THE B-CELL ROLE IN AUTOIMMUNITY

A Paper
Submitted to the Graduate Faculty
of the
North Dakota State University
of Agriculture and Applied Science

By

Marissa Marie Mindt

In Partial Fulfillment of the Requirements
for the Degree of
MASTER OF SCIENCE

Major Department:
Microbiological Sciences

April 2022

Fargo, North Dakota

North Dakota State University
Graduate School

Title

THE B-CELL ROLE IN AUTOIMMUNITY

By

Marissa Marie Mindt

The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota

State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

SUPERVISORY COMMITTEE:

Danielle Condry

Chair

Jane Schuh

Jiha Kim

Approved:

4/10/2023	John McEvoy
Date	Department Chair

ABSTRACT

This review is focused on B-cell's role in autoimmunity and was conducted by reading current papers across a variety of journals and compiling the information learned in this process. Specifically, this review paper encompasses an analysis of what autoimmune diseases are, as well as some of the characteristics of autoimmune diseases the introduction section of this paper serves as a crash course on B-cell. The disease write-up is where autoimmune diseases that are affected and mediated by B-cells, such as systemic lupus erythematosus, multiple sclerosis, and Chron's disease, are explored. The next section will compare the mechanisms behind each of the diseases to explain how B-cells can cause a large variety of symptoms as well as highlight what symptoms overlap and why. Treatment options and current research are covered throughout this paper to display an understanding of how these diseases are combated.

ACKNOWLEDGMENTS

DEDICATION

Shout out to my family and friends- without you all I wouldn't have finished this!

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

B$_{reg}$…………………………………………………………………….Regulatory B-cell

MZ…………………………………………………..…………………Marginal zone

FO…………………………………………………………………Follicular (B-cell)

NOD mouse…………………………………………………..…….. Non-obese diabetic mouse

DNA …………………………………………………………..Deoxyribonucleic acid

RNA ……………………………………………..…………………Ribonucleic acid

mRNA …………………………………………………………...Messenger ribonucleic acid

tRNA ……………………………………………………………..Transfer r ribonucleic acid

INF …………………………………………………………………………Interferon

IgD/M/A………………………………………………………. Immunoglobulin

CDXX ……………………………………………………...Cluster of differentiate

IL …………………………………………………………………………Interleukin

F$_c$ ……………………………………………………………..Fragment crystallizable

BCR……………………………………………..…………………… B-cell receptor

TCR………………………………………………………………... T-cell receptor

MS …………………………………………………………...Multiple Sclerosis

SLE ……………………………………………………………...Systemic lupus erythematosus

LN …………………………………………………………………Lupus nephritis

T1D……………………………………………………………….. Type 1 diabetes

GD ……………………………………………………………Grave's disease

IBD……………………………………………………….. Inflammatory bowel disease

CD ………………………………………………………………Chron's disease

UC ……………………………………………………………….…Ulcerative colitis

SS ………………………………………………………….…….Sjogren's syndrome

PSS ……………………………………………………...……Primary Sjogren's syndrome

SSS ……………………………………………...…Secondary Sjogren's syndrome

RA ……………………………………………...…………Rheumatoid arthritis

ADCC …………………………………………..…Antibody dependent cellular cytotoxicity

A_b …………………………………………………………..………Antibody

A_g ………………………………………………………….…….Antigen

1. INTRODUCTION

Autoimmune diseases occur when the body confuses normal, healthy tissue and cells as foreign and begins attacking them. This process can manifest in various ways, causing any one of the multiple autoimmune disorders. These diseases include systemic lupus, multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and Crohn's disease. In the United States alone, around eight percent of the population deal with the effects of autoimmune diseases. Of that eight percent, 78 percent are those assigned female at birth (1). This phenomenon may be due to estrogen levels being higher in this population. Because estrogen causes inflammation, and inflammation is common in autoimmune conditions, research is being conducted to determine if there is a link (most scientists are leaning toward that there is). However, getting a formal diagnosis for some autoimmune diseases can be an extremely long process for some of the more enigmatic conditions due to multiple test results and some inaccuracies in the typical ANA (anti-nuclear antibody) test (2, 3).

These diseases affect patients in various ways, each having a different effect on the quality of life, altering life expectancy, and even causing a predisposition to other conditions. Expected quality of life problems in patients with autoimmune diseases are anxiety, depression, stress, and pain (though where the pain is dependent on the disease). For some people, the pain is debilitating, and it makes the patient unable to go out and live the life they led before disease onset. This can contribute to the mental health issues many patients with autoimmune diseases struggle with (4). Next, stress is an essential quality of life factor for those with autoimmune conditions. Stress differs from anxiety because it has a specific trigger, and instead of being persistent, it is short-term. Stress and anxiety have even been shown to trigger flare-ups for some

1

autoimmune conditions due to the increased levels of ACTH and, by default, cortisol, which causes inflammation (5).

Autoimmunity clearly has great affects on the individual; however, those affects can extend to other individuals in their lives and nationwide systemic healthcare issues and costs. Economically, autoimmune diseases can affect patients in a variety of ways. Diseases with more severe physical symptoms can cause people to no longer be able to work to go on disability. Not being able to work (requiring disability) is the obvious area where we know there is a significant earning loss, but it has been found that there were significant earning losses for those who needed special accommodations as well due to time off dealing with disease complications. While there hasn't been a study compiling the major autoimmune diseases, each disease costs millions to billions annually at the national level. On top of earning loss, there are productivity losses when those with autoimmune diseases must take time off of work to deal with medical issues, but studies don't have conclusive data on how much is lost in this area (26, 27).

Narrowing the lens from the nationwide economic effect to the personal economic effects of autoimmune diseases, we see that those with autoimmune diseases have less buying power to put back into the economy. This is due to the systems in place as well as the monetary price of having these diseases. Most medical providers still don't recognize autoimmune diseases as a separate category of diseases. Many medical questionaries disregard family history, contributing to the long (and often expensive) process of getting a diagnosis. These diagnoses are critical to patients, though, because without them, access to medication, LFA's, and disability for those who need them. Diagnosis isn't where the spending stops, though. The cost of medicine and other healthcare costs (checkups, etc.) can cause people to go into tremendous amounts of debt. While the price of medications, trials, and other healthcare costs ranges, it is generally almost

double what someone without these diseases pays. Finally, because these diseases are often found during a person's 20s, the economic effects are often a lifelong struggle and can contribute to mental health issues (creating more debt) (26).

Some autoimmune diseases are found to even put one at risk for other diseases and autoimmune conditions. This risk can be caused by having mutations in parts of the genome that are close together. A common example of this is Celiac and type 1 diabetes. The genes for being pre-disposed to these conditions are close to each other, so having one part of the genome be affected can directly influence the other. Another way this happens is when the body's humoral immune system (B-cells) has a systemic defect rather than just a local one (6). Research is still ongoing in this area because while scientists are beginning to understand that certain genetic components make B-cells more likely to be self-reactive, there are hormonal regulation factors that affect how the B-cells develop. Specifically, ongoing research is being conducted on hormonal regulation issues that are being found to cause B-cells to express the autoimmune phenotype in mice. This leads researchers to believe that the endocrine link between B-cells and autoimmunity may be stronger and more important than originally thought (7).

To fully understand autoimmunity and the diseases this phenomenon presents, one has to understand how the immune system works normally and where the normal processes go astray. This allows scientists to understand better what goes awry when the system isn't working properly, triggering autoimmune diseases. B-cells or B-lymphocytes are a type of immune cell that is a part of both the innate and adaptive immune system. These cells create antibodies ranging in specificity against foreign antigens when working properly. They can even function as antigen-presenting cells that activate other parts of the adaptive immune response (8). Antigen presenting cells are cells such as B-cells or dendritic cells, that display antigens to other cells,

such as T-cells, to further the immune response. Unfortunately, this process can go wrong, and the cells lose their recognition of self and become self-reactive. This causes autoimmune conditions. For my paper, the three groups of B-cells I will be focusing on are the Marginal Zone B-cells, B1 cells, and Follicular B-cells.

The lesser talked about role of the B-cell is in the innate immune system. Here, the B1 and marginal zone (MZ) B-cells interact with foreign antigens as part of the body's first line of defense. Where B-cells are found is crucial to the innate immune response. Marginal Zone B-cells or MZ B-cells are found in the spleen. For the MZ B-cell, being in the spleen means they can help with a "first line of defense" against foreign antigens when found in the blood since blood passes through the spleen to be screened. These cells perform "housekeeping" duties for the body by clearing cellular debris and collecting red blood cells that are deformed in some way. Timing is critical here because blood-borne pathogens can become deadly fast, and leaving cellular debris around in the body can lead to autoimmune diseases to develop (9, 10). MZ B-cells secrete IgM and IgG antibodies to neutralize these pathogens, as well as chemokines and cytokines to attract other immune cells to the area and cause inflammation. MZ B-cells are a key component in autoimmune diseases due to how they mature and develop (11). The cells begin their lives in the spleen, but they are still immature (10). Then, they travel to the lymph tissue in the gut to mature. However, mixing with gut microbiota can cause mutations that make the MZ B-cells self-reactive (12). This causes problems to the immune system because of the high concentrations of antigens passing through the spleen and interacting with these cells. Also, personal cellular debris with self-peptides on it pass through the spleen and can trigger a response in MZ B-cells that travel through the body, causing a variety of symptoms of autoimmune diseases (10).

B1 cells are found in the peritoneal and pleural cavities, protecting the GI tract and lungs, two mucus-based regions which are more difficult to move through than other areas of the body due to the thick mucus found there. These cells releasing IgM, IgA, and possibly even IgG are crucial to getting rid of pathogens and initiating an inflammatory response that will recruit other immune cells to help fight the pathogen. When working properly, these cells can serve as antigen-presenting cells that stimulate T-cells (13). There are two subtypes of B1 cells that have been discovered, the B1-a cells and B1-b cells. B1-a cells have a CD5 marker that allows T-cell receptors and B-cell receptors to signal to each other and amongst themselves. B1-b cells are also a part of the innate system, but they don't have a CD5 marker. They are closely related to B-2 cells, as they develop alongside these cells. Overall, B1 B-cells aid in the immune response and are even being considered as a therapeutic option for fast treatment in the elderly for bacterial infections due to how they produce antibodies and stimulate the T-cell response (14). Unfortunately, in the context of autoimmunity, these cells are still in the early stages of being understood. However, the continuous secretion that can occur in B1 cells, as well as secreting natural antibodies, has been shown to lead to self-reactivity. This means that these cells can change and start attacking the patient's own tissues and trigger T-cells to stimulate B2 cells so that the process of attacking self-tissues becomes chronic, an autoimmune condition (13).

One of the many interesting attributes of the MZ B-cell and the B1 B-cell is that they don't need the antigen to be in the form of a protein to recognize it. These cells can find molecules like lipids and carbohydrates and begin producing the necessary antibodies to counteract whichever repeating pattern was found. Recognizing repeated patterns aids these cells in their reaction time because they don't need any T-cell stimulation to function. The lack of T-cell stimulation contributes to why these cells are thought to stimulate autoimmune diseases.

They only need repeated or "long" exposure (only a few hours) to the antigen in question. However, these antibodies (IgM and IgD) have a very low affinity, so the body can't rely only on them to eliminate pathogens. This gives way to the other job that these innate immune B-cells have, being antigen-presenting cells (APCs), which are needed to stimulate the adaptive immune system (15).

