may require secondary treatment measures. Arguably, the medications might have lost response from developing anti-drug antibodies, which makes the patient exhibit a clinical non-response to a given anti-genetic form of treatment. Data obtained from various randomized controlled placebo trials demonstrate safety and efficacy when it comes to TNF alpha inhibitors, such as certolizumab (Cimzia), among RA patients under secondary response inadequacy due to adverse effects of the first TNF or TNF inhibitor intolerance (Jani et al., 2014). The TNF alpha inhibitors block the activity of TNF alpha markers in the body and reduce the TNF alpha levels to help decrease the RA symptoms (Ellis & Hein, 2016). Patients who develop antibodies during their initial use of a TNF inhibitor are more at risk of developing further antibodies upon TNF inhibitors. TNF inhibitors are anti-TNF and can cause a rise in antibodies when taken as monotherapy because the immune system is responding to block inflammation. This side effect is good reason to take them with a

DMARD that lowers the antibody response. Immunogenicity might be the primary cause of lower clinical efficacy of a second TNF inhibitor as seen in the case of TNF-IR. In this scenario, altering the treatment option among patients who exhibit failure on TNF inhibitors might be a worthy alternative. For instance, the biologic agents golimumab, abatacept, rituximab, tocilizumab, and tofacitinib have been shown to elicit high levels of clinical positive response especially among patients that inadequately responded to a minimum of one TNF inhibitor (Genovese et al., 2016).

Direct evaluations of compounds from different action modes in TNF-IR do not exist. In addition, there are minimal data available on the safety and efficacy of TNF inhibitors following non-TNF-inhibiting DMARDs failure, and a second failure of IL-6 receptor inhibitor after tocilizumab had failed (Emery et al., 2008). Basically, the choice of following a DMARD from TNF-IR is not yet settled upon, apart from EULAR and ACR that recommend alternating to non-TNF biologicals in the case where a second TNF inhibitor failed (Virkki et al., 2011).

Apart from the observational data and making indirect comparisons, combination therapy comparisons to monotherapy all point to a reduced risk of infections (Rein & Mueller, 2017). No consensus has been reached regarding CD20 monoclonal antibody applications in patients undergoing rituximab (Rituxan) therapy (Cohen et al., 2006). Rituximab is a monoclonal antibody that targets the CD20 b-cells. B-cells play a major role in RA because the cytokines are released from the b-cells in response to the observance of a foreign antigen. However, in autoimmune diseases, the healthy cells in

the body become the foreign antigens. Therefore, an overproduction of inflammation occurs that leads to structural damage. The efficacy of b-cell depletion therapy using anti-CD20 rituximab is a major advance in RA therapy because of the role of b-cells in RA pathogenesis (Chen & Cohen, 2012). A collection of safety data has established a well safety profile for TNF inhibitors in RA treatments (Rubbert-Roth & Finckh, 2009). Abatacept (Orencia) exhibits a relatively accepted safety profile (Schiff et al., 2008). In contrast, a meta-analysis indicates an increase in adverse events risk with certolizumab pegol (Cimzia) use in the first treatment month (Smolen et al., 2009). RCTs for TNF inhibitors seek washout phase of 4 weeks minimum of no treatment after a trial following the previous injection or TNF inhibitor infusion (Smolen et al., 2009). ARRIVE, ACT-SURE, and EXXELARATE are clinical trials that refute the need for the washout phase (Smolen et al., 2009).

Rheumatologists have alternative treatment options to choose from other than TNF inhibitors, as well as different action modes and administrative routes. Tocilizumab, rituximab and abatacept are generally approved for intravenous access or subcutaneous use. Studies which compare the subcutaneous and intravenous administrative routes of these treatment agents reveal no major difference in clinical safety and efficacy apart from reactions that result at the subcutaneous injection site (Gabay et al., 2013; Burmester et al., 2016). Abatacept and rituximab reveals that alternating from a weekly subcutaneous TNF injection to intravenous treatments is safe and effective; and might fill a 4-week gap of treatments within one infusion (Mueller et al., 2016). In addition, 50% of

the patients receiving subcutaneous injections in real life did not feel comfortable injecting themselves and preferred intravenous infusions (Mueller et al., 2016).

Measures Outcome in Rheumatoid Arthritis Therapy

Within the evaluation of the disease, multiple variables can be dependent or independent, whose interpretation often depends on clinical judgment. In a 1994 study, with 9 years of follow-up research, the researchers found that reduced educational levels correlated with decreased function and increased mortality of RA (Pincus et al., 1994). Patients underwent psychological tests and measurements of disability. An attempt was made to correlate their psychological state with the disease activity for the patients that did not have improving results during the three-year follow-up period (Pincus et al., 1994). Therefore, RA can affect brain activity. Another study carried out on 122 women patients with RA using logistic regression showed that the ability to control work hours and family support were variables that contributed to improving the patient's ability to work.

Another study was conducted with a 2-year follow-up in patients with potential predictors of sustained remission for 2 years that observed the DAS-28 and CRP in patients using a multivariate analysis (Lee et al., 2017). Age, pain, disease aggression, functional disability index obtained from the Health Assessment Questionnaire Disability Index, and depression evaluated by the Arthritis Impact Measurement Scales were all factors with a prediction of remission of RA symptoms (Lee et al., 2017). The study

indicated that Health Assessment Questionnaire (HAQ) scores are useful when stratifying RA patients in accordance with their risk for flare-ups (Lee et al., 2017).

In 2003, a study was done to determine the prognostic factors of disability in early RA, as well as the effects on a radiographic scale and the functional course of the disease in patients with RA of less than a year who were followed-up for 5 years (Berner et al., 2018). The study resulted in a high HAQ score correlated with pain, elevated DAS-28, higher painful joint counts, and the presence of erosions by the last follow-up (Berner et al., 2018). Gender, age, RF scores, IgM or IgA antibodies, and class II genes did not contribute significantly to predicting a five-year disability (Pincus et al., 2016). Authors suggest that RF may act as an enhancer of bone loss (Van Steenbergen et al., 2015). The following year, a systematic review concluded that part of the functional outcome at work depends on a biopsychosocial mismatch between the capacity of the individual and the demands of work (Pincus et al., 2016). Rheumatologists often use a Multidimensional Health Assessment Questionnaire (MDHAQ) and/or a Routine Assessment of Patient Index Data to measure the patient's disease activity and performances on their treatments (Chua et al., 2017). Quantitative data from these MDHAQs have provided much valuable information for research studies using secondary data (Chua et al., 2017). A benefit of using quantitative methodology is to facilitate access to evidence-based secondary data rather than primary data (Gopalakrishnan & Ganeshkumar, 2013). According to the ACR rates, 20% or greater reported patient improvement in functional disability as reflected by the assessment scores for HAQ disability index (Genovese et al., 2005).

Summarization of Therapy

It should be considered that RA is a potentially catastrophic disease that requires energetic management once the diagnosis of the disease has been established. The ultimate goal of such treatment is to try to achieve a remission of the disease by putting into play the best available therapeutic resources. A particularly important premise for the treatment of RA is to start treating the disease as early and as aggressively as possible. Several studies have shown that combination therapy using two DMARDs has better results than monotherapy DMARDs; and even the combination of three DMARDs may be better than two DMARDs (Nocturne et al., 2016). Although treatments using DMARDs without a biologic, including combination DMARDS, can be therapeutic for the signs and symptoms of the disease, the control is not enough to inhibit the structural joint damage for some patients. In those cases, it may be important to consider the use of biological agents that have been patient effective, not only for the control of signs and symptoms, but also to decrease and inhibit articular damage (Cutolo & Sulli, 2018).

Over the last 50 years, the treatment strategy of RA was designed on the erroneous premise that the prognosis of the disease, in general, was favorable. It is currently known that the majority of patients with active RA are clinically disabled within the first 20 years of the disease, and that more than 90% of patients with synovitis have radiological evidence of erosions in the first 2 years after diagnosis despite conventional treatment with Functional Antibiotic Resistance Metagenomic Element (Nocturne et al., 2016).

Although a cure is not a viable goal, remission may be. A proposal for the treatment of RA was presented a few years ago in which monotherapy DMARD to be used less and less based on growing evidence that biologic agents may be more efficient (Cutolo & Sulli, 2018). However, that is not the standard treatment being utilized by rheumatologists. Therefore, more research needs to be performed for accuracy. RA centers are still overwhelmed with patients performing trial and error on medications. This study looked at a comparison of monotherapy and combination treatments using biologics at population levels to determine whether there is a difference between treatments for Caucasian women between the ages of 30 and 60 years.

The effectiveness of newly developed biological response modifiers has been demonstrated (Olson et al., 2016). The biologic modifiers, TNF, JAK and interleukins, target specific cytokines that have an important role in perpetuating the inflammation of RA through specific pathways (Ajeganova et al., 2017; Olson et al., 2016).

Recent information shows that early administration of DMARDs leads to clinical improvement and delays in the radiological progression of the disease as it has been found to occur with the use of methotrexate, leflunomide, sulfasalazine, HCQ, cyclosporine, minocycline, azathioprine, D-penicillamine and intramuscular gold (Tan & Smolen, 2016). All share some characteristics, such as the slow start of the action and a mechanism of action that is not well elucidated. In a meta-analysis of blinded and controlled studies, it was found that the relative potency of the majority of DMARDs were similar, but the HCQ and intramuscular gold were less potent (Tan, & Smolen,

2016). Compared with methotrexate, leflunomide has similar efficacy for control of clinical variables of disease activity and radiological progression (Arntz et al., 2018).

The literature on combination therapy with DMARDs refers to methotrexate as the cornerstone of therapeutic schemes. The first clinical study of combination therapy with methotrexate was made in 1995 in patients with partial response to methotrexate at the maximum tolerated doses by adding cyclosporin (2.5 to 5 mg/kg) or placebo (Sterne et al., 2016). Patients who received both DMARDs had a 25% improvement in both the painful joint count compared to the placebo group ($p = 0.02$); and 25% improvement in the count of swollen joints ($p = 0.005$) compared to the group that received only methotrexate (Goodman, 2015). The main toxicity was the increase in serum creatinine (Goodman, 2015).

In another study, 155 adult patients with RA of less than 2 years duration were randomized to either combined treatment of prednisolone (60 mg/day), oral methotrexate (7.5 mg/semester) and sulfasalazine (2 g/day); or sulfasalazine (2 g/day) as the only DMARD (Ter Wee et al., 2017). At week 40, the treatment was similar to week 28. In the combination therapy group, the prednisolone had been reduced until it was suspended at week 28, and the methotrexate was suspended until week 40 (Ter Wee et al., 2017). The researcher wanted to see a change in the RA symptoms by suspending medications. Until 28 weeks, the sulfasalazine was taken alone, and then after 28 weeks, it was taken in combination with the Prednisolone, and then a third DMARD was added at week 40, which was methotrexate. At week 28, the combined therapy group improved significantly

more than the sulfasalazine group alone (Ter Wee et al., 2017). Although the clinical improvement was similar after week 28, the radiological benefit (delay of bone damage) persisted after five years. The results of this study suggest the concept that using glucocorticoids or other medications as induction therapy yields long-term benefits.