Antigen-presenting cells are a group of cells made up of macrophages, dendritic cells, and innate B-cells. These cells act as a bridge between the innate and adaptive immune responses. Without these cells, both branches of the immune system wouldn't be able to communicate, the adaptive immune system would never be activated, and the host would die from infections not cleared by the innate response. For this part of the paper, I will be focusing on B-cells as antigen-presenting cells. The MZ and B1 B-cells start by recognizing a foreign substance. This can include proteins, lipids, or carbohydrates. These cells use a process called BCR-mediated endocytosis (16). The process allows the BCR (B-cell receptor) to recognize the antigen it is specific for. The antigen is brought into the B-cell and a signal is released to cause the cell to take in more antigen and process it so it can be displayed on the cell surface (on MHC-2) for T-cells to find and interact with. This process is activated by Syk, CD22, and other signals. In the context of autoimmunity, these genes are currently being targeted in the treatment of different autoimmune conditions, such as rheumatoid arthritis and lupus (16, 17). This is because without using B-cells as APCs, the risk of having a cell that is self-reactive, stimulating the adaptive immune response decreases. However, this research is still being conducted using synthetic antibodies because the exact details of endocytosis are intertwined with signaling, making it difficult to pinpoint exactly where problems begin (16).

After undergoing BCR-mediated endocytosis, the cell migrates to the spleen or lymph nodes to be more likely to come across the T-cell that is specific to that antigen they are presenting. This is because many naive T-cells circulate between these tissues. Eventually, the correct T-cell is found, and the antibody is presented, as peptides, to the T-cell receptor. Provided the costimulatory molecules needed (like CD40) are present from the nearby antigen-presenting cells, the T-cell is activated (17). Activation by the presented peptides and costimulatory molecules allows the T-cells to differentiate into other sub-types of T-cells, such as T-helper-cells (Th1, Th2, Th17 etc. cells) that produce the cytokines and chemokines necessary for the B-cells to start producing the correct antibodies to the foreign antigen and the chemokines to direct them to the necessary location (17). However, different cytokines stimulate different responses in the B-cells. In the context of autoimmunity, this contributes partially to the wide variety of diseases and symptoms and partially to how these diseases are chronic conditions. Between B-cells serving as APCs, T-cells, and the newly activated B-cells (the adaptive B2 cells), secreted IL-6, IL-21, CXCR5, and BCL6 are found during this process. During a typical infection, this is great, because each of these cells recruits more of an immune response through inflammation (IL-6, IL-21) and even sets the path to cell memory in motion (CXCR5 and BCL6). When looking at autoimmune diseases, recruiting more cells to the affected tissue can cause flare-ups and chronic symptoms; cell memory can cause chronic recurrences of symptoms as the body will remember to attack itself (18).

Focusing more on the adaptive immune system, B2 B-cells have various jobs ranging from synthesizing antibodies (Abs) to creating immunological memory. After the cells have seen a foreign antigen, the B-cells create the proper chemokines and cytokines, and the T-cells have stimulated activation and differentiation in the B2 B-cells, the B2 B-cells can begin creating

more specific antibodies than IgM or IgD. IgG, IgE, and IGA are some of these antibodies. Each

of these antibodies play a role in multiple autoimmune conditions as well as in typical immune

reactions (19).

As a review, IgG is typically seen in opsonization, antibody-dependent cell-mediated

cytotoxicity, and activating complement throughout the body. IgE is usually seen in

hypersensitivity reactions and helminth immunity. Finally, IgA is found in the mucosal regions

of the body (gut and lungs) and aids in immunity there (15).

Each of these antibody isotypes are created by specific B2 cells. These cells can even be

triggered to differentiate with subsequent generations having a different antibody that they

secrete and express. This is done through a process called class switch recombination. This

process begins when the B-cell is in the presence of CD40 or various combinations of cytokines.

Then, with the proper direction, the cells can differentiate and proliferate, so there are more cells

producing a more specific antibody to the antigen. This process occurs Fc, or fragment

crystallizable region, is part of the antibody that binds to the cell surface on Fc receptors. The FC

region is part of the antibody that determines its overall type (IgA versus IgM, etc.). The two

heavy chains that comprise this part of the antibody usually have less genetic variability and will

stay the same throughout a cell's life. Class switch recombination occurs when the Fc region in

the daughter B-cells is different from the original cell's Fc region due to the stimuli discussed

above (20).

Even though these antibodies are more specific than their innate counterparts, the

immune system developed a way to fine-tune the antibodies made by the B-cells to the specific

antigen they are fighting against. To set the stage for this process, somatic hypermutations in the

Fab regions on the antibody are caused by activation-induced deaminase. These two regions are

the outermost portions of the antibody and are what bind to antigens. The somatic mutations only affect a few nucleotides at a time but occur at an average rate of 106 times more than mutations normally would (21). Mutations in this part of the antibody allow for the antibodies from some cells to be better equipped to bind the specific antigen. The selection process, or affinity maturation, selects the B-cells creating the most effective antibodies and allows the selected cells to keep proliferating while the other less effective cells die off due to lack of stimulation by the antigen. Extended exposure allows the process to continue, and the B-cells response becomes more fine-tuned over time (21, 22). Eventually, signals such as CD27 cause the cells to no longer secrete antibodies and become memory cells. Memory B-cells are cells with high affinity to the antigen that don't secrete antibodies. They circulate around in the blood and can live anywhere from months to years. If the same antigen is found, the memory cells begin making a new population of cells that will secrete the high-affinity antibody, clearing the infection faster and more efficiently than before (15). Unfortunately, the above processes of somatic hypermutation, affinity maturation, and even creating memory cells play a major role in autoimmune diseases. Sometimes, the high affinity autoantibody is selected for and mass-produced. This process has been shown to affect the severity of diseases such as lupus, rheumatoid arthritis, and even type one diabetes (21).

Another important component of B-cells, as well as the adaptive immune system, that works well in typical situations but contributes to autoimmunity is cross-reactivity. Cross-reactivity occurs when the B-cells produce antibodies against an antigen, but those antibodies bind to a different but similar antigen. In practice, this is great because it gives the immune system an edge against different genetic variants of diseases. Without this feature of antibodies, any genetic variations in infection would need separate antibodies (23). The energy necessary for

creation of separate antibodies occurring through new B cell recognition and maturation, especially during co-infections of different disease variants, would be extremely hard for the body to produce. On the flip side, having cross-reactivity also means that the immune system can become "confused" and begin reacting to antigens that aren't hazardous. This leads to conditions such as allergies to pollen and foods but has been observed as a major player in the context of autoimmunity (24). This can happen due to exposure to certain bacterial or viral infections that have similar antigens to tissue in the host. When there is cross-reactivity in these circumstances, B-cells begin producing antigens against self-tissue, causing an autoimmune disease to present (25).

Overall, research on the role of B-cells in autoimmune conditions as well as B-cell-focused treatment options is still ever-growing. It is crucial that scientists fill in the gaps in knowledge in this field for both patients and society as a whole. The personal and economic impact displays how much of an impact these diseases have on our society, let alone the more personal impacts of these diseases.

2. SYSTEMATIC LUPUS ERYTHEMATOSUS AND LUPUS NEPHRITIS

This section explores the B-cell role in Systemic Lupus Erythematosus and Lupus Nephritis (LN). Systemic Lupus Erythematosus (SLE) is an autoimmune disease that affects anywhere between 161,000 and 322,000 individuals in the United States alone (28). SLE primarily affects those assigned female at birth because estrogen affects B-cells in ways that can lead to autoreactivity. Lupus symptoms usually begin sometime between the ages of 15 and 45, but it can take years to identify as SLE. This makes diagnosis difficult, and the data for how many people truly suffer from this disease is skewed lower than the estimated number of people with the disease (28). According to the CDC, SLE affects patients in various ways, contributing to the difficult diagnostic process. Symptoms range from arthritis, butterfly rashes, abdominal issues, and Raynaud's to seizures, heart problems, blood clots, and kidney failure. Each of these symptoms is caused by B-cells that create antibodies going astray and becoming autoreactive as well as recruiting a severe inflammatory response.

Not only do these symptoms impair a patient's quality of life when flare-ups occur, but they can affect the buying power of the patients and have a cost on their employers. The specific cost to employers hasn't been explored, but the average cost per patient ranges from 2,239 per year to 35,540 USD for patients without kidney problems per year. The cost can be as high as 63,000 USD without insurance for patients with lupus nephritis. These costs come from doctors' visits and medication. The true impact of lost income and how much the employers lose from workers being sick remains difficult to accurately reflect but economic studies are underway so that the true impact of those diagnosed is understood (29).

Focusing on what happens at the cellular level, B-cells are an integral part of the process that leads to SLE symptoms. This is due to their stimulation of T-cells, interaction with dendritic

cells, and antibody production. B-cells can produce cytokines that affect other immune cells' responses and crucial gene pathways that select for autoreactivity. Even hormones are found to affect the functionality of B-cells when looking at SLE patients (30). This can be seen in each of the three noteworthy lupus symptoms: skin lesions, cardiovascular problems, and kidney failure (31, 32).

Because symptomatic SLE and LN are found in those with more estrogen, it is vital to understand estrogen's role in symptom development. In the lab, estrogen can help protect faulty B-cells from B-cell-mediated apoptosis. So far, the genes found to be dysregulated in the presence of estrogen are CD22, shp-1, bcl-2, and VCAM-1 (33). Each of these genes plays a crucial role in B-cell development. CD22 allows for immature cells to differentiate into mature plasmablasts. It allows for cytokine production by B-cells to stimulate other cells and even helps to regulate TLR-7 mediate and induce apoptosis in autoreactive B-cells by not allowing them to activate properly. Shp-1 helps negatively regulate some of the internal components of cells. By withholding transcription, its theorized that dysfunctional cells can evade detection and, therefore, evade apoptosis for longer periods of time (34). Bcl-2 is a protein that is involved in cell death. By dysregulating bcl-2, cells that should be dying due to apoptosis, such as autoreactive B-cells, will survive and proliferate to create more cells that cause autoimmune disease, in this case, SLE and LN (34). While estrogen's exact role in these pathways isn't apparent yet, scientists are sure that it plays a crucial role. To further this thought, a study that was composed of transgender women was conducted to look for dermatology problems. This study eventually found that after long-term estrogen therapy, women who hadn't had any symptoms of SLE began having symptoms emerge (35). Not only were they suffering from skin conditions associated with SLE, but some patients began to see cardiovascular and renal

problems, developing LN. There are studies currently being organized for transgender men as well to see if there is a reduction in SLE symptoms after taking testosterone long-term. Overall, the role that estrogen plays in mediating autoimmune conditions is still being explored and is a key area for future SLE research, but for now, scientists can confirm that estrogen protects autoreactive B-cells- inducing the symptoms of SLE (30, 35, 36).

After differentiating and proliferating, B-cells begin to secrete other signals that aid in the progression of SLE symptoms. These cytokines and chemokines induce reactions such as inflammation. The two major cytokines B-cells produce that progress SLE symptoms are INF-α, IL-6, and IL-10. INF-α stimulates B-cells as well as T-cells. This cytokine increases CD80 and CD86, which, alongside B-cells, stimulate CD4T cells. When these T-cells are stimulated, they begin attacking the patient's own tissue, leading to the symptoms of both SLE and LN. These T-cells can even aid in activating B-cells further, creating even more autoantibodies (37). In mouse models, this INF-α was shown to lead to the activation of TLR7 and TLR9. TLR7 allows for B-cells to begin producing inflammatory cytokines as well as IgD and IgG. When these antibodies are reactive to the patients' tissue, they recruit other cells to attack and cause the symptoms seen in SLE (37, 38). Also, by activating inflammation pathways, more B-cells and the rest of the immune system see the patient's tissue as a problem. Even the inflammatory cytokines alone can cause symptoms of SLE by irritating the skin and damaging vessels. This was further confirmed when mice and then humans were given anti INF-α drugs. In phase one trials, patients began to see the skin symptoms of SLE improve. However, symptoms for LN patients were not found to be statically significantly changed (37, 39).

Even though the role of INF-α is crucial to setting the pathway to symptomatic SLE in motion, IL-6 is thought to be another culprit of stimulating SLE symptoms. A wide variety of

cells secretes IL-6, but in this context, the secretion of IL-6 in B-cells is what is explored here. When B-cells secrete IL-6, it helps stimulate other B-cells to create IgG (37). IgG activates inflammatory cells and even stimulates them to create cytokines like INF- α, allowing this cycle to start over and continue. IgG is what recruits cells like neutrophils to the glomerulus. This deposit of IgG directly leads to symptoms of LN, causing cells to attack the kidneys and leading to loss of function (41–43). IL-6 is also found to activate the JAK1 protein. Once JAK1 interacts with the cytokine receptor inside the cell, it begins to phosphorylate the receptor. Then, STAT proteins are recruited and form a dimer with the phosphorous from the JAK protein. This allows for DNA transcription to take place. In the context of autoimmune diseases, this JAK/STAT pathway is crucial to creating autoantibodies (43, 44). After this process is activated, a B-cell begins to produce functional autoantibodies, creating the symptoms of SLE. In combination with activated BAFF, transcription of protected antibodies goes unchecked, allowing the progression of symptoms and disease onset (44). IL-6 has even been found to cause hyperactivation in surrounding cells when secreted. This was demonstrated in mice when blocking the IL-6 receptor in their cells led to slower disease progression, especially in the kidneys. Also, when mice were given IL-6 in excess, disease progression was accelerated. This led doctors to observe IL-6 levels in patients, concluding that IL-6 is elevated in patients with SLE and LN (particularly with LN). However, studies linking IL-6 and disease progression in humans have been contradictory. Some studies see significant differences while others don't, leading scientists to believe that either the exact mechanism is still not fully understood or that the mechanism is dictated by more specific factors such as genes, hormones, and small differences in body chemistry in the patients themselves (37, 38).

Next, IL-10 is another cytokine secreted by B-cells as well as a variety of other immune cells to help regulate the immune response as an anti-inflammatory. In SLE and LN, there is a high amount of anti-IL-10 antibodies. In LN, these anti-IL-10 antibodies are found in the glomerulus and in urine samples from patients. Because there is a depletion of anti-inflammatory molecules, there is no regulation of inflammation, which makes the symptoms of both SLE and LN worse. When in combination with IL-6, there is no way to stop the cycle of inflammation in the kidneys, contributing to eventual kidney failure in patients with LN. Anti-IL-10 antibodies were even correlated with anti-dsDNA titers, but why this correlation exists is still unknown. Unfortunately, even with IL-10 being given to patients, the symptoms sometimes slow- but still progress. Again, the individuality of SLE makes understanding the exact mechanisms at play difficult to control (44, 46).

Another subset of molecules produced by the immune system, chemokines, is also a significant player in SLE progression. Specifically, the chemokine CXCL13 (BCA-1) plays a role in SLE and LN disease progression. While produced by other cells, these chemokines aid in attracting naive B-cells to germinal centers and aids in turning them into effector cells that will go on to create antibodies after binding to CXCL13. After activation, effector B-cells can create more autoantibodies and worsen symptoms in mice models. CXCR5 is also elevated in these patients, which allows for autoreactive B-cells to stimulate T-cells that become self-reactive to the patient's tissue, which worsens symptoms too. In patients, this was displayed when a study was conducted in which CXCL13 and CXCR5 were found to be elevated in patients with SLE compared with their non-affected counterparts (33). These numbers were further elevated in patients with LN. This demonstrates that these chemokines play a significant role in advancing disease by recruiting B-cells that create anti-dsDNA antibodies to self-tissue. Finally, this

chemokine can even serve as a diagnostic tool to help predict how severe symptoms will become, especially in children. When values are high in children, increased medication can be started to reduce the severity of a flareup. If, after remission, the value remains highly elevated, then the kidneys can and should be watched more closely as these chemokines are located in the B-cell-containing lesions found in patients with severe SLE and LN (33, 38).

Specific B-cell types creating antibodies and cytokines can greatly influence which if any, symptoms patients with SLE and LN experience. They even can control how severe or often flareups occur. The three major symptoms explored here will be skin, cardiovascular, and kidney problems. While there are other symptoms of SLE that impact those with the disease, these are the three most severe symptoms that B-cells mediate. Between autoantibody production and the stimulation of other cell types, B-cells of multiple subtypes can cause significant damage to patients with SLE and LN (41, 47).

Starting with MZ B-cells, three significant issues are found in patients with SLE. Due to MZ B-cells being a part of the innate immune system, these cells are found to be one of the first to act up when a flare-up occurs. By secreting autoreactive IgM to the body's tissue, MZ B-cells begin a chain reaction that causes inflammation and even serves as antigen-presenting cells for nearby T-cells. Unfortunately, this allows for the flareup to be more intense, as these T-cells are found to cause more damage to nearby tissue (40). The IgM created by the MZ B-cells usually damages the vessels causing vasculitis in SLE patients. Over time, the flareups and vasculitis can cause long-lasting problems with breathing and circulation (48). Also, inflammation can cause skin reactions in patients with SLE. These reactions can range from minor rashes that itch to painful skin lesions depending on the severity of the flareup, which is directly comparable to the amount of IgM being produced in patients (35). The third and key component to the MZ B-cell

role in SLE and LN is that they aren't found in the marginal zone in the same way as in a non-effected patient. Instead, they are found inside the follicles, most often times with a BCR mutation that makes the cells autoreactive. This change in the location allows for the cells to have direct contact with T-cells, rather than having to migrate to the follicle to present the antigen to the T-cells. These defective MZ B-cells proliferate faster than their normal counterparts that aren't in the follicle. The location of these cells is important, some are near the kidneys, and others near important vessels, leading to less time before severe cardiovascular and kidney problems develop for patients with defective MZ B-cells (40).

B2 B-cells cause the more severe and prolonged symptoms of SLE and LN. After being stimulated by T-cells, B2 cells create IgG against self-tissue in the kidneys, leading to LN symptoms. These cells respond to different cytokines and begin creating more specific antibodies, driving the disease severity (41). For SLE and LN, this more specific antibody is IgG. Somatic hypermutations, as well as heavy chain class switching, lead to more specific IgG antibodies. In SLE and LN patients, cells expressing VH4-34 are usually selected during the process of affinity maturation. This tilts the scales in favor of autoimmunity. Then, cells with more accurate and powerful antibodies are selected over time. This process leads to the more severe symptoms of LN, like kidney failure (49). The strong reaction against tissue in the glomerulus combined with IgG clustering in groups causes the kidneys to no longer be able to filter out waste from the blood, which can lead to severe complications when left unchecked. After undergoing affinity maturation for subsequent generations to create the most effective antibodies, some cells become memory cells. For SLE patients, this makes reaching long-term remission difficult. While some treatments help reduce symptoms by reducing some immune cells, having self-antigen stored in the immune system's memory allows for relapse, sometimes

months or years after a patient is in remission. Some studies have even shown that memory cells could be the origin of this disease, showing defective IgG production can be stimulated by defective mutations in memory B-cells that allow for the antibodies to be cross-reactive. This means that in the presence of certain bacteria and viruses, SLE symptoms could be worsened (42, 43). A few genes, such as VH4-34, have been identified as markers due to the frequency in which they appear in autoreactive cell antibodies, but it appears that there needs to be multiple mutations at different checkpoint alleles to cause symptoms. This area of B2 B-cells has many areas left to explore; discovering different combinations and their outcomes could lead to more effective diagnostics as well as therapeutic agents (50).

Currently, there are limited drug options to try and help reduce symptoms and flare-ups caused by SLE. Steroids and other anti-inflammatory medications can be used to treat skin problems, joint pain, and inflammation. Even though steroids and NSAIDS (non-steroidal anti-inflammatory drugs) are helpful in treating these symptoms, unfortunately they can be problematic for other SLE symptoms (51). Steroids help as an anti-inflammatory but can exacerbate eye problems and even cause osteoporosis and diabetes. NSAIDS can exacerbate skin problems associated with SLE, making sunburning easier. They also can cause digestive issues. Most notably, with SLE, NSAIDs can damage the kidney with prolonged use. This damage, along with SLE symptoms, can cause the kidneys to fail quicker than without this exposure (51). Drugs such as Mycophenolate Mofetil (MMF) are immunosuppressant drugs that decrease B-cell production. This drug targets B-cells, thus reducing overall antibodies they produce. By decreasing activated cells that not only create autoantibodies but recruit other cells that damage tissue through inflammation, MMF has been shown to decrease SLE symptoms. Specifically, cardiovascular symptoms were reduced in patients on MMF. Unfortunately, MMF has been

18

linked to skin problems (itching, burning, etc.), kidney problems, and chest pains; each of these are complications of SLE (52).

When looking at more focused options for treating SLE, the first idea was to use B-cell suppressing medications such as Rituximab to help alleviate symptoms. Multiple studies such as "EXPLORER" and "LUNAR" tested the effects of Rituximab on SLE patients both with and without renal disease. Unfortunately, both of these studies demonstrated that Rituximab wasn't effective against SLE. Even though many of the B-cell's roles in causing SLE symptoms have been discovered, there are clearly more roles to be researched so there can be a better drug to help patients alleviate symptoms from the source. Researchers are currently still limited to T-cell-dependent pathways as well as symptom management, such as those explored above (53–55).

When looking to the future, drugs that focus on inhibiting TLR7 seem to show a promising path forward. These drugs, while still in the developmental stages, would make TLR7 unable to be activated. This would lead to the termination of many germinal center reactions, limiting the high-affinity autoreactive B-cells from being produced. Also, this could help patients long term by limiting cell memory production for autoreactive antibodies. There are some obvious drawbacks to these medications, such as lower vaccine efficiency and an overall weaker immune system that is predisposed to recurrent infection (56).

Tofacitinib is a drug that is in the early clinical stages. While Tofacitinib is shown to improve arthritis symptoms, this trial focuses on the drug's ability to block the JAK-STAT pathway. In mice with SLE, Tofacitinib blocks the interferons and cytokines that activate this pathway. By blocking JAK/STAT, the hope is that symptoms will be alleviated- however, this research is still in the preliminary stages (57).

Both researchers and physicians have compared the symptoms of SLE to be "like snowflakes" in the sense that they vary so much from patient to patient and almost seem individual. Due to this, many experts are leaning toward a more personalized care option tailored to a patient's specific needs rather than just one catch-all solution. While personalized medicine is still in early stages and is very expensive, an NIH study predicts that, in time, this approach will lower the financial burden on patients with a variety of conditions, not just SLE (58). Finally, arguably the most promising area of future research to treat SLE (and other autoimmune conditions) is using CAR-T cells. This would use the patient's own cells to kill any B-cells with a specific antigen. This would specifically deplete the B-cells that have antibodies to the patient's own tissue. The downside of this treatment is that it requires chemo to weaken the immune system, and it depletes B-cells for a few months, leaving the patient at risk for infection. However, in some patients, the B-cells begin to come back over time. One area researchers are concerned about using this treatment is if symptoms stay gone or if they come back over time due to exposure to hormones or through other means (59).

3. MULTIPLE SCLEROSIS

Multiple sclerosis, or MS, is an autoimmune disease in which the patient's body attacks the myelin sheath around nerves and the cells that produce and protect it. This can lead to a wide range of painful and debilitating symptoms. These symptoms drastically change the lives of those diagnosed with the disease and even shorten the lifespan of those affected. In the US, about one million people have been diagnosed with MS, but that number is rising due to better diagnostic tools and understanding of the disease. Like other autoimmune diseases, MS is more commonly found in those assigned female at birth. Symptoms usually start to present in patients between 20 and 40 years old, but depending on the type of MS, it can take years to definitively diagnose. This waiting period, combined with the symptoms of MS can lead to mental health problems and financial stress, impacting the patient's quality of life further (47).

The symptoms of MS greatly affect those with the disease and their caregivers. The main symptoms of MS are extreme fatigue, muscle spasms, weakness, loss of vision, seizures, and problems thinking. Each of these can lead to lifechanging issues like bladder and bowel problems (losing control), loss of mobility, and even having to give up or change careers. Symptoms progressively get worse in patients over time, but in most cases, they get worse after major flare-ups (47). Each of these symptoms can be traced back to B-cells or B-cells acting as APCs to stimulate other cells to react against the patient's myelin. Because this disease's impact can take years to become visible, there is no definitive way to test for MS, contributing negatively not only to the patient's mental health but to their economic capabilities too (60).