Although glucocorticoids are not included as DMARDs, recent studies have demonstrated their ability to slow bone damage in early RA, although the side effects limit their use for prolonged periods as monotherapy for the control of RA (Goodman, 2015). Glucocorticoids in equivalent doses of 10 mg or less of prednisone per day are used to treat 30 to 60% of patients with RA (Goodman, 2015). The use of combination therapy of DMARDs until less than a decade ago was not so common, but now more than 30% of RA patients are treated with combination DMARD therapy. This increase has been due to the results of studies that demonstrated the additional benefit of adding another DMARD to patients on methotrexate with active disease (Cutolo & Sulli, 2018). With methotrexate as the only DMARD, one-third of patients improved 50% after 2-4 years; and the addition of oral folic acid prevented liver toxicity (elevation of transaminases) without reducing the efficacy of methotrexate (Cutolo & Sulli, 2018). Oral and parenteral therapy of methotrexate has fallen into disuse due to its prolonged initiation of intolerable side effects (Taylor et al., 2019). Subcutaneous is the preferred method of administration (Taylor et al., 2019).

There is no cure for RA (Wilson et al., 2004). The present treatments focus on slowing disease progression and providing symptomatic relief (Wilson et al., 2004).

DMARDs are the main choice of treatment for RA (Rubbert-Roth & Finckh, 2009). Methotrexate was the initial commonly used treatment, and it was effective on standard clinical measures of DAS and was cost-effective (Rubbert-Roth & Finckh, 2009). It was not well tolerated, however. Biologic agents were a major advance in the treatment of RA (Rubbert-Roth & Finckh, 2009). The biologic agents target immune effector cells (T lymphocytes, B lymphocytes and macrophages), which are responsible for inflammation and structural damage in affected joints, bone, organs and the signaling molecules involved in their activation (Rubbert-Roth & Finckh, 2009). TNF inhibitors were the first approved biologic agents for the treatment of RA (Rubbert-Roth & Finckh, 2009). TNF inhibitors are effective at improving RA symptoms and slowing or preventing structural damage (Rubbert-Roth & Finckh, 2009). Biologics are intended to inhibit inappropriate cytokine activity and have been used with substantial efficacy to alter the progression of RA by targeting cells and molecules that are thought to be functionally important to the biologic pathway (Wilson et al., 2004). DMARDs target the entire immune system, and biologics target specific areas of the inflammatory process. When taken as a combination, DMARDS suppress the immune system to reduce the frequency of the infectious antibodies being produced in response to the biologic. In combination, the DMARDs lower the antibodies being produced and the biologic targets the specific inflammatory sites by working as an inflammatory blocking agent.

Chapter 3: Research Method

Research and Rationale

This study compared the therapeutic efficacy of DMARD treatments with a biologic to DMARDs without a biologic at population levels for Caucasian Alabamian women aged 30 to 60 years that have been diagnosed with RA. The study focused on the effectiveness of the two groups, monotherapy DMARD treatments and combination treatments with a biologic, for the target population using the following additional covariates: age of patient, anti-rheumatic action of treatment, and DAS. Data required for answering the stated research question were obtained from the AR-PoWER database which was a research network of patients with RA that provides data from patient-centered research associated with PCORnet (Fleurence et al., 2014). By and large, the study was quantitatively built on the tenets of a cross-sectional study in which secondary data were used to test the stated hypothesis.

Methodology

The study was quantitative. It focused on a cross-sectional study design that was used to analyze the association between variables using statistical analyses (Grand Canyon University, Center for Innovation in Research and Teaching [CIRT], 2019). The methods style was observational and used a predicted hypothesis. Quantitative research requires that the statistical data be reliable and measured accurately (CIRT, 2019). This methodology used a nominal and ordinal scale of measurement to distinguish between the groups (CIRT, 2019). Therefore, the object measured was placed into categories (CIRT,

2019). Logistic regression was the statistical method used for this study to analyze the relationship between an outcome (dependent variable) and two or more predictors (independent variables). Logistic regression is useful in research to explain the relationship between the independent variables and the outcome. The model does not assume a sequence of random variables, statistical normality, or linearity (Starkweather & Moske, 2011). In this study, the three independent variables (predictor variables) were the anti-rheumatic actions of treatment (DMARDs with a biologic and DMARDs without a biologic), DAS, and age. The dependent variable, which was dichotomous, was the therapeutic effectiveness of RA treatments. The control variables were gender, ethnicity, and diagnoses.

Population

The population was based on location, gender, age, and ethnicity. The population data were derived from the AR-PoWER national database that focuses on patients that reside in the United States for the purposes of data collection and analysis at population levels. Since RA is 2-3 times more common in women than men, the study population was composed of women with RA. The age range for this population was 30 to 60 years. Although RA can affect all ethnicities, this research was limited to Caucasians. The therapeutic efficacy of combining DMARDs and biologics has never been comprehensively studied at these population data levels. The rheumatology clinics stay full of patients and may take up to a year for initial evaluation. For example, the rheumatology clinic at the University of Alabama (UAB) handles more than 20,000

patient visits annually, which is about 80 patients a day, and the majority of the patients are women (UAB, 2020).

Sample Size Estimation

The statistical software used for the sample size determination was the g*power 3.1.9.4 version, as indicated below:

z tests - Logistic regression

Options:	Large sample	
Analysis:	A priori: Compute required sample size	
Input:	Tail(s)	= One
	Pr(Y=1|X=1) H1	= 0.1
	Pr(Y=1|X=1) H0	= 0.2
	α err prob	= 0.05
	Power (1-β err prob)	= 0.95
	R^2 other X	= 0
	X distribution	= Normal
	X parm μ	= 0
	X parm σ	= 1
Output:	Critical z	= -1.6448536
	Total sample size	= 103
	Actual power	= 0.9502378

The scores of the variables were calculated through a nominal scoring. G*Power is a statistical software that was used to calculate effective sample size according to the statistical testing that was used. The appropriate testing was contingent on the hypothesis. According to the G*Power analysis, this study needed to have 103 total participants to have an appropriate sample size with a probability value of 0.05. The probability value determines the statistical significance of the output for each participant data being tested.

This study included 100 cases, which consisted of two independent study groups. Group 1 included 51 cases using DMARD treatments without a biologic (monotherapy

DMARD group). Group 2 included 49 cases using DMARD treatments with a biologic (combination DMARD & biologic group).

Sampling

The sampled data collection was of the target population. The database, AR-PoWER, consisted of secondary data that were randomly selected. The selection was performed by stratified random sampling. The data were separated from the bulk population into exclusive sub-population sets, such as gender, age, and ethnicity. Once the exclusive sub-population parameters were set, the simple random data sampling began by obtaining 100 random samples from the stratified random selection of data to structure a test group. Stratified random sampling ensures that the subgroups within the population provide better coverage of the population because there is more control over the subgroups to ensure that all groups are represented in the sampling (Murphy, 2019). Stratified random sampling reflects the population being studied more accurately than simple random sampling because it divides the population into subgroups, rather than merely choosing subjects from an entire population (Murphy, 2019). Choosing from an entire population group without parameters can cause potential confounding in the study.

Data Collection

Data were collected through the AR-PoWER national database. The patients had already signed consent forms that their results may be used for research, but their personal information would not be released. The data used were categorical data that indicated how each patient rated her medication according to the patient's success or

improvement while on the medication. The data were specific to the population requirements for the study. Therefore, parameters were set for the data according to Caucasian women aged 30 to 60. Once the parameters were indicated, the data chosen for the study were presented at random according to their treatment plan. There were 50 cases collected for the monotherapy DMARD group and 50 cases for the combination biologic group to perform chi-square statistical testing and logistic regression.

Operationalization of Constructs

This research was quantitative in nature. The quantitative statistical analysis involved a small data collection from the data presented to AR-PoWER database from actual RA results that were submitted from actual patients. The data used secondary data for the purpose of integrating valid and reliable findings in this research (Gopalakrishnan & Ganeshkumar, 2013). The statistical test performed for this research was logistic regression that models a binary outcome of three independent variable groups in the same population: the anti-rheumatic action of treatment (DMARDs with a biologic and DMARDs without a biologic), DAS, and age. The actual data for the study were secondary data from the national database AR-PoWER, which includes data obtained from the UAB Hospital of Rheumatology. The random cases were assigned to the conditions based on the above criteria of the baseline characteristics. The data were randomly assigned through the national database. A contingency table was formed to enter the categories of the independent variables to be analyzed with the dependent

variable. Each column represented an observational subject with the nominal categorical variables. Each row was represented by the individual sample numbered 1-100.

Statistical Data Analysis

Logistic regression was used to predict a nominal dependent variable with nominal categorical independent variables (Laerd Statistics, 2018) and any covariates that consisted of continuous and nominal variables that related to the dependent variable. The dependent variable for this study was the therapeutic effectiveness of RA treatments. The dependent variable contained binary nominal categories (No = 0, Yes = 1). The covariates for this study were: age of patient, anti-rheumatic action of treatment, and DAS. The covariates are the independent variables in a logistic regression model. Each of the three independent variables being analyzed were all categorical. All the independent variables were entered into the dialog box for covariates because in the Statistical Package for the Social Sciences (SPSS) software for logistic regression models, if the independent variables relate to the dependent variable, then all will be tested as covariates. The values were entered into SPSS for analyzing the dataset to determine an outcome (Laerd Statistics, 2018). SPSS was used to compute the data and provide a logistic distribution based on the relationship between the independent and dependent variables. This statistical model produced parameter estimates that analyze how much each predictor variable contributes to the likelihood of the outcome. If the p-value is less than or equal to significance level (alpha-α) of 0.05, then the null hypothesis can be rejected which means there was a difference in the therapeutic efficacy between

combination therapy and monotherapy in treating RA patients, and the alternate hypothesis is supported (Bruin, 2006). The variables and cases were first entered into a crosstab contingency table for the logistic regression model. The 100 test cases were entered in rows. The test variables were entered in the columns. A statistical output was generated. The regression test provided a predictor model of percentages for the DMARDs with and without a biologic that are therapeutically effective. The logistic regression provided a classification table that explained how good the model was at predicting the outcome. In this study, it represented the percentage of how good the model predicated the therapeutic efficacy of the DMARDs with and without a biologic. A logistic regression can provide an odds ratio (OR) table that provides the odds of the therapeutic effectiveness of DMARDs with a biologic and without a biologic. The higher the ratio, the better the odds are for therapeutic efficacy. A model summary was provided that detailed the "R squared" percentage that explained how much of the outcome (therapeutic effectiveness) was explained by the predictor variables (DMARDs with and without a biologic).