Despite the diagnosis of MS being relatively uncommon in the United States, the economic effect this disease has on patients, their caregivers, and their employers is estimated to be around 85.3 billion USD annually and is predicted to rise to 105 billion USD by 2039 due to

inflation as well as more people being diagnosed (61). This study did include profit losses due to being on disability, and the shortened lifespan of those who suffer from MS. For patients, medical costs (not including mental health services) is around 29,000 USD more per year than for the average citizen. Even with insurance, this affects how much money these people must spend, influencing the economy in other ways too. Unfortunately, the economic effect MS has doesn't stop at the patient's; it effects caregivers too. It is estimated that caregivers give about 30 hours a week of informal care to those with MS. The reach that the disease has on those who aren't affected is beginning to be looked at more closely, but with having to take off work and losing money to care for family members does create an economic burden on caregivers. Annually, this number is projected to be around 18 billion USD. Clearly, research on how to lessen the severity and slow progression of MS is needed not only to better patients' (and their caregivers') quality of life but to help society and the economy (61, 62).

Looking at what is happening at the cellular level for patients with MS, one must first understand what myelin, oligodendrocytes, and nerve fibers do for the body and what is supposed to happen when the system is working correctly. Myelin is a substance that protects nerve endings (axons). When intact, myelin speeds up the electrical impulses sent from nerve cells to their tissues. Myelin helps to maintain the intensity of the signal as it travels to its destination. Oligodendrocytes are cells that surround the neurons found in the central nervous system (CNS). These cells help to produce and protect the myelin sheath and even play a role in regulating axons. Finally, nerve fibers (or axons) are what allow neurons to connect and communicate with each other. These fibers provide a variety of functions, such as being able to feel heat and pain; they even help regulate muscle movements and breathing. In MS, these

functions are disrupted due to the immune system attacking the cells highlighted above, creating the symptoms of MS (47).

Changing gears, the immune system can greatly impact the nerve cells in MS patients by causing chain reactions that produce the symptoms and disease severity. Starting with one of the first steps in this chain reaction, the cytokines that B-cells produce (or lack) have a major impact on MS symptoms. These cytokines include IL-6, IL-10, IL-8, and CCL19. IL-6 and IL-8 each play a significant role in recruitment of other cells. When expressed by B-cells, each of these cytokines recruits different immune cells to cross the blood-brain barrier (63, 64).

In the case of IL-6, patients with relapsing-remitting MS had significantly more IL-6 than control groups that were disease-free and among others with MS. This led scientists to begin studies to see if IL-6 was upregulated in the patients B-cells in general or if there were differences between relapses and times of remission. It was discovered that IL-6 was upregulated during relapses (63, 64). This is most likely due to IL-6's ability to recruit T-cells as well as cause The differentiation which leads to further B-cell stimulation. This stimulus can lead to B-cells producing IgG against myelin and contributes to the creation of memory B-cells which contribute to the progression of MS. Next, IL-8 also plays a role in the progression and severity of MS symptoms. This happens by recruiting both neutrophils and T-cells to the CNS. By recruiting T-cells to the CNS, more B-cell-to-T-cell interactions occur, allowing for a more effective immune response against the patient's own myelin, which can progress the degradation process (65, 66). As for the neutrophils, studies are being conducted to better understand their role in autoimmune diseases, specifically MS, as neutrophil reduction leads to less severity in symptoms. It is hypothesized that their ability to increase inflammation plays an important role in this, though. Also, in MS, it was found that IL-8 damages the blood-brain barrier, allowing for

more cells to slip through. Because of this concentration, IL-8 in MS patient's serum is lower than in others, but the concentration of it in the CNS is significantly higher (65–67). CCL19 is yet another cytokine to influence the B-cell role in MS. B-cells have the receptor CCR7, that is the receptor for CCL19. In healthy individuals, CCL19 helps recruit and regulate DC, T-cells, and B-cell's journey into lymph nodes during inflammation or infection. However, in MS patients, there is an upregulation of CCL19 in the CNS, allowing for B-cells to recruit T-cells to the CNS for activation. While CCL19 is secreted by DCs, B-cells being able to detect and use this to enter lymph nodes leads to their ability to act as an APC and to be stimulated by other cells so they can make better, more specific antibodies (68–70). In MS, this leads to further demyelination due to the increase in specificity and interactions with T-cells. Finally, in MS patients have been found to have less IL-10 in the CNS than healthy individuals. Secreted by both T and B-cells, IL-10 works as an anti-inflammatory cytokine that begins the end of an immune response. Without this cytokine present in appropriate concentrations, the immune system can no longer regulate the immune response. IL-10 has been seen to help regulate the repair of the CNS after injury, and downregulation of IL-10 in the brain's B-cells is linked to other neurodegenerative disorders other than MS. Because MS patients need more protection in this region than others, the lack of IL-10 in the CNS predisposes patients to more severe MS symptoms. In MS patients, the myelin and B-cells are thought to be genetically predisposed to have decreased IL-10 production by having mutations in certain transcription factors such as CREB and MEF2D (65). Due to its reduction in the CNS, inflammation and tumor growth can remain unchecked which leads to further demyelination and the brain lesions found in those with MS.

After being activated, the B-cells begin to undergo class switching and affinity maturation to produce specific high-affinity antibodies such as IgA and IgG. For patients with MS, increased IgA targets the albumin in the blood-brain barrier. This leads to degradation and allows for even more autoreactive cells to enter the CSF(71). Also, a study was done on patients that showed that IgA from the stomach can be recruited to the CSF in patients with MS. This is important because if a patient is exposed to bacteria that is similar to the genetic structure of the myelin or oligodendrocytes, then cross-reactivity can occur and create MS symptoms (72). Another study demonstrated that IgA is elevated in patients experiencing an active relapse rather than a remission. This highlights the role that IgA plays in the event of relapses and growing brain lesions. IgA was the main focus of a subsequent study where gut IgA was found in the CSF of MS patients. Not only does this finding relate to the idea that an infection in combination with genetic factors can lead to MS and that the blood-brain barrier is made more porous in MS patients, but it even goes to show how important the gut-brain axis is (47,48,). While this finding is still relatively new and more research is being conducted, autoreactive IgA clearly plays a major role in MS progression- highlighting the role that B-cells have too.

IgG is the other important antibody for MS patients. IgG deposits, as well as bands of the antibody, are commonly found in MS patients both within the CNS and in brain lesions (64, 73). Specifically, IgG1 and IgG3 are the most common subtypes in MS and have been linked to brain degradation and lesion production that is caused by activating complement as well as immune cell cytotoxicity. Without other regulatory immune cells present, the lesions are allowed to grow and multiply. Myelin is another common target that the IgG sticks to, recruiting other immune cells to come and degrade it, causing the hallmark of MS disease progression. IgG3 is especially important to some MS patients as it can find antigens that are less exposed, making it perfect for

infiltrating the myelin sheath. IgG3 makes complement reactions more common, which may explain the first step in myelin degradation as holes appear and the sheath becomes porous. IgG1 is important too as it heightens the ADCC reaction that eventually causes regulatory cells and repair cells to die off, allowing the disease to progress (64, 74). Where IgG's role becomes complicated and disputed is that it isn't expressed in high amounts of all MS patients. Even some IgG reducing therapies alone aren't enough to completely reduce symptoms, suggesting that B-cells and antigen production aren't the only mediator of disease, even if they do play a major role for some patients. Again, this goes to show that the variability of MS makes it a very tricky disease to treat with a single method (50, 51).

Memory B-cells play a crucial role in MS progression. Even though memory cells don't produce antibodies, they can still cause disease symptoms through a variety of ways. First, it's important to understand why there are so many more memory B-cells present in the CNS of MS patients rather than others not effected by disease (76). This is because memory B-cells are attracted to CCL9 and migrate towards wherever it is expressed (which is in the CNS of MS patients). Once in the CNS, memory B-cells are activated by the immune response and generate a new generation of B-cells that are more rapid and strong in their response, even if it's to self-tissue(69). Another interesting finding regarding memory B-cells in the CSF of MS patients is that they have higher levels of costimulatory molecules such as CD80 and CD86. Memory cells in MS were shown to interact better with CD4T cells better due to this increase (45,51,52). Furthermore, this process is done where myelin antigens are present, increasing the risk for autoreactivity to occur as the memory B-cells function as great antigen-presenting cells. After being in contact with the antigen in question, the memory B-cells begin the process of generating more antigen-secreting plasma cells, which progresses the disease severity (42,52).

Memory B-cells don't just work as antigen-presenting cells but allow for the process of disease progression to start again. In MS patients, memory B-cells express HLA-DR15 more frequently. This genetic mutation is estimated to cause up to a 60% increase in the risk of developing MS. This happens because CD4T cells try to interact with the memory B-cells expressing this haplotype and migrate to the CNS, causing damage to the blood-brain barrier and the myelin sheath. This haplotype has even been thought to play a part in the selection of T-cells that become autoreactive, being able to survive and multiply in the thymus and CNS. This would allow autoreactive cells to outcompete their healthy counterparts(77). Due to memory B-cells regulation of HLA-DR15, they clearly play an important role in re-starting the cycle of disease pathogenesis (78). Finally, Epstein Barr virus and certain coronaviruses, alongside memory B-cells are thought to increase the risk of developing MS due to it having cross-reactive antigens with myelin (78, 79). Memory B-cells expressing HLA-DR15 were found to be cross-reactive with a protein (RASGRP2) found on these viruses. When the memory B-cells infected with EBV migrate to the brain, the risk becomes significantly higher as there is a higher likelihood that they will interact with autoreactive T-cells, leading to the degradation of myelin (53). Unfortunately, the exact mechanisms are unknown in humans as samples are taken post-mortem, but this is the most likely scenario based on animal models (53).

Overall, one of the main characteristics that cause the severity of MS symptoms is the location of the cells. There are many similarities between MS and other autoimmune conditions but having the inflammation and autoreactive cells located in the CNS is almost as important as any genetic markers that make patients predisposed to this disease. Being located near the myelin, the blood-brain barrier, and oligodendrocytes each allow for the symptoms of the disease

to present as they do despite the similarities in where things go awry that MS has to other autoimmune diseases (65, 77).

Treatments for MS are varied. Some treatments try to subdue symptoms and focus more on management. Others focus on reducing brain lesions and relapses over time. While there are many different options for MS treatment, this paper will be highlighting Ocrelizumab, Fingolimod, Ublituximab, inhibition of Bruton's tyrosine kinase (BTK), Botox, steroids, and stem cell therapies as they each are a display of the different approaches to MS treatment.

Starting with B-cell therapies, Ocrelizumab is an IgG monoclonal antibody that has been humanized, a process where antibodies from another animal (such as a mouse) have some proteins changed so they can mimic those found in humans more closely. This medication works in MS patients by killing B-cells through a process called antibody-dependent cell mediated cytotoxicity. In the case of Ocrelizumab, this process is carried out by coating the B-cells in IgG antibodies. These antibodies have a Fc region that has a high affinity for NK cells and macrophages. These killer cells then attack the B-cells that the antibody is attached to, significantly reducing the population of B-cells in the body. For MS patients, this drug was shown to reduce annual relapses in patients by 46 percent. Better still, patients treated with Ocrelizumab had reduced Gd+ lesions by 94 percent. While this doesn't prevent demyelination and all the symptoms caused by it, Ocrelizumab does help alleviate the symptoms of MS caused by brain lesions. If the MS is caught early, this route of treatment can stop many of the symptoms of MS before they can become debilitating, highlighting the need for better early detection measures (80, 81).

Ublituximab is another monoclonal antibody that uses a IgG to bind to CD20. However, Ublituximab binds to a different epitope than other medications like rituximab. Due to this

difference in location, Ublituximab was proven to be more efficient in binding to CD20 and mediating ADCC. Ultimately, B-cells with CD20 are attacked and their population is lowered by an effector cell that targets the antibody. The B-cells in these patients were lowered by around 98%. For patients with MS, lowering the B-cells present to generate autoantibodies and cytokines such as those discussed above leads to a decrease in brain lesion size and density. This medication is still in the trial phase (phase 2) so the long-term effectiveness for combating MS progression and symptoms is unknown (81, 82).

Fingolimod is also used to treat the symptoms of MS. This medication dropped the annual relapses, overall disease progression, and tumor sizes in most patients with most types of MS. Unfortunately, this medication can't be used in those with heart conditions, as it can cause bradycardia and blockages. However, the success of Fingolimod has affirmed some of the roles that both T and B-cells play in MS progression, as well as raised a few questions about the functions these cells have play in the disease (83). Fingolimod works by changing the sphingosine 1-phosphate receptor (S1PR) by causing its internalization and degradation in both B and T-cells. S1PRs have multiple jobs, but in the role of MS, they are found to effect naive T-cells and B-cells exit from lymph organs (83, 84). Also, when knocked out, the maturation of current B-cells isn't affected, but the new population generated is greatly reduced. In patients with MS, it was found that primarily memory B-cells were found in the CNS. These cells have a slightly altered job, however, and produce inflammatory cytokines and present myelin antigens to T-cells. Each of these properties causes the progression of MS as the myelin is sufficiently degraded. By treating patients with Fingolimod, regulatory B-cells can enter the CNS fluid and produce anti-inflammatory cytokines, which not only suppress the need for further B-cell creation but can help reduce the effects of the T-cells in the CNS by increasing local IL-10

production. CD80 is reduced in patients taking Fingolimod which leads to B-cells having their ability to present antigens at a high concentration suppressed slightly. With more regulatory B-cells being allowed to cross the blood-brain barrier and reducing the amount of memory cells found, patients with MS had more similar cell counts to those without the disease. Finally, some questions brought up by this treatment are how innate immune cells are involved with the progression of MS, as S1PRs are found on these cells as well and how much of a role location and cell migration play in MS (59, 60). Each of these are questions that, because of current MS treatments, could be explored further.

Inhibiting Bruton's tyrosine kinase (BTK) is another way that medication can treat MS. Tolebrutinib is an inhibitor of BTK that is currently being tested and is in the third phase of clinical trials. This drug would be delivered as a pill and would help reduce new brain lesions, which would stall disease progression and lessen symptom severity. A key feature of this medication is its ability to quickly cross the blood/brain barrier to begin inhibiting BTK in B-cells that send the signals to create tumors (85). Specifically, BTK aids the B-cell receptor's response to antigens though a variety of methods such as CD40, chemokine receptors, TLRs, etc. Another important quality of BTK is that autoreactive B-cells rely on it for survival in higher quantities than normal B-cells. This means that autoreactive B-cells would be more likely to stimulate the subsequent T-cells as CD40 is affected, providing the right costimulatory molecules to the cells that will ultimately cause more damage to the myelin. BTK can even be used to activate B-cells, so by having more BTK around, there is more room for error just in population size. Also, by selecting for autoreactive cells, high levels of BTK leads to more autoreactive B-cells, their antibodies, and ultimately, symptom progression. By just decreasing the amount of BTK present, a selection for normal, non-reactive B-cells would take place. This

medication will be extremely useful as it doesn't fully deplete the body's B-cell population and causes less side effects than other treatment options. Finally, due to the versatility of BTK, treating MS patients with this medication allows for more types of MS to be treated with only one medication (86–88).

Moving on to symptom management approaches, steroids, botox, and anti-seizure medication have been shown to improve the lives of those with MS greatly. Corticosteroids such as methylprednisone can help to relieve pain from flare-ups. Steroids work by reducing inflammation in areas like the brain stem, eyes, or muscles. By reducing inflammatory cytokines, the flare up can be ended sooner, even if the disease isn't cured (47). Anti-seizure medication is currently being researched as an option in aiding T-cell homeostasis in MS patients, but for now, any effect on the immune system is still unknown. While this treatment doesn't actively affect the immune system, it is still important to discuss as it can interact with other medications and is key in maintaining some independence for patients with MS (80).

Botox is another emerging therapy that has been found to be successful in helping reduce muscle spasms and bladder incontinence in severe cases. By injecting botulinum toxin from *Clostridium botulinum*, acetylcholine release from T-cells and nerve endings is blocked. Blocking acetylcholine allows for the muscles to relax by opening the muscle cell's receptors allowing contraction to occur in a way that patients with MS can control. Due to this, mobility can be restored after injections, which can be life-changing for patients. In the immune system, acetylcholine inhibits cytokines and controls some innate immune responses. Finally, in the bladder, acetylcholine is used to narrow the muscles, forcing urine out of the bladder. In excess, this can lead to incontinence. Even though the effects of Botox start to wear off after about six months post-injection, being able to stay mobile without mobility aids and being able to control

their bladder greatly improves the quality of life for patients with MS and takes some stress off their caregivers. Unfortunately, even though Botox is useful, antibodies to the toxin can form over time. Sometimes switching to a different form of the toxin is helpful, but other times the antibodies are cross-reactive and render the other forms useless (89, 90). As a short-term solution as well as prolonging mobility issues, Botox is a great option, but as a long-term solution, it falls short.

Looking toward the future of MS treatments, stem cell research is showing promise to combat the neurodegenerative issues that MS creates. While not targeting the immune system to kill a specific type of cell, a hematopoietic stem cell transplant is an option that is in clinical trials for patients with MS. This type of transplant uses cells from the bone marrow to try to restart and reset the immune system to stop the progression of the disease (91). In Italy, a study showed that after 10 years, 65% of the study group didn't have any more symptom progression post-transplant. Patients using this treatment type wouldn't have to worry about the long-term effects of B-cell depletion either, as the immune system would be repaired with transplant (92, 93). This type of treatment would be life-changing for those normal medications can't help. The major downsides seen for this type of treatment are the cost, the need for chemotherapy to prepare the body for transplantation, and that it can't reverse the symptoms that are present (69). However, being able to stop progression is a huge step in the right direction for treating MS and could someday lead to the reversal of symptoms with more research.

4. RHEUMATOID ARTHRITIS

Rheumatoid arthritis or RA is an autoimmune disease that affects the joints due to inflammation causing pain, stiffness, and less function over time. RA is a systemic disease, and if left untreated (or treated ineffectively), can affect many areas of the body. Due to all of these symptoms, the average lifespan of those with RA is reduced by around 10 years (94). A study even highlighted that the cause of death for RA patients are infectious diseases like pneumonia that others without the disease would commonly recover from (95). Between the symptoms and shortened lifespan, RA truly changes the lives of those affected by it, highlighting how important the B-cells' role in the immune system is for normal function. In the United States alone, 58.5 million people have RA (96). While typically developing in adults aged 40 to 60, RA can even affect young adults. The Cleveland Clinic estimated that 8 in 100,000 young adults have been diagnosed with RA. However, this autoimmune condition in young people is usually due to a combination of genetic factors and sports-related trauma to a specific joint (95, 96).

The symptoms of RA are usually standard among patients. Joint pain due to inflammation and the synovial lining being attacked by the immune system is common. Because RA is an autoimmune disease, finding symmetrical arthritis is common, especially older patients. Also, pain in specific, smaller joints such as the wrist, fingers, and ankles is extremely common among older patients. Diagnosis is becoming easier for this population, as a blood test for rheumatoid factor, c-reactive protein, and imaging make the diagnosis clear as the disease has time to develop before symptoms become noticeable (97). Unfortunately, because the disease takes time before symptoms progress, combined with older patients being wary of seeking treatment, other symptoms tend to occur, making patients need more care as time progresses. These symptoms

can include eye problems, skin issues (nodules over bony areas), heart damage, lung damage, and blood vessel damage if flares aren't managed properly (95, 97). These more severe symptoms can take away the independence of the patient, leading to mental health problems outside of those caused by the joint pain. Younger patients with RA have the advantage of being able to undergo genetic testing for RA if family history is established, making early detection and treatment more possible (98). However, because rheumatoid factor takes time to develop, imaging tests are more relied upon. Also, because many cases are trauma-induced, the symmetrical nature of RA isn't seen in younger patients right away. This can prolong the diagnostic process, highlighting a need for a more diverse screening procedure for younger patients. Finally, long-term studies on younger patients show that more severe damage to joints and bones/bone marrow can occur over time if not properly managed (95, 98).

Due to the physical nature of these symptoms, RA is the leading cause of disability in the United States (96). Combining the costs of lost earnings and medical care every year, the total cost is around 303.5 billion dollars per year. Because the onset of RA is typically farther along in one's career, many people have reported that aspects of their job become too difficult to do, especially during disease flare-ups. Unfortunately, with more younger people getting diagnosed and the retirement age increasing, these annual costs are likely to increase (99, 100).

Understanding what happens at the cellular level is key to understanding the pathogenesis of RA and developing better medication and screening for the disease. B-cells have multiple jobs that cause RA symptoms such as creating autoantibodies, acting as APCs, and by recruiting other immune reactions (101, 102). In RA, B-cells act as APCs to local T-cells. One study showed that B-cells in RA may have disrupted CLIP expression. Low-affinity CLIP receptors were found in RA patients, leading scientists to believe that cells with this receptor could make a mistake, lose

self-tolerance, and begin presenting auto-antigen to T-cells (103). B-cells act as the primary

APCs to present and activate the T-cell response in RA. This was displayed across multiple

studies that showed after CD20 B-cell depletion, T-cells weren't being activated in RA. In mouse

models, ridding all the B-cells greatly limited the symptom severity (102, 104–106). B-cells in

RA were found to secrete higher amounts of INF, IL-6, and IL-1. Each of these cytokines aids in

recruiting not only other B-cells but other immune cells to the synovium, leading to RA

symptoms (107). Regarding B-cells, IL-6 is particularly important in RA pathogenesis. IL-6

initiates the B-cell proliferation and recruits other cells. In mouse models, eliminating IL-6

production lessens the severity of RA symptoms (103, 107).

In RA, B-cells were found to have enhanced activation after migrating to the synovium.

Antibody-secreting B-cells populations are found to be higher in RA patients than in others

without the disease. By secreting autoreactive IgG and combining with rheumatoid factor in

immune complexes, other cells are recruited to the area. When these immune complexes interact

with typical synovial tissue, those cells become marked and the immune system clears them,

usually through the complement or ADCC pathway. This causes the tissue damage that leads to

RA symptoms (103, 107). Something particularly interesting about this is that a study showed

rheumatoid factor alone wasn't inflammatory or problematic but that it did become problematic

when introduced to the immune complexes that B-cells produce. This may be due to B-cells in

the synovium having already completed the process of somatic hypermutation. AID and

rheumatoid factor is upregulated in the synovium of RA patients, allowing for somatic

hypermutation and more production of autoantibodies (106). This hyperactivation may be caused

by dysfunctional CD40 and dysfunctional CD40L on the B-cells in RA patients. This mutated

CD40 would lead to abnormal B-cell selection, which may lead to increased autoantibody

production. This hypothesis would coincide with studies that indicate CD40L expression is related to autoantibody titers (both rise and fall together). Finally, upregulated BAFF expression contributes to the hyperstimulated B-cells found in RA. When combined with CD40 and CD40L upregulation, long-lasting B-cells can be created that secrete autoantibody, leading to the chronic symptoms of RA(103).

Two areas of future research focusing on the B-cell role are impaired checkpoints and trauma's role in RA. Impaired checkpoints in B-cell development are thought to be one of the reasons B-cell functions in RA are atypical. If these checkpoints are disrupted, autoimmune B-cells can develop and not be forced to undergo apoptosis (103). However, this area needs more research to confirm this theory. Another area of future research is the role trauma plays in RA development, especially in younger patients. One study showed that after breaking a bone, almost all patients had abnormal labs a year after the injury had healed. In non-break injuries (ex: ACL tears), around 80% of patients had abnormal labs up to a year later. The correlation of this data and another study's data that indicated those with sports-related injuries were more likely to develop RA at a younger age is something that should be further explored. When trauma occurs, the immune system is recruited to the area. The hypothesis is that through trauma, the recruited B-cells could invade the synovium and become autoreactive, leading to RA in younger individuals(108, 109).