Potential Confounders

Potential confounders can cause bias in the data by increasing the variance of the dependent variable. Confounders act as additional independent variables that are not included in the study. Potential confounders for this study consisted of the year that the medication was started, the year the medication was ended, the year that the patient entered into the AR-PoWER database and the name of the medications. This study was

performed on women only. Gender was a restricted variable and was not a confounder. Whether the patient had insurance and/or a comorbidity may affect the data and be permitted as a potential confounder as well.

Threats to Validity

The lack of multiple experimentation may be a threat to the validity of the research. Multiple experiments were needed for replication and cross-validation before the results can be theoretically interpreted with confidence (Ohlund & Yu, n.d.). Therefore, the choice of testing was a factor for internal validity. A potential factor for external validity was multiple treatment interference. Patients with RA tried several different medications prescribed by the physician for a yearning of pain relief. Therefore, the multiple changes in treatment options could have interfered with the effects of the current treatment (Ohlund & Yu, n.d.).

Methods Summary

Is there a difference in the therapeutic efficacy of combination DMARD treatments with a biologic, compared to monotherapy DMARDs without a biologic, in U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA? This research may be used for future comparisons with other research at population levels to compare differences among populations. The data were collected through the AR-PoWER National database for an estimated fifty samples for each treatment group (Group 1: Monotherapy and Group 2: Combination Therapy). The data were sampled using stratified random sampling. The research was quantitative in nature. The statistical

test performed was logistic regression that compared the relationship of the two independent predictors in the same population to the dependent outcome. There was a contingency table to enter the categories for the variables to be analyzed in SPSS. The logistic regression generated a comparative analysis among the predictor variables to the outcome. Logistic regression and chi-square testing were performed to reduce any potential threats to validity through statistical analysis. The comparative analysis using logistic regression and chi-square testing were both used for a two-way association between the monotherapy treatments and the combination treatments for women patients with RA. The logistic regression adjusted for age.

Hypothesis

Is there a difference in the therapeutic efficacy of combination DMARD treatments with a biologic, compared to monotherapy DMARDs without a biologic, in U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA?

Null Hypothesis: There is no difference in the therapeutic efficacy between combination therapy and monotherapy in treating U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA.

Alternative Hypothesis: There is a difference in the therapeutic efficacy between combination therapy and monotherapy in treating U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA.

Chapter 4: Results

Introduction

The purpose of this study was to compare the therapeutic efficacy of RA treatments between monotherapy DMARD drug treatments and combination therapy drug treatments in women aged 30 to 60 years. A quantitative methodology was used to compare monotherapy treatments to combination therapy treatments using secondary data from the AR-PoWER database. The goal was to reveal a variation of differences in the forms of treatments (DMARD with a biologic and DMARD without a biologic) as the basic formation of statistical analysis. Logistic regression was performed, and it presented no association between the effectiveness of the treatments to the anti-rheumatic action, such as a monotherapy DMARD or a combination DMARD with a biologic.

Research Question Analysis

Is there a difference in the therapeutic efficacy of combination DMARD treatments with a biologic, compared to monotherapy DMARDs without a biologic, in U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA?

The dependent variable (i.e., the therapeutic effectiveness of RA treatments) and the association of the independent variables (i.e., the antirheumatic action of treatment: monotherapy DMARD treatments and combination DMARD with biologic treatments, DAS, and age) were examined using the following hypothesis:

Null Hypothesis: There is no difference in the therapeutic efficacy between combination therapy and monotherapy in treating U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA.

Alternative Hypothesis: There is a difference in the therapeutic efficacy between combination therapy and monotherapy in treating U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA.

The following data sections (data collections, results, and summary) will detail the data process further and produce an interpretation of the results.

Data Collection

The data collection began the day after Christmas 2020, 3 days after the IRB data approval of the research agreement with Global Healthy Living Foundation (GHLF) for the use of their database AR-PoWER. The data obtained from the database were consistent with the variables described in Chapter 3. The selection of the data was performed by stratified random sampling of 100 cases that were Caucasian women aged 30 to 60 years. The participants were assigned to the database according to their baseline conditions which were women patients diagnosed with RA. The data collection originated from the actual RA results submitted from actual patients to the AR-PoWER database through the GHLF. The descriptive statistics were calculated using SPSS. A chi-square test provided an unadjusted two-way association to test the hypothesis. A logistic regression was performed as well, which allowed the data to be adjusted for age.

The categorical dependent variable indicated whether the medication was effective as indicated by the patient's improvement while on the medication. The independent variables were categorized by the two groups: monotherapy treatments and the combination treatments. The independent variables consisted of the following: three different age groups of patients: 30-39, 40-49, and 50-60; the DAS; and the anti-rheumatic action of treatment (which was the monotherapy and combination therapy drug treatments).

Results of Descriptive Statistics

The data consisted of a small sample of 100 cases. There were no missing cases. A frequency distribution was analyzed to summarize the measurements of the categorical independent variables. There were 100 total cases observed for age of patient (Table 1). Out of the 100 cases, 17% were aged 30-39 years, 37% were aged 40-49 years, and 46% were aged 50-60 years.

Table 1

The Proportion of Research Participants by Age Group

Age groups	Frequency	Percent	Valid percent	Cumulative percent
30-39	17	17	17	17
40-49	37	37	37	54
50-60	46	46	46	100
Total	100	100	100	

Regarding the type of treatment, as seen in Table 2, 51% of the patients used a DMARD monotherapy regimen, and 49% of the patients used a biologic regimen with a DMARD concurrently.

Table 2

The Proportion of Research Participants by the Anti-Rheumatic Action of Treatment

Anti-rheumatic action of treatment	Frequency	Percent	Valid percent	Cumulative percent
DMARD monotherapy	51	51	51	51
Biologic combination	49	49	49	100
Total	100	100	100	

The frequency distribution of the DAS can be seen in Table 3. Out of the 100 cases, 2% scored in remission range with their regimen; 4% scored low disease activity with their regimen; 37% scored moderate disease activity with their regimen; and 57% scored high disease activity with their regimen. Thus, only 6% of the patients succeeded with their regimen to receive the goal of remission to low disease activity. A crosstabulation was performed to observe how the DAS was affected by the monotherapy DMARD treatments and the combination treatments with a biologic and a DMARD (Table 4). Out of the 2% of the patients that scored in the remission range, all were treated with a monotherapy DMARD. Out of the 4% of the patients that scored in the low disease activity range, only one patient received combination therapy, while the other three patients were treated with a monotherapy DMARD. Out of the 37% that scored in

the moderate range, there were 28 patients on combination therapy and 29 patients on monotherapy.

Table 3

The Proportion of Research Participants by the Disease Activity Score

	Frequency	Percent	Valid percent	Cumulative percent
< 2.6: Disease remission	2	2.0	2.0	2.0
2.6 – 3.2: Low disease activity	4	4.0	4.0	6.0
3.2 – 5.1: Moderate disease activity	37	37.0	37.0	43.0
>5.1: High disease activity	57	57.0	57.0	100.0
Total	100	100	100	

Table 4

The Cross-Tabulation of the Anti-Rheumatic Action of Treatment & Disease Activity Score

Anti-rheumatic action of treatment	< 2.6: Disease remission score	2.6 – 3.1: Low disease activity score	3.2 – 5.1: Moderate disease activity score	>5.1: High disease activity score	Total cases
Monotherapy DMARD	2	3	17	29	51
Combination biologic & DMARD	0	1	20	28	49
Total frequency	2	4	37	57	100

Results of Chi-Square Tests

A chi-square analysis provided a two-way association between the independent variables and the dependent variable. The cross tabulation provided a verification that the test itself was consistent with the data. A table was developed (Table 5) that presented a relationship between the dependent variable (Effectiveness of Treatment) and the independent variable (Age of Patient). Fourteen patients from age group 30-39 stated the medications were effective, and three patients stated that the medications were not effective. Thirty patients from age group 40-49 stated that the medications were effective, and seven patients stated that the medications were not effective. Thirty-nine patients from age group 50-60 stated that the medications were effective, and seven patients stated that the medications were not effective. Table 6 provided the chi-square analysis. The

Pearson value of 0.205 indicated that there was not much association. The p-value was 0.902 which was above the alpha level of 0.05. I failed to reject the null hypothesis that there is no difference between the combination therapy and monotherapy in treating RA patients based on the lack of association of the effectiveness of treatments and the ages of the patients.

Table 5

The Cross-Tabulation of the Effectiveness of Treatment & Age of Patient

		Age group: 30 - 39	Age group: 40 - 49	Age group: 50 - 60	Total
Effectiveness of treatment	Yes	14	30	39	83
Effectiveness of treatment	No	3	7	7	17
Total		17	37	46	100

Table 6

The Chi-Square Test: Effectiveness of Treatment & Age of Patient

	Value	DF	P-Value
Pearson chi-square	.205	2	.902
Likelihood ratio	.205	2	.902
N of valid cases	100		

* 1 cell (16.7%) have expected count less than 5. The minimum expected count was 2.89. (This is still below the 20%, so the assumption has not been violated).

A cross-tabulation was developed (Table 7) that presented a relationship between the dependent variable (Effectiveness of Treatment) and the independent variable (Anti-Rheumatic Action of Treatment). Forty-four patients stated the DMARD monotherapy treatments were effective, and seven patients stated that the DMARD monotherapy treatments were not effective. Thirty-nine patients stated the biologic combination treatments were effective, and 10 patients stated that the biologic combination treatments were not effective. Thus, 83% of the patients stated that their regimen was effective, whether it be monotherapy DMARD treatments or biologic combination treatments. Table 8 provides the chi-square analysis. The Pearson value, which was 0.791, indicated there was some variation and slight association. However, the p-value was 0.374 which was above the alpha level of 0.05. Therefore, I failed to reject the null hypothesis for the association of the effectiveness of treatments and the anti-rheumatic action of treatment.

Table 7

The Cross-Tabulation of the Effectiveness of Treatment & Anti-Rheumatic Action of Treatment

		Monotherapy DMARD	Combination biologic & DMARD	Total
Effectiveness of treatment	Yes	44	39	83
Effectiveness of treatment	No	7	10	17
Total		51	49	100

Table 8

The Chi-Square Test: Effectiveness of Treatment & Anti-Rheumatic Action of Treatment

	Value	Df	P-Value	Exact sig. (2-sided)	Exact sig. (1-sided)
Pearson chi-square	.791	1	.374		
Likelihood ratio	.794	1	.373		
Continuity correction	.388	1	.533		
Fisher's exact test				.432	.267
N of valid cases	100				

* 0 cells (0.0%) have expected count less than 5. The minimum expected count was 8.33.

Results of Logistic Regression Model

A logistic regression was performed to determine whether there was an association between the type of RA drug treatment and its effectiveness. The dependent variable was the outcome, the effectiveness of the treatments. The dependent variable was coded categorically according to the effectiveness: 0 = no, 1 = yes. The independent variables were indicated as covariates in SPSS. There were three independent variables. The first independent variable was categorized according to the anti-rheumatic action of the drug treatment: the DMARD monotherapy drug treatments and the combination biological drug treatment with a DMARD. Another independent variable was age of the individuals set in three age groups: 30-39 (n=17), 40-49 (n=37), and 50-60 (n=46). The last independent variable was the DAS which was measured by the swelling and achiness of the joints: 0 = score < 2.6 (patient in disease remission), 1 = score 2.6 – 3.1 (patient

with low disease activity), 2 = score 3.2 – 5.1 (patient with moderate disease activity), and 3 = score >5.1 (patient with high disease activity).

The log likelihood summary contains the R^2 statistic which provides representation that the model is a good fit for the data. The "Cox and Snell R Square" calculated the variation among the independent variables in association with the dependent variables. The "Nagelkerke R Square" measures the same and is typically between 0 and 1. The Cox and Snell are usually more conservative with the calculation. According to the model summary, there was a 4 – 6.8% variation that explained the therapeutic efficacy of RA treatments among the three independent variables. Therefore, the model built for this study did fit the data. However, the stronger the model, the higher the R^2 statistic. An algorithm was computed for the likelihood ratio (LR) = 87.050. Therefore, the model did hold true to provide an estimation of "good enough" fit for the data.

The Hosmer and Lemeshow Test is a goodness-of-fit statistical test. This test works well for variables with a binary response. As in this study, there was a binary response of "yes" the treatment was effective or "no" the treatment was not effective. Hosmer and Lemeshow tests are used in logistic regression to measure whether a model is satisfactory for the study. The significant value determines if the model is a poor fit if, $p < 0.050$. The significant value for this study was > 5%; $p < 0.585$. Therefore, this model was an adequate fit for the data.

The logistic regression model provided details as to whether or not the model had a significant association between the effectiveness of the treatments and the predictor independent variables. The coefficients of the model were labeled "B". A positive coefficient with a $p \leq 0.050$ would indicate a positive association between the variables. The data in Table 9 did not support a significant association between the predictor variables and the outcome variable. In standard regression coefficients (B), the null hypothesis must have a value ≤ 0 in a population; and the alternative hypothesis would have a value > 0. The coefficients for the logistic regression in this study were < 0 and supported the null hypothesis. In addition, the coefficients were also the log odds that relate to the linearity of the independent variables (Table 9).

The OR of the model was labeled "Exp. B". In a standard regression, if OR = 1, then there is no relationship between the independent and dependent variables. If the odds ratio is > or < 1, then there could be a potential relationship between the variables. The age of the patient OR = 1.150, which could have a potential relationship with the dependent variable. The action of treatment OR = 0.638, and the DAS OR = 0.480, which are both < 1, which could mean that there was a potential relationship between the independent variables and the dependent variable. However, the significant value of the variables was > 0.050 which indicated there was no association.

The 95% confidence interval (C.I.) is useful for hypothesis testing. In a standard regression, if the upper and lower bounds go through 1 then the model supports the null

hypothesis. As in this study, the 95% C.I. for each of the predictor variables supported the null hypothesis.

Logistic regression requires no multicollinearity (strong correlation) among independent variables. This can be measured is SPSS by observing the collinearity diagnostics of the independent variables. The collinearity of two or more scale independent variables must be tested and tested again in reverse order to measure for any strong correlation. The threshold for the variance inflation factor (VIF) is 3. Therefore, any VIF greater than 3 may potentially have multicollinearity issues. The VIF for this study was 1.000 for each of the two variables tested. Also, there were not many independent variables for this study, thus decreasing the probability of multicollinearity.

Table 9

The Logistic Regression Model – Variables in the Equation

	B	S.E.	Wald	Df	Sig.	Exp. B	95% C.I. Upper	95% C.I. Lower
Age of Patient	.140	.361	.151	1	.698	1.150	.567	2.333
Action of Treatment	-.449	.546	.676	1	.411	.638	.219	1.862
Disease Activity Score	-.735	.519	2.004	1	.157	.480	.173	1.327
Constant	3.550	1.513	5.505	1	.019	34.798		

Summary

The purpose of this study was to compare the effects of the DMARD monotherapy drug treatments and the biologic combination drug treatments with a DMARD. The Cox and Snell R^2, Nagelkerke R^2, and Hosmer and Lemeshow Tests are all in agreement that the model fits the data. However, according to the data in relation to the statistical associations of variables, there was no significant evidence that supported the alternative hypothesis. The logistic regression coefficients in the model were < 0. The null hypothesis had been failed to be rejected. The 95% C.I. was in the appropriate range for null hypotheses. The chi-square models also supported the null; there was no association between the variables. The null hypothesis was not rejected in any of the tests. In lieu of all the evidence, there was no significant difference in the therapeutic efficacy of RA treatments. The monotherapy drug treatments were no more or less effective than the combination therapy drug treatments, according to the logistic regression model. The logistic regression model met all requirements for the analysis to test the hypothesis. The research question, "Is there a difference in the therapeutic efficacy of combination DMARD treatments with a biologic, compared to monotherapy DMARDs without a biologic, in U.S. Caucasian women between the ages of 30 and 60 that have been diagnosed with RA?", was answered by there was no significant difference in the drug treatments for RA. RA is an autoimmune disease that will affect each individual differently. The medications that are prescribed will respond to each individual's cellular structure differently.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this study was to compare the therapeutic efficacy of RA treatments between monotherapy DMARD and combination therapy of DMARD plus biologic using quantitative statistical analysis. The goal was to reveal a variation of differences in the forms of treatments as the basic formation of statistical analysis. The chi-square tests and the logistic regression generated a comparative analysis among the predictor variables to the outcome variable. The chi-square test results were important for testing the hypothesis in addition to the logistic regression model. While the chi-square tests provided an unadjusted two-way association, the logistic regression model observed the same association, but adjusted for age. The p-value for the chi-square tests did not significantly indicate an association, and I therefore did not reject the null hypothesis. The logistic regression model also reported a low statistical power in failing to reject the null hypothesis.

Previous research investigated the safety of biologics and DMARDs and observed the clinical patient responses to the medications individually. Previous studies identified prognostic factors of RA and calculated their disease activity. I conducted a quantitative correlational design to analyze the association between predictor variables and the outcome variable using statistical analyses of secondary data. Correlation designs are an observation of data collection and not for cause and effect (CIRT, 2019). This methods style was observational and uses a predicted hypothesis. The chi-square tests are specifically tested for correlation. The logistic regression is a predictive analysis that

explains the relationship between the variables. In this study, the three independent variables (predictor variables) were the anti-rheumatic actions of treatment (DMARDs with a biologic and DMARDs without a biologic), DAS, and age. The dependent variable was indicated as the therapeutic effectiveness of RA treatments. There was no statistical association between these variables in this study.

Interpretation of the Findings

This study was conducted on 100 RA data cases. There were two sub-groups that were used as predictor variables. The monotherapy DMARD sub-group contained 51 cases, and the combination biologic and DMARD sub-group contained 49 cases. A sample size estimation was performed prior to the analysis using the G*power statistical software 3.1.9.4 version. The analytical software indicated an estimation of 103 data cases was needed for the study. Therefore, the total number of cases was slightly under the estimated recommendation by three cases.

A chi-square test was performed to evaluate a possible association between the effectiveness of the treatment (dependent variable) and the age of the patient (independent variable). The test was not statistically significant with $p = 0.902$. I failed to reject the null hypothesis. A chi-square test was performed to evaluate a possible association between the effectiveness of the treatment (dependent variable) and the anti-rheumatic action of treatment (independent variable). The test was not statistically significant with $p = 0.374$. I failed to reject the null hypothesis. The chi-square test was

not able to be performed on DAS (independent variable) because it was continuous data; it contained interval data that was measured according to a scale.

The statistical analysis for this study found no association between the dependent variable and the independent variables. Therefore, there was no significant difference between the monotherapy treatments and combination treatments for the therapeutic effectiveness for RA. The results of this study were not consistent with the research findings of other researchers, such as Cutolo and Sulli (2018), who were observing osteoclastic functioning of RA patients using biologic DMARD therapy. However, the results of this study were consistent with the research findings of Parida et al. (2015) who were comparing the efficacy and infectious side effects of non-biologics versus biologics. Those researchers found that monotherapy, combination therapy, and triple therapy of non-biologics (DMARDs) were similar to the efficacy of combination anti-TNF biologic agents with methotrexate, and this was observed across various populations (Parida et al., 2015).

This research did not support the idea that combination drug treatments using a DMARD, and a biologic agent are more effective than monotherapy DMARD treatments for the population studied. In fact, the results of the logistic regression and chi-square testing of this study provided evidential support that there is no difference in the treatments for the specific population of Caucasian women aged 30 to 60 years. The p-values for these tests were not significant and therefore indicated no association between the effectiveness of the treatments and the predictor independent variables. The

coefficients for the logistic regression in this study were < 0 and supported the null hypothesis.

Limitations of the Study

Limitations are characteristic constraints that result in unanticipated challenges within the study. There were several limitations to this study that needed to be addressed. One limitation was that this study was conducted using secondary data. The data were patient reported to the GHLF and incorporated into the AR-PoWER Database. Most of the data were obtained from a large source, the UAB Rheumatology Hospital in Birmingham, Alabama. However, the database is a national database, and I was not able to determine that all the data came from UAB as opposed to from another rheumatology clinic. A second limitation is that the data observed Caucasian women only and was not compared to other ethnicities or gender. A third limitation was the sample size. The sample size of 100 cases was slightly smaller than recommended. A larger sample size could potentially provide more precision. A fourth limitation was in the methodology. More independent variables could have possibly yielded different results. However, there was limited access to the specifics of the secondary data, such as the time the medications were tried and stopped, as well as the location of the patient, which resulted in unavailability of further data. The only data that was available was the gender, race, disease activity score, medication taken, and if it was stopped or continued. A fifth limitation is that the participants had comorbidities that altered their DAS. However, this information was unavailable from the database.