RA is usually treated using Rituximab. While other medications are used for RA, Rituximab has been shown to have very good results as well as work better if fewer other drugs are tried before starting Rituximab. Rituximab is an IgG chimeric antibody that targets the CD20 found on most B-cells. By marking these cells for death, the population of B-cells is depleted, even if the cell isn't set up to be autoimmune. While Rituximab is more effective in patients with

early RA symptoms, it still works well in patients who have had the disease for longer periods, reducing the frequency of flare-ups and other pains associated with the disease (110). By reducing B-cell numbers, rheumatoid factor, T-cell activation flare ups were decreased in patients. Rituximab remains tolerated for 10 years (that's as far away I could find for studies), showing it has the ability to be used as a long-term aid in RA patients, keeping flare-ups at bay. Because symptoms were resolving with B-cell depletion, the critical roles B-cells play in RA were brought to light, leading to other research on B-cell's roles in autoimmune diseases. While combining Rituximab with other biologic drugs can help those with severe RA symptoms, adverse reactions like being prone to other infections (usually more severe infections like TB) do increase. However, when combined in the early stages of RA, these drugs can lead to the disease affecting less joints. Ultimately, it is up to the patient to determine which options are more appealing to them. Looking to the future of RA research, a better understanding of genetic predisposition factors as well as developing drugs that create less co-morbidities, will most likely be of focus (111, 112).

5. INFLAMMATORY BOWEL DISEASE

In this section, the role of B-cells in Inflammatory bowel disease, or IBD, is explored. IBD is a catch-all term for two conditions, Chron's disease (CD) and ulcerative colitis (UC). These diseases, while very similar (especially in the early stages) and take time to distinguish, have some key differences that will be explored in this section as well. IBD affects around 1.3 million people in the United States alone but is rising. These diseases are thought to be caused by a combination of genetic and environmental factors that cause cells in the GI track to begin harming self-tissue. Both CD and UC can cause a wide variety of symptoms during flareups as well as progressing "quietly" when flareups aren't occurring. Symptoms of IBD usually begin between ages 15 and 35 (113). However, symptoms are found in young children, but they are usually not formally diagnosed until later due to the invasive nature of arriving at a specific diagnosis. Because many people live with their symptoms without being diagnosed until their later years, data on how many people actually have this disease is thought to be slightly lower than the true numbers (114, 115).

To diagnose IBD, MRIs, CT scans, stool samples, and blood tests are conducted. Each of these tests look for inflammation, damage to GI tissue, and remaining gut flora. Unfortunately, these tests don't distinguish between CD and UC, only between IBS versus IBD. An endoscopy and colonoscopy must be done to be formally diagnosed with CD or UC. The invasive nature of both of these procedures deters younger people who otherwise would not need these exams from getting diagnosed, leading to the discrepancy talked about previously (113–115).

IBD affects patients in a variety of ways that can affect the patient's mental and physical health. Symptoms range from diarrhea, fatigue, and stomach pain, and skin reactions to anxiety,

liver disease, and GI cancers. Because of these symptoms, life expectancy of patients with CD or

UC is expected to be around 5 years less than those without it. While life expectancy isn't

severely impacted, the quality of life for these patients can be changed greatly after symptoms

begin. The economic impact of IBD totaled to be between 14 and 31.6 billion USD in 2014, but

that number is thought to have climbed in recent years. Original estimates of cost were incorrect

as some studies didn't include lost labor in the impact. Due to the unpredictability of IBD

symptoms, the individual costs of the disease can't be predicted perfectly. However, lifetime

losses are thought to be around 230,000 and 416,000 for UC and CD respectively (provided the

diagnosis is before age 50. Between the personal and economic issues, better understanding of

IBD is necessary so that more efficient drugs can be developed (116, 117).

Moving to the cellular level of IBD, B-cells play a key role in disease pathogenesis and

distinction. There are many way B-cells can induce autoimmunity in IBD ranging from secreting

autoreactive antibody, secreting inappropriate cytokines, and becoming confused due to cross-

reactivity to genetic defects. Each of these areas is equally important, as there isn't a consensus

on which area is most important. This lack of consensus is not only an area where more research

is needed for a better understanding of the disease but would aid in the creation of better

medications that would slow the progression of the disease as well as more effectively manage

symptoms (118–121).

One current area of major research is understanding how a westernized diet can affect

IBD symptoms, as the disease is most often found in the US and Europe (122). The hygiene

hypothesis that, as a society, we are over-sterilizing food will affect our ability to fight off

infections as well as leave us open to more autoimmune conditions is recognized as the starting

point for diseases like UC and CD to begin. Without bacterial stimulation (at the appropriate

amount), regulatory B-cells are formed less frequently. These regulatory cells stop reactions that could continue for too long, leading to a higher likelihood of cross-reactivity events (118). When looking at IBD patients, scientists observed a lower regulatory B-cell count in the intestines, which allows for IBD to progress into CD or UC. Regulatory B-cells are mediator cells that, once they catch up to the autoimmune reaction taking place, stop flareups by secreting cytokines such as IL-10 that stop the immune reaction from happening. By stopping the release of more inflammatory cytokines, IL-10 doesn't allow for further T-cell differentiation as well as slows B-cell differentiation. In sterile environments, IL-10 was found to be secreted in lesser amounts. A phenomenon also found in IBD patients. In multiple studies, regulatory B-cells were found to suppress the symptoms of UC and CD (118, 123, 124). However, when testing, IL-10 was less frequently found in the blood of CD patients, where UC patients serum levels were closer to normal levels, and the only changes were found in the colon (125). The reason for this distinction is still being researched. Another way B-cells affect IBD symptoms and progression is through cytokines. As stated above, Il-10 is a key component in the progression of IBD. However, it is not the only cytokine involved in this process; Il-2, IL-23, and, IL-8. In CD patients, CD36 and B-cells that produce IL-8 (sometimes spontaneously) are increased (120, 126). However, what the TLR responds to that induces IL-8 production varies from patients with CD versus UC. In CD patients, spontaneous IL-8 production is more common. Also, TLR4 is less expressed on B-cells, increasing the amounts of IL-8 allowed to circulate the GI tract (127, 128). *E. coli* LPS is the main trigger for IL-8 production in UC patients. This allows for the symptomatic distinction between the diseases, as the <u>E. coli</u> is found at higher frequencies in the lower smaller intestine and the colon (127). Further still, expression of TLR2 and TLR4 have been found to act as homing mechanisms to attract other B-cells, T-cells, and other parts of the adaptive and humoral

immune systems to the area affected. This increases inflammation, which not only worsens symptoms but can cause even more chronic damage to the lining of the area they are recruited to (129).

Genetic factors such as dysfunctional Gai2, NOD2, and MLH1, genes have been found to influence the risk of IBD, causing adverse reactions to natural/normal gut bacteria. Gai2 -/- genotypes are commonly found in mouse models of UC. This genotype exhibits LPS proliferation, which could lead to IBD symptoms as high amounts of LPS in the gut would lead to chronic stimulation. NOD2 is another gene that has been found to influence IBD susceptibility. NOD2 mutations were found to impair the ability of cells to recognize the differences in structure between normal flora and pathogenic bacteria, leading to IBD symptoms as the immune system attack self-tissue. NOD ligands have been identified as a B-cell activator in humans that causes proliferation which can further this problem. MLH1 expression was found to be decreased in colorectal cancer brought on by UC. This loss of function is critical to UC patients as this gene manages parts of the DNA repair pathway, mediating the mismatch repair process. Overall, these genetic studies vary greatly. Race can change what gene abnormality combinations induce disease, making finding a consensus on the gene's role in IBD difficult. Understanding how these genes affect the individual cells in the immune system to cause a chain reaction is something that isn't yet understood (130–132).

Autoreactive antibodies and the location of where those antibodies are located contribute to IBD risk and symptom severity. While IgA is commonly found in the gut, in patients with IBD, IgA is decreased, causing the endothelial lining of the GI-tract to lose a protective measure. This can lead to patients being more susceptible to environmental changes that cause IBD to worsen and be more vulnerable to autoreactive IgG (119, 120). In patients with IBD, IgG is

raised in the intestines or colon. A study showed that blood levels of IgG producing B-cells was lowered but IgG-producing B-cells in the gut were elevated in IBD patients, the idea that homing these cells to the GI tract was problematic was highlighted. However, when comparing CD and UC, blood levels of IgG were higher in UC patients. Elevating IgG levels in the intestines is thought to cause IBD, as IgG is a very variable polyreactive antibody. Certain upregulated IgG subsets (IgG1) being so polyreactive is where problems arise in the colon and GI tract. For patients with UC, this means that B-cells local to the small intestine and colon become cross-reactive. These cells were even found to have upregulated CD138, making these cells stick to nearby endothelial tissue. The LPS from *E.coli* in the area is similar to the endothelial lining in these areas. When the B-cells undergo class switching, the wrong antibodies can be made-leading to tissue damage through complement reactions or through cytokine secretions that recruit in more immune cells (inflammatory response). In this case, B-cells begin to make autoantibodies to endothelial cells. In UC, IgG1 is more commonly found; however, in CD, IgG2 is more common. This makes sense in UC because the damaged tissue is clustered together. IgG binding to the small intestine and colon and recruiting in molecules like C3b to induce complement reactions lead to the tissue being damaged in one large area. Between complement reactions and the immune system recruiting T-cells, neutrophils, and dendric cells, all of the damage is found in the space where IgG is concentrated, having all the tissue damage in one area is to be expected. For patients with CD, the areas affected are scattered along the whole GI tract, and healthy tissue is alongside the dead tissue. Higher levels of IgG are still thought to greatly contribute to inflammation and tissue death (for the same reasons stated above) (119, 120, 124, 133).

The question of why the tissue isn't clustered has evaded research and remains an area of further research. The presence of these autoreactive B-cells is important because as antibody-secreting B-cells' population expands, the regulation of Treg cells becomes disrupted. This means that not only can the B-cell response not be regulated properly, but the T-cell response can't either, crippling both of the major arms of the adaptive immune system (134). Not only do autoreactive antibodies cause symptoms, but they cause disease progression. In mouse models, B-cell depletion led to a reduction in cancer incidence. While B-cell therapies are still being tested for their efficiency in humans, it is an important area to keep researching (119).

Finally, B-cells could play an interesting role in passing IBD along to future generations. IgG secreting B-cells can pass through the placenta's barrier. While genetic mutations are easier to follow when tracing diseases through families, the importance of passing autoreactive antibodies through the placenta is underrated and needs further research. While studies have shown that during pregnancy, IBD symptoms can either worsen or resolve depending on if conception occurred during a flareup (135). The mechanism behind this phenomenon is unknown but is worthy of further research, as this could also affect the likelihood of disease in future generations.

One area that is still understudied but is up-and-coming research is how *Clostridium difficile* (*C.diff*) infections can affect the immune system, inducing or worsening IBD symptoms, specifically UC. Some areas of the immune system have been explored in this context such as the increased mortality rate of IBD patients who contract *C.diff,* but current research is being conducted to better understand how B-cells are affected by this bacterium and change the course of one's IBD (136). One avenue that is being explored is how *C.diff* kills the natural microbiome of the intestines, and upon re-entry through probiotics or fecal transplantation, natural flora may

be mistaken for problematic bacteria, causing inflammation and, ultimately IBD(137). Another avenue to explore is how the antibiotics used to treat *C.diff* can create a very sterile environment, reducing regulatory B-cell populations and inducing symptoms through the lack of regulation (138, 139). Finally, understanding how UC or CD can develop through this pathway and be able to predict outcomes more accurately is important to patient care as well as treatment options.