Recommendations for Further Study

The findings of this study may help enhance the knowledge on how to appropriately use DMARD and biologic treatments to control the inflammatory response to prevent severe bone erosion and joint deformity. The literature may provide knowledge on potential comorbidities that follow the autoimmune disease, such as cardiovascular and pulmonary diseases. The statistical analysis may close the gap in literature for Caucasian women ages 30 to 60 years on the therapeutic efficacy of DMARD treatments that stop the inflammatory cells from being produced and the biologic treatments that stop the immune system from being overactive. Although combination biologic DMARD therapy may work well together for some RA patients, it is not a standard treatment for all patients. According to the results of this study, there was no difference in the therapeutic efficacy between combination therapy and monotherapy in treating U.S. Caucasian women between the ages of 30 and 60 years that have been diagnosed with RA. Public health, insurance providers and physicians are the ones that design the policies of standard regimen for diseases. This research can possibly make an impact on their policies of treatments for patients being diagnosed with RA. The findings of this study may help bring social change by providing evidence as related to the efficacy of combination therapy for RA, compared to the standard monotherapy treatment, which would be valuable in developing more effective clinical and/or public health practices for healthcare policy regulations to ensure regulatory standards are being met. With all potential benefits being stated, I would recommend that future studies

broaden the research by comparing data from other ethnicities and gender. I would also recommend incorporating comorbidities to see if it would influence the findings of the study. A retrospective cohort study would be recommended to incorporate time analysis as well as comparative analysis.

Implications for Positive Social Change

The purpose of this study was to compare the therapeutic efficacy of RA treatments. A positive social change implication of this study's findings is that the assessment of the efficacy of DMARDs with a biologic agent and DMARDs without a biologic agent may warrant further investigation in which studies with large sample sizes that include various populations are used. In this study, there was no difference between the monotherapy and combination therapy treatments for Caucasian women aged 30 to 60 years. The findings of this study did not influence medical policies for public health issues on the effectiveness of combination therapeutics as the potential RA standard regimen.

It is apparent that the prescribed treatments for the autoimmune disease will respond to each individual's cellular structure differently. Biological agents are made in a laboratory from living organisms. These agents target specific cellular pathways in the body. Each RA patient will have inflammatory responses due to various reasons whether it be environmental, infectious, genetic, or hormonal. There is not a specific RA test that determines which type of biologic is needed, so it is trial and error. For example, biologics that target interleukins will use a recombinant monoclonal anti-interleukin

receptor to interrupt the pathway. However, if the patient's RA is not flaring from inflammation in the interleukin pathway, that biologic will not work. Then, the patient must wait for the medications half-life or until the medication has exited from the bloodstream. Conventional DMARDs are immunosuppressive agents. These drugs are initial treatments because they have less severe side effects on the body. DMARDs are good for long-term use, but do not activate as quickly as a biologic. The disease activity and severity, comorbidities, allergies, and even patient preference (including cost, oral administration versus injection administration, and frequency of monitoring) all play a pivotal role in the determination of DMARD therapy (Benjamin, Bansal, Goyal &Lappin, 2020). However, all DMARDs work the same by suppressing inflammatory responses no matter the pathway.

Conclusion

RA is an autoimmune disease that can attack the entire body through inflammation. DMARD treatments target the entire immune system, whilst biologics target specific areas of the inflammatory process. When taken as a combination, the DMARD can suppress the immune system to reduce the frequency of the infectious antibodies being produced in response to the biological agent. This occurrence is relevant for combination treatments because the DMARDs lower the antibodies being produced while biologic agents target specific inflammatory sites, such as TNF or interleukins, by working a blocking agent. However, the results for this study did not find a significant association between the effectiveness of the drug treatments with the anti-rheumatic

monotherapy treatments or the combination action of treatment. Having adjusted for age, logistic regression was used to examine the association between the therapeutic effectiveness and the treatment modality (DMARDs without a biological agent and DMARDs with a biologic agent) with an OR > 1 for age; OR < 1 for DAS and action of treatment; all of which had a potential relationship with the dependent variable. Therefore, the action of treatment, DMARD with a biologic and DMARD without a biologic, had < 1% effectiveness on a therapeutic outcome. However, the significant value result indicated that there was no significant association between treatment effectiveness and treatment modality. Therefore, according to the statistical findings of this study, the combination drug treatments were no more or less effective than the monotherapy therapy drug treatments. The effectiveness of the treatment depends on the cellular structure of the individual.

References

Ajeganova, S., van Steenbergen, H. W., Verheul, M. K., Forslind, K., Hafström, I., Toes, R. E. M., ... & van der Helm-van Mil, A. H. M. (2017). The association between anti-carbamylated protein (anti-CarP) antibodies and radiographic progression in early rheumatoid arthritis: A study exploring replication and the added value to ACPA and rheumatoid factor. *Annals of the Rheumatic Diseases, 76*(1), 112-118. https://www.ncbi.nlm.nih.gov/pubmed/27117699

Alam, J., Jantan, I., & Bukhari, S. (2017, August). Rheumatoid arthritis: Recent advances on its etiology, role of cytokines and pharmacotherapy. *Journal of Biomedicine & Pharmacotherapy.* 92, 615-633. https://pubmed.ncbi.nlm.nih.gov/28582758/

Aletaha, D., Neogi, T., & Silman, A. J. (2010). Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum., 69*(9), 1580-1588. https://www.ncbi.nlm.nih.gov/pubmed/20872595

American College of Rheumatology. (2018). RISE (Qualified Clinical Data Registry). https://www.rheumatology.org/I-Am-A/Rheumatologist/Registries/RISE

Arduengo, M. (2020, July). Antibodies, Immunity and Vaccines: A Short Primer on the Adaptive Immune Response. https://www.promegaconnections.com/antibodies-immunity-and-vaccines-a-short-primer-on-the-adaptive-immune-response/

Arntz, O. J., Pieters, B. C., Thurlings, R. M., Wenink, M. H., van Lent, P. L., Koenders, M. I., ... & van de Loo, F. A. (2018). Rheumatoid arthritis patients with

circulating extracellular vesicles positive for IgM rheumatoid factor have higher disease activity. *Frontiers in Immunology, 9*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6215817/

Arthritis Foundation. (2017). DMARDs overview: Understand these treatments for inflammatory arthritis. http://www.arthritis.org/living-with-arthritis/treatments/medication/drug-types/disease-modifying-drugs/drug-guide-dmard s.php

Arthritis Foundation. (2019). Understanding arthritis. https://www.arthritis.org/alabama/

Babikir, M., Babikir, O., Eldeen, N., & Gaufri, A. M. (2017, April). Association of fibrinogen, erythrocyte sedimentation rate and c-reactive protein levels with rheumatoid arthritis. *Open Access Library Journal, 4*(4), 1-8. https://www.scirp.org/journal/PaperInformation.aspx?PaperID=75369

Benjamin, O., Bansal, P., Goyal, A., & Lappin, S. L. (2020, July). Disease modifying anti-rheumatic drugs (DMARD). *Journal of Public Health*. https://www.ncbi.nlm.nih.gov/books/NBK507863/

Berner, C., Haider, S., Grabovac, I., Lamprecht, T., Fenzl, K. H., Erlacher, L., & Dorner, T. E. (2018). Work ability and employment in rheumatoid arthritis: A cross-sectional study on the role of muscle strength and lower extremity function. *International Journal of Rheumatology*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6093007/

Bigbee, C. L., Gonchoroff, D. G., Vratsanos, G., Nadler, S. G., Haggerty, H. G., & Flynn,

J. L. (2007). Abatacept treatment does not exacerbate chronic *Mycobacterium tuberculosis* infection in mice. *Arthritis Rheum*, *56*, 2557-65. https://www.ncbi.nlm.nih.gov/pubmed/17665452

Bokarewa, M. (2014). Correlation between cardiovascular co-morbidity, inflammation, and pain in patients with rheumatoid arthritis, an observational study. https://gupea.ub.gu.se/bitstream/2077/37199/1/gupea_2077_37199_1.pdf

Bombardieri, S., Ruiz, A. A., & Fardellone, P. (2004). The effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford), 6*, 1191-9. https://www.ncbi.nlm.nih.gov/pubmed/17504821

Bhosale, A. M., & Richardson, J. B. (2008, September). Articular cartilage: structure, injuries, and review of management. *British Medical Bulletin*, *87*(1), 77–95. https://doi.org/10.1093/bmb/ldn025

Bouchnita, A., Eymard, N., Moyo, T. K., Koury, M. J., & Volpert, V. (2016, January). Bone marrow infiltration by multiple myeloma causes anemia by reversible disruption of erythropoiesis. *American Journal of Hematology, 91*(4), 371-378. https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.24291

Bruin, J. (2006). Command to compute new test. UCLA: Statistical Consulting Group. https://stats.idre.ucla.edu/stata/ado/analysis/

Burmester, G. R., Rubbert-Roth, A., & Cantagrel, A. (2016). Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with

traditional DMARDs in patients with RA at week 97 (SUMMACTA). *Ann Rheum Dis, 75*, 68–74. https://www.ncbi.nlm.nih.gov/pubmed/26056119

Bykerk, V. P, Ostor, A. J., & Alvaro-Gracia, J. (2012). Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. *Ann Rheum Dis*, *71*, 1950–4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3595980/

Campbell, L., Chen, C., Bhagat S. S., Parker R. A., & Ostor, A. J. (2011). Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatology (Oxford)*, *50*, 552–62. https://www.ncbi.nlm.nih.gov/pubmed/21078627

Chatzidionysiou, K., Emamikia, S., Nam, J., Ramiro, S., Smolen, J., van der Heijde, D., & van Vollenhoven, R. (2017). Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. *Annals of Rheumatic Diseases, 76*(6), 1102-1107. https://www.ncbi.nlm.nih.gov/pubmed/28356243

Chen, D. R., & Cohen, P. L. (2012, April). Living life without B cells: is repeated B-cell depletion a safe and effective long-term treatment plan for rheumatoid arthritis?. *Journal of Clinical Rheumatology,* 7(2), 159–166. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3392126/

Cherascu, B. (2011). Diagnosing Rheumatoid Arthritis. *Journal of Ethics*, *13*(5), 295-298. https://journalofethics.ama-assn.org/article/diagnosing-rheumatoid-arth

Chua, J. R., Castrejon, I., & Pincus, T. (2017). Assessment of pain and other patient symptoms in routine clinical care as quantitative, standardized, "scientific" data. *Clin Exp Rheumatology, 35*(107), S13-S20. https://www.ncbi.nlm.nih.gov/pubmed/28967369

Chung, E. S., Packer, M., Lo, K. H., Fasanmade, A. A., & Willerson, J. T. (2003). Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy against Congestive Heart Failure (ATTACH) trial. Circulation. *Clinical Trial Circulation, 107,* 3133–40. https://www.ncbi.nlm.nih.gov/pubmed/12796126

Chung, W. H., Hung, S. I., & Chen, Y. T. (2007). Human leukocyte antigens and drug hypersensitivity. C*linical Immunology*. *7*(4), 317-323. https://www.ncbi.nlm.nih.gov/pubmed/17620823

Cleveland Clinic. (2019). Rheumatoid Vasculitis. https://my.clevelandclinic.org/health/diseases/13290-rheumatoid-vasculitisritis/2011-05

Cohen, S., Cannella, A., Furst, D. E., & Romain, P. L. (2019, June). Patient education: Disease-modifying antirheumatic drugs (DMARDs) (Beyond the Basics). *Journal of Disease-Modifying Antirheumatic Drugs*.

https://www.uptodate.com/contents/disease-modifying-antirheumatic-drugs-dmards-beyond-the-basics

Cohen, S. B., Emery, P., & Greenwald, M. W. (2006). Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum*, *54*, 2793–806. https://www.ncbi.nlm.nih.gov/pubmed/16947627

Costenbader, K. H., Feskanich, D., & Mandl, L. A. (2006). Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. *Am J Med, 119*(6), 503-509. https://www.ncbi.nlm.nih.gov/pubmed/16750964

Craven, J. (2017, March). EULAR Updates Rheumatoid Arthritis Treatment Guidelines for DMARDs. https://www.rheumatologyadvisor.com/home/topics/rheumatoid-arthritis/eular-updates-rheumatoid-arthritis-treatment-guidelines-for-dmards/

Cubero, C. C. Prieto, E. V., Peña, I. A., Vega, J. A., Vallinas, J. S., Medina, M. M., & Perez, M. V. (2016). AB0173 Role of Anti Citrullinated Protein Antibodies in Follow-Up and Radiographic Damage in A Group of Patients with Early Rheumatoid Arthritis. *Annals of Rheumatic Diseases, 75*(2). https://ard.bmj.com/content/75/Suppl_2/955.3

Cunha, J. P. (2016, September). Remicade Side Effects Center. https://www.rxlist.com/remicade-side-effects-drug-center.htm

Cutolo, M., & Sulli, A. (2018). Testing the anti-osteoclastic function of biologic DMARDs. *Nature Reviews Rheumatology, 14*(8), 446. https://www.researchgate.net/publication/326341843_Testing_the_anti-osteoclastic_function_of_biologic_DMARDs

Deighton, C., O'Mahony, R., & Tosh, J. (2009). Management of rheumatoid arthritis: summary of NICE guidance. *BMJ, 338*, 702. https://www.ncbi.nlm.nih.gov/pubmed/19289413

Dellabella, Hannah. (2018). Rheumatoid Arthritis Mortality Rate Declining, But Still Prevalent. https://www.rheumatologyadvisor.com/rheumatoid-arthritis-advisor/rheumatoid-arthritis-mortality-declining-in-recent-years/article/777624/

Din, C., & Paskevich, D. (2013, June). An Integrated Research Model of Olympic Podium Performance. *International Journal of Sports Science & Coaching, 8*(2), 431–444. https://journals.sagepub.com/doi/abs/10.1260/1747-9541.8.2.431

Dunkin, M. A. (2015, April). More Than Just Joints: How Rheumatoid Arthritis Affects the Rest of Your Body. https://www.arthritis.org/about-arthritis/types/rheumatoid-arthritis/articles/rhemuatoid-arthritis-affects-body.php

Edwards, C. J., & Cooper, C. (2006, January). Early Environmental Factors and Rheumatoid Arthritis. *Journal of Translational Immunology, 143*(1), 1–5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1809562/

Ellis, M. E., & Hein, D. (2016, September). RA Treatments: DMARDs and TNF-Alpha Inhibitors. https://www.healthline.com/health/rheumatoid-arthritis/dmards-tnf-alpha-inhibitors

Emery, P., Gottenberg, J. E., & Rubbert-Roth, A. (2015). Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. *Ann Rheum Dis, 74,* 979–84. https://www.ncbi.nlm.nih.gov/pubmed/24442884

Emery, P., Keystone, E., &Tony, H. P. (2008). IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biologicals: results from a 24-week multicenter randomized placebo-controlled trial. *Ann Rheum Dis, 67,* 1516–23. https://www.ncbi.nlm.nih.gov/pubmed/18625622

Emrich, L. (2009). Rheumatoid Arthritis and Congestive Heart Failure. *Journal of Rheumatoid Arthritis*. https://www.healthcentral.com/article/rheumatoid-arthritis-and-congestive-heart-failure

Firestein, G. S., & Kelley, W. N. (2009). *Etiology and Pathogenesis of Rheumatoid Arthritis* (8). Kelley's Textbook of Rheumatology.

Fleurence, R. L., Curtis, L. H., Califf, R. M., Platt, R., Selby, J. V., & Brown, J. S. (2014, July). Launching PCORnet, a national patient-centered clinical research network.

Journal of the American Medical Informatics Association, 21(4), 578–582. https://academic.oup.com/jamia/article/21/4/578/2909226

Freeman, J. (2018, October). RA and Anti-CCP: What is the Purpose of an Anti-CCP Test?. https://www.rheumatoidarthritis.org/ra/diagnosis/anti-ccp/

Gabay, C., Emery, P., & van Vollenhoven, R. (2013). Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomized, double-blind, control phase 4 trial. *Lancet Journal, 381,* 1541–50. https://www.ncbi.nlm.nih.gov/pubmed/23515142

Generics and Biosimilars Initiative Online. (2017). Biosimilars approved in Europe. http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe.

Genovese, M. C, Durez, P., & Richards, H. B. (2014). One-year efficacy and safety results of secukinumab in patients with rheumatoid arthritis: phase II, dose-finding, double-blind, randomized, placebo-controlled study. *Journal of Rheumatology, 41,* 414–21. https://www.ncbi.nlm.nih.gov/pubmed/24429175

Genovese, M. C, Greenwald, M., & Cho C, S. (2014). A phase II randomized study of subcutaneous ixekizumab, an anti-interleukin-17 monoclonal antibody, in rheumatoid arthritis patients who were naive to biologic agents or had an inadequate response to tumor necrosis factor inhibitors. *Arthritis Rheumatology, 66,* 1693–704. https://www.ncbi.nlm.nih.gov/pubmed/24623718

Genovese, M. C., Becker, J. C., & Schiff, M. (2005) Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med*, *353,* 1114–23.

https://www.nejm.org/doi/10.1056/NEJMoa050524?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov

Genovese, M. C., Cohen, S., & Moreland, L. (2004). Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum, 5,* 1412–9. https://www.ncbi.nlm.nih.gov/pubmed/15146410

Genovese, M. C., Fleischmann, R., & Kivitz, A. J. (2015). Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. *Arthritis Rheumatology, 67,* 1424–37. https://onlinelibrary.wiley.com/doi/full/10.1002/art.39093

Genovese, M. C., Kremer, J., & Zamani, O. (2016). Baricitinib in patients with refractory rheumatoid arthritis. *Journal of Medicine, 374,* 1243–52. https://www.nejm.org/doi/full/10.1056/nejmoa1507247

Goldman, F. D., Gilman, A. L., Hollenback, C., Kato, R. M., Premack, B. A., & Rawlings, D. J. (2000, June). Hydroxychloroquine inhibits calcium signals in T cells: a new mechanism to explain its immunomodulatory properties. *Clinical Research in Hematology, 95*(11), 3460-6. https://pubmed.ncbi.nlm.nih.gov/10828029/

Goodman, S. M. (2015, June). Rheumatoid arthritis: perioperative management of biologics and DMARDs. *Seminars in Arthritis and Rheumatism, 44*(6), 627-632. https://www.ncbi.nlm.nih.gov/pubmed/25747348

Gopalakrishnan, S., & Ganeshkumar, P. (2013). Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. *Journal of Family Medicine and Primary Care, 2*(1), 9–14. https://doi.org/10.4103/2249-4863.109934

Graudal, N., Hubeck-Graudal, T., Tarp, S., Christensen, R., & Jürgens, G. (2014). Effect of Combination Therapy on Joint Destruction in Rheumatoid Arthritis: A Network Meta-Analysis of Randomized Controlled Trials. *PLOS One, 9*(9). https://doi.org/10.1371/journal.pone.0106408

Grand Canyon University, Center for Innovation in Research and Teaching (CIRT). (2019). Quantitative Approaches. https://cirt.gcu.edu/research/developmentresources/research_ready/quantresearch/approaches

Greenwald, M. W., Shergy, W. J., Kaine, J. L., Sweetser, M. T., & Gilder, K. L. (2011, March). Evaluation of the safety of rituximab in combination with a tumor necrosis factor inhibitor and methotrexate in patients with active rheumatoid arthritis: results from a randomized controlled trial. *Arthritis Rheum, 63,* 622–32. https://www.ncbi.nlm.nih.gov/pubmed/21360491

Guthrie, K. A., Dugowson, C. E., &Voigt, L. F. (2010). Does pregnancy provide vaccine-like protection against rheumatoid arthritis?. *Arthritis Rheum, 62*(7), 1842-1848. https://www.ncbi.nlm.nih.gov/pubmed/20309863

Guo, Q., Wang, Y., Xu, D., Nossent, J., Pavlos, N., & Xu, J. (2018, April). Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Research, 6*(15). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5920070/

Hua, C., Barnetche, T., Combe, B., & Morel, J. (2004). Effect of methotrexate, anti-tumor necrosis factor alpha, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken), 66,* 1016–26. https://www.ncbi.nlm.nih.gov/pubmed/24339395

Huizinga, T. W., Conaghan, P. G., & Martin-Mola, E. (2015). Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study. *Ann Rheum Dis, 74,* 35–43. https://ard.bmj.com/content/annrheumdis/74/1/35.full.pdf

Iliades, C. (2017). Treating Rheumatoid Arthritis: DMARDs vs Biologics. https://www.everydayhealth.com/hs/rheumatoid-arthritis-treatment-management/dmards-biologics/

Jani, M., Barton, A., Warren, R. B., Griffiths, C. E., & Chinoy, H. (2014). The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic

inflammatory diseases. *Rheumatology (Oxford), 53,* 213–22. https://www.ncbi.nlm.nih.gov/pubmed/23946436

Jimenez-Boj, E., Redlich, K., Birgit, T., Hanslik-Schnabel, B., Wanivenhaus, A., Chott, A., … & Schett, G. (2005). Interaction between Synovial Inflammatory Tissue and Bone Marrow in Rheumatoid Arthritis. *Journal of Immunology, 175,* 2579-2588. https://www.jimmunol.org/content/175/4/2579

Kaaja, R. J., & Greer, I. A. (2005). Manifestations of chronic disease during pregnancy. *JAMA*, *294*(21), 2751-2757. https://jamanetwork.com/journals/jama/article-abstract/201942