Treating IBD has mostly focused on T-cell regulation, overall immune suppression, and rebuilding the normal gut flora. However, there has been a recent shift towards focusing on B-cell-related therapies. Treatments such as infliximab and aminosalicylates (5-ASAs) are currently in use for CD and UC, respectively. However, due to side effects and medication costs, only about 16 percent of patients use biologics like infliximab and only 53% of patients use 5-ASAs (140–142).

While anti-inflammatory drugs can help reduce IBD symptoms during a flareup, these drugs don't help the long-term symptoms or even create long periods of remission. Infliximab was developed as an agent to help regulate B-cell population numbers. In patients with IBD, memory B-cells are reduced, but IgA and IgG secreting cells are elevated. After infliximab treatments, these numbers stabilized and were more compatible with control samples. Significant differences were found in reducing IgA and IgG secreting cells. However, while the number of memory cells did increase, the numbers showed no statistically significant change. Regardless, symptoms improved (141–143). B-lymphocyte populations around granulomas were also reduced with infliximab, even though these granulomas still occur without antibodies. This demonstrates the medication's ability to reduce multiple types of B-cells. The exact mechanisms behind this medication remain unclear. Its effectiveness raises questions about how chronic stimulation and impaired memory B-cell formation can affect the symptoms of CD and UC.

Finally, using these cell population values could give medical professionals better insights into the effectiveness of new treatments based on the individual needs of the patient, leading to more efficient and personalized medical care in the future. Unfortunately, the side effects of Infliximab treatments are troubling. Higher risks of malignancy in epithelial tissue and reactivation of viruses such as EBV, infusion reactions, and anti-chimeric antibody formation have each been reported (144).

Other monoclonal antibodies are used to treat IBD with varying effects. Belimumab reduces BAFF, lowering the number of B-cells that are allowed to be activated. While this suppresses part of the humoral immune system, it improves IBD symptoms caused by secreted antibodies (126). Also, CD38 inhibitors such as Daratumumab are used to deplete the co-stimulatory molecules that B-cells need to interact with their environment and proliferate. This lowers the number of replications the B-cells are allowed to undergo, reducing the population. These medications are found to have more success in CD rather than UC (144).

The last type of treatment discussed in this section is 5-ASAs. These medications are more successful in UC patients than CD patients, further highlighting that while these diseases have a similar origin and both fall under the IBD umbrella, they are distinct from each other. Two examples of 5-ASAs are Mesalamine and Sulfasalazine. Mesalamine is a drug that was found to reduce native B-cells as well as CD27 cells. Without CD27 receptors, CD27 can't be used as a costimulatory molecule. While the mechanism behind this is still unclear, one could hypothesis that due to CD27's role in regulating survival and activation of B-cells, depleting it would deplete B-cell populations too. Another hypothesis that this drug helps patients with UC is by depleting the κB in the body, which reduces the amount of cytokines produced by NK cells. This medication was also found to inhibit TNF, which limits the inflammatory cytokines

produced because of TNF's role in proliferation and anti-apoptosis in NK cells but research is still being conducted on this (145).

Sulfasalazine is a combination of 5-ASA and an antibacterial agent, sulphapyridine. This medication suppressed B-cell functioning by limiting IgM and IgG production. Another type of cell that appeared to be decreased was plaque-forming B-cells. However, CD4 T-cells appeared to be unaffected by this medication. Post-depletion, the symptoms of UC appeared to resolve. While the damaged tissue wouldn't be repaired, other symptoms, such as diarrhea, were resolved. The downside to sulfasalazine is that it is being prescribed to fewer patients due to side effects. The incidence of sulfa-drug allergies is relatively common, affecting about 8% of the population (146, 147).

Finally, two areas that are being looked at for the future of UC treatment are stem cells. While adipose-derived stem cells from mice with IBD were found to not be as immunosuppressive as researchers would like and rejection is a side effect, advancing the field to allow for modifications to the patient's own stem cells would be a way forward in personalizing IBD medications for both UC and CD (148).

6. GRAVE'S DISEASE

Grave's disease (GD) is an autoimmune condition that affects the thyroid, causing hyperthyroidism in patients. The hyperthyroidism caused by the body's immune system attacking the thyroid can lead to a variety of symptoms, with B-cells playing a major role in pathogenesis. Many people worldwide are affected by GD, however, according to the national institute of health, 1 in every 100 Americans is affected. Estimates show that 4 out of every 5 causes of hyperthyroidism in the US is caused by Grave's disease. Like other autoimmune diseases, GD is more commonly found in those assigned female sex at birth. Usually, people with Graves' disease are diagnosed before turning 40, and many patients have other autoimmune disorders as well (149).

Symptoms of GD include anxiety, hand tremors, heat sensitivity, weight loss, menstrual cycle changes, an enlarged thyroid, etc. The most identified symptom of GD is orbitopathy, where the eyes appear to be bulging. According to the Mayo Clinic, approximately 30% of patients diagnosed with GD will develop Grave's orbitopathy. These patients will develop a variety of symptoms ranging from bulging eyes, pressure, and gritty feelings in the eyes, to vision loss based on the progression of the autoimmune response due to the B-cells. If left untreated, GD can even lead to heart problems. When testing for GD, a hormone panel is conducted to determine the amounts of triiodothyronine (or T3) and Thyroxine (or T4). If lower levels of thyroid stimulating hormone, but higher levels of thyroid hormones (T3 and T4) are found, then a diagnosis of Grave's disease can be confirmed (149).

The overall economic effects GD vary from patient to patient ranging from around 400 to 2000 USD annually. However, socioeconomic status has been found to influence GD treatment,

affecting how severe symptoms become. In poorer areas, the first step patients take to resolve their GD is a thyroidectomy while in areas with more money, medications that usually stop symptoms are the first defense. This is because the one-time cost of surgery outweighs the lifetime cost of medications. However, this can cause other problems if supplemental hormone therapies aren't abided by, which in poorer communities is likely to be the case (150).

At the cellular level, B-cells act as a control center driving progression and symptoms of GD. IGF-1 is one important receptor that is defective in the B-cells of patients with Graves disease. In GD patients, IGF-1 receptor expression is upregulated in B-cells. This ultimately leads to an expansion of the B-cell population. IGF-1 was found to stimulate IgG and IgM production (151). In GD, this means that having more receptors for activation lead to a higher likelihood that the B-cells will become activated and able to produce thyroid damaging autoreactive IgG antibodies. Another important characteristic of cells with this phenotype is that they appeared to produce IL-7 dependent B-cells. IL-7 is often associated with inflammation as well as a growth factor for B-cells. In areas where an immune reaction is taking place, such as in the thyroid of GD patients, having another inflammatory cytokine in the mix can prove problematic. Furthermore, B-cells with more IGF-1 receptors have been found to produce anti-TSHR antibodies and lowering TSH receptors has been found to cause GD symptoms by leading to uncontrollable thyroid hormone production (151, 152).

Another B-cell subset that has been shown to affect the development of GD are the regulatory B-cells. Studies show that B-regulatory cells directly correlate with anti-TSHR antibodies found in Grave's disease patients. Also, their numbers are in the process of being explored as a potential biomarker for GD progression as well as how likely medications like methimazole will work (153, 154). Researchers hypothesize that when fewer regulatory B-cells

are found, the less likely certain medications are to work. While this hasn't been backed in the research yet, the coincidences between patients with fewer regulatory B-cells and poor medication outcomes shouldn't be ignored. B-cells with CD19, CD24, and CD27 were found to be reduced in GD patients. This phenotype would normally suppress an inflammatory reaction by secreting IL-10 and inducing IL-10 secretion in other cells (153, 155). However, because this phenotype is reduced in GD, less IL-10 is present. An interesting finding through this experiment was cells that do have this correct phenotype in GD patients still produce less IL-10 than their counterparts in controls. Finally, in graves patients, more IL-6 than IL-10 was found to be secreted. The decrease in IL-10 is partially supported by the reasons above, but the increase in CXCR3 and decrease of CXCR5 in the B-cells of GD patients plays a role. These chemokine receptors recruit other, inflammation inducing cells to the thyroid. These cells even have a higher IgG secretion capacity, furthering the problems of GD when the IgG is autoreactive (156, 157).

Yet another way that B-cells affect GD is by having genetic mutations that modify proliferation and survival. These mutations are found to occur in the TCL1-A and SH2 regions. These regions encode for survival and cell-to-cell communication by identifying certain protein targets. Because these are also oncogenes, mutations here could lead to uncontrolled proliferation, which would contribute to higher amounts of autoantibodies in GD (153, 158).

Treatments for GD can vary from taking medication to suppress thyroid hormone formation such as methimazole and propylthiouracil combined with B-cell suppressants such as Rituximab, to beta-blockers to undergoing a thyroidectomy (159–161). While beta-blockers aren't a B-cell related treatment, they can reduce GD symptoms by reducing the active form of T3 by blocking T4 from converting to T3 (162). Methimazole is another, non-immune cell related medication but is often paired with one to treat GD. Methimazole and propylthiouracil

work by making it more difficult to produce TSH and thyroid hormones. This occurs by blocking the thyroid peroxidase which converts iodide to iodine, which is used in the amino acid synthesis needed to create hormones needed to activate the thyroid. Reducing these hormones would reduce the overall output that causes symptoms of hyperthyroidism in most cases, however, some patients need a boost by pairing this drug with B-cell suppressant drugs (159).

There are multiple treatments for Grave's orbitopathy, but so far, the most promising (where most patients enter remission) is using Rituximab infusions. Rituximab utilizes anti-CD20 antibodies to induce apoptosis through antibody-dependent cellular cytotoxicity (ADCC). This process occurs when the antibodies bind to antigens on the B-cell surface. Fc regions found on complement and natural killer cells find and recognize the antibodies that are bound to cells, then attach, and cause the B-cells to enter the lytic cycle, causing apoptosis. The reason Rituximab is so effective is due to B-cell expression of CD20 antigens throughout their life cycle (160, 163–165). One surprising discovery through using Rituximab infusions was that depleting the B-cells led patients to enter a state of remission from Grave's orbitopathy, even though levels of IgG were not affected (only IgM was found to be reduced) (166). Even a year later, IgM values hadn't returned to problematic levels. Because symptoms were thought to primarily be due to IgG, this discovery has caused scientists to re-evaluate how broad the effects of B-cells in GD are (164).

Getting rid of thyroid hormones fully isn't an option as they are necessary for B cell development. This is why some researchers are turning to BAFF as another pathway that could be influenced to decrease symptom progression in GD patients. Serum BAFF levels in some GD patients were elevated. However, research has yet to be conducted on the role BAFF plays in GD progression. A better understanding of how blocking this system could alleviate the symptoms of

GD is required before medication can be developed, but this is one promising area of future research on GD (167, 168).

7. HASHIMOTOS THYROIDITIS

Hashimoto's thyroiditis is another autoimmune thyroid disease. While the B-cell role in Hashimoto's thyroiditis is less understood and less significant than in Grave's disease, their role is still an important one to discuss. According to the CDC, in the US alone, 5 out of every 100 people have Hashimoto's thyroiditis. In the case of Hashimoto's thyroiditis, the thyroid isn't working correctly, and hypothyroidism occurs. The average age that Hashimoto's thyroiditis symptoms appear in people aged 30 to 50, but due to hereditary reasons, is becoming more prevalent in younger people as well. Again, like Grave's disease, Hashimoto's thyroiditis is found more often in those assigned female at birth. Risk factors for developing this disease include having other autoimmune conditions like Sjogren's syndrome, SLE, and type one diabetes. Unfortunately, the symptoms of an underactive thyroid can take time to diagnose, leading to symptom progression (169–171).