Karlson, E. W., Mandl, L. A., & Hankinson, S. E. (2004). Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum, 50*(11), 3458-3467. https://www.ncbi.nlm.nih.gov/pubmed/15529351

Karlson, E. W., Shadick, N. A., & Cook, N. R. (2008). Vitamin E in the primary prevention of rheumatoid arthritis: The Women's Health Study. *Arthritis Rheum*, *59*(11), 1589-1595. https://onlinelibrary.wiley.com/doi/full/10.1002/art.24194

Kavanaugh, F., & Lipsky, P. E. (2012, October). Immunological Aspects of Rheumatic Diseases. *Clinical Immunotherapeutics, 3,* 209–216. https://link.springer.com/article/10.1007/BF03258507

Kassas, M., Alboraie, M., Mostafa, A., Ezzat, R., El Tahan, A., Afify, S., … & Esmat, G. (2018, March). After successful hepatitis C virus antiviral therapy: It looks that

normal alanine aminotransferase level is not the normal. *Journal of Clinical Lab Analysis, 32*(3), e22296. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6817060/

Kelly, C., & Hamilton, J. (2007, February). What kills patients with rheumatoid arthritis?. *British Journal of Rheumatology, 46*(2), 183-184. https://doi.org/10.1093/rheumatology/kel332

Kerkar, P. (2018). Rheumatoid Arthritis (Chronic Inflammation of Joints): Types, Causes, Symptoms, Treatment, Surgery. https://www.epainassist.com/arthritis/rheumatoid-arthritis-or-chronic-inflammation-of-joints

Koopman, F. A., Tang, M. W., Vermeij, J., de Hair, M. J., Choi, I. Y., Vervoordeldonk, M. J., … & Tak, P. P. (2016, April). Autonomic Dysfunction Precedes Development of Rheumatoid Arthritis: A Prospective Cohort Study. *Elsevier Journal of Biomedicine, 6,* 231–237. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4856742/

Laerd Statistics. (2018). Multinomial Logistic Regression using SPSS Statistics. https://statistics.laerd.com/spss-tutorials/multinomial-logistic-regression-using-spss-statistics.php

Lahiri, M., & Dixon, W.G. (2015). Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatology, 29*, 290–305. https://www.ncbi.nlm.nih.gov/pubmed/26362745

Lange, E., Blizzard, L., Venn, A., Francis, H., & Jones, G. (2016). Disease-modifying anti-rheumatic drugs and non-melanoma skin cancer in inflammatory arthritis patients: a retrospective cohort study. *Rheumatology, 55*(9), 1594-1600. https://academic.oup.com/rheumatology/article/55/9/1594/1744701

Laurent, L., Anquetil, F., Clavel, C., Ndongo-Thiam, N., Offer, G., Miossec, P., & Serre, G. (2015). IgM rheumatoid factor amplifies the inflammatory response of macrophages induced by the rheumatoid arthritis-specific immune complexes containing anticitrullinated protein antibodies. *Annals of Rheumatic Diseases*, *74*(7), 1425-1431. https://www.ncbi.nlm.nih.gov/pubmed/24618262

Lee, K. E., Choi, S. E., Xu, H., Kang, J. H., Park, D. J., & Lee, S. S. (2017). HAQ score is an independent predictor of sustained remission in patients with rheumatoid arthritis. *Rheumatology International, 37*(12), 2027-2034. https://www.ncbi.nlm.nih.gov/pubmed/28956118

Levine, B. (2017, June). Why Early Treatment for Rheumatoid Arthritis Is So Important. https://www.everydayhealth.com/rheumatoid-arthritis/treatment/why-early-treatment-for-rheumatoid-arthritis-is-so-important/

Liao, K. P., Alfredsson, L., & Karlson, E. W. (2009, May). Environmental Influences on Risk for Rheumatoid Arthritis. *Journal of Current Opinion in Rheumatology, 21*(3), 279–283. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2898190/

Liu, D., Yuan, N., Yu, G., Song, G., & Chen, Y. (2017). Can rheumatoid arthritis ever cease to exist: a review of various therapeutic modalities to maintain drug-free

remission?. *American Journal of Translational Research, 9*(8), 3758–3775. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5575190/

Lunardo, E. (2016, May). Rheumatoid arthritis triggered by estrogen and progesterone hormone imbalance in women: Study. https://www.belmarrahealth.com/rheumatoid-arthritis-triggered-by-estrogen-and-progesterone-hormone-imbalance-in-women-study/

Mandal, A. (2018). What is Efficacy?. https://www.news-medical.net/health/What-Does-Efficacy-Mean.aspx

Mayo Clinic. (2019). Rheumatoid Arthritis. https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/diagnosis-treatment/drc-20353653

Mease, P. J., Cohen, S., & Gaylis, N. B. (2010). Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. *Journal of Rheumatology, 37,* 917–27. https://www.ncbi.nlm.nih.gov/pubmed/20194448

Mercer, L. K., Askling, J., & Raaschou, P. (2017). Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. *Ann Rheum Dis, 76*, 386–9. https://www.ncbi.nlm.nih.gov/pubmed/27307502

Mochan, E., & Ebell, M.H. (2008). Predicting rheumatoid arthritis risk in adults with undifferentiated arthritis. *Am Fam Physician*, 77(10); 1451-1453. https://www.ncbi.nlm.nih.gov/pubmed/18533381

Molina, E., Rincon, I. D., Restrepo, J. F., Battafarano, D. F., & Escalante, A. (2015). Mortality in Rheumatoid Arthritis (RA): factors associated with recording RA on death certificates. *British Medical Journal of Musculoskeletal Disorder, 16,* 277. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4595199/

Mori, S., Ueki, Y., & Akeda, Y. (2013). Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. *Ann Rheum Dis*, *72*, 1362–6. https://www.ncbi.nlm.nih.gov/pubmed/23345600

Mueller, R. B., Gengenbacher, M., Richter, S., Dudler, J., Moller, B., & von Kempis, J. (2016). Change from subcutaneous to intravenous abatacept and back in patients with rheumatoid arthritis as simulation of a vacation: a prospective phase IV, open-label trial (A-BREAK). *Arthritis Res Ther, 18,* 88. https://www.ncbi.nlm.nih.gov/pubmed/27074795

Murphy, C. B. (2019, April). Stratified Random Sampling: Advantages and Disadvantages. https://www.investopedia.com/ask/answers/041615/what-are-advantages-and-disadvantages-stratified-random-sampling.asp

National Research Council. (2018). Integrated Research Model Approach. https://www.ifc.cnr.it/index.php/en/ricerca/l-approccio-ifc

National Rheumatoid Arthritis Society. (2019). The DAS28 score. https://www.nras.org.uk/the-das28-score

Nocturne, G., Virone, A., Ng, W. F., Le Guern, V., Hachulla, E., Cornec, D., & Wendling, D. (2016). Rheumatoid factor and disease activity are independent

predictors of lymphoma in primary Sjögren's syndrome. *Arthritis & Rheumatology, 68*(4), 977-985. https://www.ncbi.nlm.nih.gov/pubmed/26606524

Ohlund, B., & Yu, C. H. (n.d.). Threats to validity of Research Design. https://web.pdx.edu/~stipakb/download/PA555/ResearchDesign.html

Olson, S. A., Furman, B. D., Kraus, V. B., Huebner, J. L., & Guilak, F. (2016). Does progranulin account for the opposite effects of etanercept and infliximab/adalimumab in osteoarthritis?. *Journal of Orthopedic Research*, *34*(1), 15-16. https://profiles.wustl.edu/en/publications/reply-to-does-progranulin-account-for-the-opposite-effects-of-eta

Parida, J. R, Misra, D. P., Wakhlu, A. & Agarwal, V. (2015, March). Is non-biological treatment of rheumatoid arthritis as good as biologics?. *Journal of Orthopedic Research*, *6*(2), 278–283. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4363810/

Park, J. K., Lee, M. A., & Lee, E. Y. (2017). Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomized clinical trial. *Ann Rheum Dis*, https://www.ncbi.nlm.nih.gov/pubmed/28468794

Pincus, T., Brooks, R. H., & Callahan, L. F. (1994). Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. *Annals of Internal Medicine*, *120*(1), 26-34. https://www.ncbi.nlm.nih.gov/pubmed/8250453

Pincus, T., Chua, J., Bergman, M. J., Yazici, Y., & Gibson, K. A. (2016). *PROMs (MDHAQ/RAPID3) and Physician RheuMetric Measures*. Springer, Cham. https://link.springer.com/chapter/10.1007/978-3-319-32851-5_3

Pipe, T. B. (2017). Optimizing nursing care by integrating theory-driven evidence-based practice. *J Nurs Care Qual*, *22*(3), 234-238. https://pubmed.ncbi.nlm.nih.gov/17563592/

Plessner, H. L., Lin, P. L., & Kohno, T. (2007). Neutralization of tumor necrosis factor (TNF) by antibody but not TNF receptor fusion molecule exacerbates chronic murine tuberculosis. *J Infect Dis*, *195*, 1643–50. https://www.ncbi.nlm.nih.gov/pubmed/17471434

Ramiro, S., Gaujoux-Viala, C., & Nam, J. L. (2016). Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis*, *73*, 529–35. https://www.ncbi.nlm.nih.gov/pubmed/24401994

Ravelli, A., Felici, E., & Magni-Manzoni, S. (2005). Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. *Arthritis Rheum*, *52*(3), 826-832. https://www.ncbi.nlm.nih.gov/pubmed/15751057

Rein, P., & Mueller, R. (2017, December). Treatment with Biologicals in Rheumatoid Arthritis: An Overview. *Rheumatology Therapy, 4*(2), 247–261. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5696285/

Remy, A., Avouac, J., Gossec, L., & Combe, B. (2011). Clinical relevance of switching to a second tumor necrosis factor-alpha inhibitor after discontinuation of a first tumor necrosis factor-alpha inhibitor in rheumatoid arthritis: a systematic literature review and meta-analysis. *Clin Exp Rheumatol, 29,* 96–103. https://www.ncbi.nlm.nih.gov/pubmed/21269578

Rubbert-Roth, A., & Finckh, A. (2009). Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. *Arthritis Research & Therapy, 11*(1). https://arthritis-research.biomedcentral.com/articles/10.1186/ar2666

Saag, K. G, Teng, G. G, & Patkar, N. M. (2008). American College of Rheumatology recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*, *59*(6), 762-784. https://www.ncbi.nlm.nih.gov/pubmed/18512708

Salliot, C., Dougados, M., & Gossec, L. (2009). Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. *Annals of Rheumatic Diseases*, *68*(1), 25–32. https://doi.org/10.1136/ard.2007.083188

Sauna, Z. E. (2020, June). Immunogenicity of Protein-based Therapeutics. *Journal of Biologics*. https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/immunogenicity-protein-based-therapeutics

Schiff, M., Keiserman, M., & Codding, C. (2008). Efficacy and safety of abatacept or

infliximab vs placebo: a phase III, multi-center, randomized, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis*, *67*, 1096–103. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564802/

Schiff, M. H., von Kempis, J., Goldblum, R. Tesser, J. R., & Mueller, R. B. (2014). Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomized, multicenter, double-blind, and 12-week study, followed by a 12-week open-label phase. *Ann Rheum Dis, 73,* 2174–7. https://www.ncbi.nlm.nih.gov/pubmed/24972708

Scott, D. L., Wolfe, F., & Huizinga, T. W. (2010). Rheumatoid arthritis. *Lancet* Journal, *376*(9746), 1094-1108. https://www.ncbi.nlm.nih.gov/pubmed/20870100

Shiel, W. (2018). Rheumatoid Arthritis (RA). https://www.medicinenet.com/rheumatoid_arthritis/article.htm#rheumatoid_arthritis_ra_facts

Shiel, W. (2019). Medical Definition of Tumor necrosis factor. https://www.medicinenet.com/script/main/art.asp?articlekey=25458

Shiboski, C. H., Shiboski, S. C., Seror, R., Criswell, L. A., Labetoulle, M., Lietman, T. M., & Mariette, X. (2017). American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data□driven methodology involving three international patient

cohorts. *Arthritis & Rheumatology*, *69*(1), 35-45. https://www.ncbi.nlm.nih.gov/pubmed/27785888

Singh, J. A., Cameron, C., & Noorbaloochi, S. (2015). Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet Journal, 386,* 258–65. https://www.ncbi.nlm.nih.gov/pubmed/25975452

Singh, J. A., Saag, K. G., & Bridges, S. L. (2016). American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatology, 68,* 1–26. https://www.ncbi.nlm.nih.gov/pubmed/26545940

Smolen, J. S., Agarwal, S. K., & Ilivanova, E. (2017). A randomized phase II study evaluating the efficacy and safety of subcutaneously administered ustekinumab and guselkumab in patients with active rheumatoid arthritis despite treatment with methotrexate. *Ann Rheum Dis, 76,* 831–9. https://www.ncbi.nlm.nih.gov/pubmed/28087506

Smolen, J. S., Burmester, G. R., Combe, B., Curtis, J. R., Hall, S., Haraoui, B., …Fleischmann, R. (2016). Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomized EXXELERATE study. *Lancet Journal, 388,* 2763–74. https://www.ncbi.nlm.nih.gov/pubmed/27863807

Smolen, J. S., Emery, P., & Ferraccioli, G. F. (2015). Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind,

randomized, placebo-controlled trial. *Ann Rheum Dis, 74,* 843–50. https://ard.bmj.com/content/74/5/843

Smolen, J. S., Kay, J., & Doyle, M. K. (2009). Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors (GO-AFTER study): a multicenter, randomized, double-blind, placebo-controlled, phase III trial. *Lancet Journal, 374,* 210–21. https://www.ncbi.nlm.nih.gov/pubmed/19560810

Smolen, J. S., Landewe, R., Bijlsma, J. (2017). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis, 6,* 960–77. https://www.ncbi.nlm.nih.gov/pubmed/28264816

Smolen, J. S., Landewe, R., Bijlsma, J., Burmester, G., Chatzidionysiou, K., Dougados, M., ,,, van der Heijde, D. (2017, June). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Annals Rheumatic Diseases, 76*(6), 960-977. https://www.ncbi.nlm.nih.gov/pubmed/28264816/

Smolen, J. S, Nash, P., & Durez, P. (2013). Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomized controlled trial. *Lancet Journal, 381,* 918–29. https://www.ncbi.nlm.nih.gov/pubmed/23332236

Spriggs, B. B., & Boynes-Shuck, A. (2016, December). Biologics, Joint Damage, and

Rheumatoid Arthritis: What You Need to Know. https://www.healthline.com/health/rheumatoid-arthritis/biologics-joint-damage-and-rheumatoid-arthritis#1

Starkweather, J. & Moske, A. K. (2011). Multinomial Logistic Regression. https://it.unt.edu/sites/default/files/mlr_jds_aug2011.pdf

Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., ... & Carpenter, J. R. (2016). ROBINS-I: a tool for assessing the risk of bias in non-randomized studies of interventions. *BMJ*, 355, 4919. https://www.ncbi.nlm.nih.gov/pubmed/27733354

Strangfeld, A., Eveslage, M., & Schneider, M. (2011). Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis, 270, 1*914–20. https://www.ncbi.nlm.nih.gov/pubmed/21791449

Strangfeld, A., Richter, A., & Siegmund, B. (2017). Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. *Ann Rheum Dis, 76,* 504–10. https://www.ncbi.nlm.nih.gov/pubmed/27405509

Tan, E. M., & Smolen, J. S. (2016). Historical observations contributing insights into the etiopathogenesis of rheumatoid arthritis and the role of the rheumatoid factor. *Journal of Experimental Medicine, 213*(10), 1937-1950. https://www.ncbi.nlm.nih.gov/pubmed/27621417

Taylor, P. C. (2019, March). Biologic Markers in the Diagnosis and Assessment of Rheumatoid Arthritis. *Journal of Clinical Medicine, 8*(4), 515. https://www.uptodate.com/contents/biologic-markers-in-the-diagnosis-and-assessment-of-rheumatoid-arthritis

Taylor, P., Criado, A. B., Mongey, A. B., Avouac, J., Marotte, H., and Mueller, R. B. (2019, April). How to Get the Most from Methotrexate Treatment for Your Rheumatoid Arthritis Patient? Methotrexate in the Treat-to-Target Strategy. *Journal of Clinical Med,8*(4), 515. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6518419/

Taylor, P. C. & Feldman, M. (2009). M. Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. *PubMed Journal of Nature Reviews Rheumatology,* (5), 578-582. https://www.researchgate.net/publication/26864403_Taylor_P_C_Feldmann_M_Anti-TNF_biologic_agents_still_the_therapy_of_choice_for_rheumatoid_arthritis_Nat_Rev_Rheumatol_5_578-582

Teja, S. P., & Damodharan, M. (2018). 23 Full Factorial Model for Particle Size Optimization of Methotrexate Loaded Chitosan Nanocarriers: A Design of Experiments (DoE) Approach. *BioMed Research International*, *2018*(9). https://doi.org/10.1155/2018/7834159

Ter Wee, M. M., Coupé, V. M., den Uyl, D., Blomjous, B. S., Kooijmans, E., Kerstens, P. J., ... & Lems, W. F. (2017). Cost-utility of COBRA-light versus COBRA therapy in patients with early rheumatoid arthritis: the COBRA-light trial. *British Medical Journal of Rheumatic and Musculoskeletal Diseases, 3*(2). https://rmdopen.bmj.com/content/3/2/e000502

Tilea, I., Petra, D., Ardeleanu, E., Hutanu, A., & Varga, A. (2018, March). Clinical Conditions and Predictive Markers of Non-Dipper Profile in Hypertensive Patients. *Journal of George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Târgu Mureş, 68*(1). https://doi.org/10.2478/amma-2018-0006

Tubach, F., Salmon, D., & Ravaud. (2009). Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum, 60,* 1884–94. https://www.ncbi.nlm.nih.gov/pubmed/19565495

University of Alabama. (2020). Rheumatoid Arthritis. https://www.uabmedicine.org/patient-care/conditions/rheumatoid-arthritis

Van der Helm-van Mil, A. H., le Cessie, S., van Dongen, H., Breedveld, F. C., Toes, R. E. M., & Huizinga, T. W. (2007, February). A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis. *Arthritis Rheum, 56*(2), 433-440. https://www.ncbi.nlm.nih.gov/pubmed/17265478

Van Steenbergen, H. W., Ajeganova, S., Forslind, K., Svensson, B., & van Der Helm-van Mil, A. H. (2015). The effects of rheumatoid factor and anticitrullinated peptide antibodies on bone erosions in rheumatoid arthritis. *Annals of Rheumatic Diseases, 74*(1). https://ard.bmj.com/content/74/1/e3

Van Venrooij, W. J., & Pruijn, G. J. M. (2000, May). Citrullination: a small change for a protein with great consequences for rheumatoid arthritis. *Arthritis Res, 2*(4), 249–251. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC130012/

Virkki, L. M., Valleala, H., & Takakubo, Y. (2011). Outcomes of switching anti-TNF drugs in rheumatoid arthritis—a study based on observational data from the Finnish Register of Biological Treatment (ROB-FIN). *Clin Rheumatology, 30,* 1447–54. https://www.ncbi.nlm.nih.gov/pubmed/21644062

Weinblatt, M., Combe, B., Covucci, A., Aranda R., Becker, J. C., & Keystone, E. (2006). Safety of the selective co-stimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a 1-year randomized, placebo-controlled study. *Arthritis Rheum, 54,* 2807–16. https://www.ncbi.nlm.nih.gov/pubmed/16947384

Wilsdon, T. D., & Hill, C. L. (2017, April). Managing the drug treatment of rheumatoid arthritis. *Journal of Australian Prescriber, 40*(2), 51–58. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5408004/

Wilson, A., Yu, H. T., & Goodnough, L. T. (2004). Prevalence and outcomes of anemia in rheumatoid arthritis. *Am J Med,* 116(suppl 7A), 50S-57S. https://www.ncbi.nlm.nih.gov/pubmed/15050886

Winthrop, K. L., Park, S. H., & Gul, A. (2016). Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Ann Rheum Dis, 75,* 1133–8. https://www.ncbi.nlm.nih.gov/pubmed/26318385

Winthrop, K. L., Silverfield, J., & Racewicz, A. (2016). The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis, 75,* 687–95. https://www.ncbi.nlm.nih.gov/pubmed/25795907

Yun, H., Xie, F., & Delzell, E. (2005). Risk of hospitalized infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy. *Ann Rheum Dis, 74,* 1065–71. https://www.ncbi.nlm.nih.gov/pubmed/24608404

Zengin, O., Onder, M. E., Kalem, A., Bilici, M., Türkbeyler, I. H., Ozturk, Z. A., …& Onat, A. M. (2018, March). New inflammatory markers in early rheumatoid arthritis. *Z Rheumatology, 77*(2), 144-150. https://pubmed.ncbi.nlm.nih.gov/27604908/

Zerbo, O., Leong, A., Barcellos, L., Bernal, P., Fireman, B., & Croen, L. (2016, May). Immune Mediated Conditions in Autism Spectrum Disorders. *Brain Behavior Immun*ology, *46*, 232–236. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4414798/