Symptoms of Hashimoto's thyroiditis include development of a goiter, tiredness, weight gain, muscle weakness, mental sluggishness, reproductive issues, and anxiety/depression. Each of these symptoms can affect the lives of patients with Hashimoto's thyroiditis (171). Each of these symptoms add to the economic burden that these patients face due to their disease. Because 4.6% of the US population has Hashimoto's thyroiditis, it comes as no surprise that the disease can lead to costing somewhere between 384 million to 2.1 billion USD per year (172). Even with the relatively inexpensive costs of iodine treatment, costs of Hashimoto's thyroiditis are still high for patients due to some of the other symptoms associated with the disease in combination with needing more sick days (leading to lost income). To diagnose Hashimoto's thyroiditis, symptoms must be evaluated and a blood test must be ordered. Then, a decrease of T4 production but an increase of TSH production in the blood is found. A decrease in iodine and increase of anti-TPO

antibodies are commonly found in patients with Hashimoto's thyroiditis. If left untreated, symptoms of Hashimoto's thyroiditis can lead to heart problems and myxedema (where the body's functions slow to critical levels) (169).

B-cells play a few important roles in Hashimoto's thyroiditis. They create autoantibodies to thyroid peroxidase (TPO) and serve as antigen-presenting cells that induce T-cell reactions. Faulty B-cells in Hashimoto's thyroiditis take in thyroid and thyroid peroxidase antigens and present them to CD4T cells using MHC2 (173). MHC2 as well as multiple T-cell populations have been found to be increased in Hashimoto's thyroiditis patients (174). This means that the B-cells have more receptors to communicate with local T-cells, adding more fuel to the problem when the antigen presented is self-antigen. Not only do B-cells act as excellent APCs in Hashimoto's thyroiditis, but they also secrete IgG. A study displayed that there were higher amounts of IgG in Hashimoto's thyroiditis patients' serum as well as higher plasma cell counts. Increased IgG has been found in patients that have significantly more fibrosis of the thyroid, leading to a higher risk of end-stage Hashimoto's thyroiditis, myxedema (156, 174–176). This increase could be due to genetic factors, environmental factors, or increased T-cell interactions that allow for more cellular cross-talk. By presenting thyroid antigen to T-cells, recruitment of an immune response is created against the thyroid tissue. This causes inflammation that can lead to fibrosis in combination with the autoantibodies that infiltrate the tissue, and cause antibody-dependent cellular toxicity, directly killing thyroid cells (175). However, B-cells create autoantibodies against TPO in Hashimoto's thyroiditis. This is a sneakier pathway to create symptoms but can do as much damage as creating antibodies against the thyroid. When TPO is attacked by the immune system, iodine into iodide, a chemical that is critical in the creation of thyroglobulin. Thyroglobulin in turn is used to create thyroid hormones that regulate a variety of

bodily functions. Without it, symptoms of Hashimoto's thyroiditis begin to start (177). While studies on the pathways B-cells use outside of IgG secretion are sparse, the role these cells play in progressing Hashimoto's thyroiditis cant be ignored and is a target for future research.

Treatment for Hashimoto's thyroiditis is T-4 replacement therapy with levothyroxine. This medication's dosage has to be heavily monitored as overtime, a patient's needs can change and symptoms can progress if the dosage isn't correct. This medication is used to reverse myxedema and prevent symptoms. However, in rare cases, poor outcomes occur. Because of this, future research on Hashimoto's thyroiditis is targeting regulatory B-cells and using them to mediate the autoimmune reactions in the thyroid. Using CAR-T therapies in combination with aiding regulatory B-cells has been hypothesized to be an avenue to regaining tolerance to self-antigens in the thyroid (178).

Finally, areas of future Hashimoto's thyroiditis research focus on genes that could act as risk factors and better diagnostic tools. Without understanding the disease at a genetic level, hereditary risks can't be understood other than Hashimoto's thyroiditis being found in families. Also, because serum IgG has only been found in around 25% of patients with Hashimoto's thyroiditis, the question has been raised if there aren't two diseases at play (177, 179). Having a better understanding of both the B and T-cell role in disease pathogenesis would help researchers create better and more effective medication if there is truly more than one disease at play, aiding the lives of many.

8. TYPE 1 DIABETES

Type one diabetes (T1D) is an autoimmune condition where the pancreas doesn't produce enough insulin. Due to a lack of insulin, blood sugar can build up in the body, causing organ damage outside the pancreas. However, if not regulated, low blood sugar levels can occur too. In the US alone, 1.45 million people have T1D. However, more people under 20 are being diagnosed with T1D, and an estimate predicts that by 2040, 2.1 million Americans will have the condition. Disease onset usually occurs during childhood or young adulthood, but some patients do get diagnosed later as well (180–182).

Symptoms of T1D include drowsiness, extreme thirst, eye and weight changes, as well as frequent urination. Each of these are warning signs that blood sugar levels are unbalanced, and if left ignored, can lead to more severe symptoms like hypoglycemia and diabetic ketoacidosis (182). Hyperglycemia in diabetics can be caused by a variety of things, such as having too much insulin, working out for longer than usual, or waiting too long to eat. Diabetic ketoacidosis is a complication that occurs in diabetics when there isn't enough insulin present to allow sugar into cells. These conditions are both life-threatening if not treated quickly. The levels of insulin one needs to stay regulated change during development, such as during puberty, and again in one's early 20s (183). This, combined with other lifestyle choices and daily activities for patients with T1D can make insulin regulation difficult. Another effect that T1D can have on people with the disease is mental health problems. Patients with T1D are at an increased risk for developing anxiety and depression, especially surrounding eating and drinking (184). Economically, the US spends 16 billion on T1D related expenses such as lost income and healthcare costs (185). The diagnostic process for T1D is an A1C test as well as an antibody test to see if there are anti-insulin and anti-islet cell antibodies against the ß-cells (182). If these are found, then the patient

is said to have T1D. These autoantibodies are secreted by B-cells, highlighting their role in this disease.

B-cells contribute to the development of T1D by acting as APCs and secreting autoantigens against ß-cells and insulin. There are certain mutations that lead to these B-cell abnormalities. Each subset plays a role in the disease and while most research is still on mouse models, as many human studies are done postmortem. However, recently this is beginning to change, leading to more human studies that generate data that is more applicable than the NOD mouse model. Starting with the gene that may cause some of the defects seen in the B-cells of T1D patients, a mutation on the PTPN22 gene was identified (186). This gene lowers Fas-R expression on B-cells, leaving them able to have more defects and less able to induce apoptosis. This is thought to protect autoreactive cells because in mouse models, B-cells without this receptor had more severe T1D (187). Also, in humans, there was a report that stated T1D patients had fewer rearrangements than in control counterparts. This could permit more autoreactive B-cells to survive, but this mechanism is poorly understood. Finally, MHC is upregulated in pancreatic B-cells of T1D patients, allowing them to act as better APCs to the local T-cell population. This furthers the damage done to the pancreas, worsening symptoms of T1D. Without the presence of B-cells, ß-cell populations rose and there were less anti-insulin antibodies in mice (188, 189).

MZ B-cells are one of the specific subsets that have been studies in T1D patients and in mouse models. MZ B-cells are thought to act as APCs. This is partially due to their hyperresponsiveness to TCRs and CD40, which would allow them to present autoantigens to T-cells more efficiently. In mouse models, MZ B-cells have higher populations in the spleen and more CD80 and MHC expression, allowing for more contact with T-cells. These cells were

found to have higher IgM expression than control mice. After observing the spleen, MZ B-cells were found to have larger populations than in the pancreas of T1D mice indicating they most likely followed cytokine expressions and permeated the pancreas. These cells then capture ß-cell autoantigen and present it to the local T-cells. MZ B-cells' role as APCs was further highlighted when the incidence of insulitis increased with MZ-B cell population size in mice with T1D (10, 190, 191).

Another subtype that has been explored in relation to T1D is regulatory B-cells. IL-10, a necessary cytokine to decrease inflammation is made by regulatory B-cells. In NOD mice, these cells were defective. Many B-regulatory cells didn't produce IL-10, and those that did, produced it at a lower rate, indicating a defect. These cells were found to be unable to stop the Th1 and Th17 responses that are crucial in diabetes development. In another study on mouse models, transferring regulatory B-cells from the spleen to the pancreas could prevent insulitis in some cases. In the mouse model, eliminating regulatory B-cells from the pancreas made diabetes symptoms worse. Finally, treating NOD mice with regulatory B-cells when they were babies postponed T1D onset (192, 193). Unfortunately, each of these studies have been on mouse models, highlighting a need for more research on these B-cells in humans.

Autoantigen producing cells are important to T1D development too. By presenting autoantibodies to both insulin and proteins found in ß-cells, these cells direct the immune response towards the patient's own tissue. In the NOD mouse model, reducing these cells led to ß-cell function restoration (189). Also, it was discovered that location and being nearby dysfunctional MZ B-cells could influence anti-insulin expression (194). This is most likely due to proximity to T-cell stimuli. Regardless, directing the immune response to the patient's own tissue drives T1D pathogenesis. Again, many of these studies to better understand the

mechanisms that drive this creation are done in mice, but these autoantigens are found in humans and thought to act in the same or a similar manner (191).

Treatments for T1D mostly focus on managing symptoms. Insulin remains the main method of treatment. Insulin helps T1D patients regulate their blood sugar but doesn't slow the progression of the disease or work to counteract the disease at the immune level. Rituximab has been shown to partially help T1D patients. After four treatments, both NOD mice and human patients required less insulin to stay regulated than their control counterparts(195). A separate study showed that, ß-cells were partially preserved (196). Both of these outcomes highlight the importance that B-cells creating autoantibodies has on the disease. Finally, future research is being conducted on blocking the BAFF receptor in pancreatic B-cells to try and reduce MZ B-cell numbers, but these drugs are still in the very early stages of development (197).

9. SJOGREN'S SYNDROME

Sjogren's syndrome (SS) is an autoimmune condition where the secretory glands in the eyes and mouth are damaged due to autoreactive antibodies. SS in patients is categorized into two groups, Primary Sjogren's syndrome (PSS) and Secondary Sjogren's syndrome (SSS) (198). PSS patients only suffer from SS, but the symptoms of the disease are usually more widespread, causing other glands to be affected too. SSS patients suffer from multiple autoimmune conditions such as SLE or rheumatoid arthritis. However, in SSS patients, symptoms are usually milder and only affect the eyes and mouth. In the United States alone, up to 4 million people are thought to have SS (199). Symptoms of SS vary based on if the patient has PSS or SSS, genetic factors and environmental factors. Most often, patients are around 40 around the time they are diagnosed, however, patients younger than 40 do exist. Like other autoimmune diseases, SS is affected by estrogen levels. To diagnose patients with SS, dry mouth, dry eyes, and poor saliva production needs to be established. Then to confirm SS, antinuclear antibodies and a positive rheumatoid factor need to be identified through a blood test. Because many people have SSS, the disease can go undiagnosed for long periods of time (200).

While studies showing the full economic impacts of SS aren't clear in the US, studies do show that patients with PSS have 2.9 times the annual medical costs than non-effected peers. In comparison, SSS patients have 1.6 times the annual medical costs (relating to just SS symptoms) than peers. Another major area of economic impact for patients with SS is that SSDI doesn't pay out just because of a SS diagnosis (200). In order to qualify, patients need to prove that the disease has affected at least 2 major organs. The economic burden for patients faced with this stage of disease is huge and should be considered when talking about the economic burden SS causes. The quality of a patient's life who has major organ damage decreases dramatically,

reducing their buying power as well as how they contribute to the work force. Because of this, the true economic impact of SS has yet to be understood(199).

Symptoms of SS range from dry eyes and mouth, and lung and liver problems, to an increased risk of lymphoma (201). These symptoms are due, in part, to the B-cells role in disease pathogenesis. B-cells greatly contribute to SS disease progression and symptom onset. Starting with cytokines, BAFF is found to be increased in SS patients. While B-cells aren't the only cells that secrete BAFF, BAFF was found in the salivary glands of patients with SS. This cytokine allows for B-cell survival and protects them against apoptosis. In patients with SS, this could be one of the contributing factors leading to mutated B-cell survival. BAFF was found to activate MZ B-cells in the salivary glands, as well as other glands affected by PSS. Due to BAFF secretions and IL- 6 secretions by local B-cells, more T-cells begin to migrate to the glands (202, 203). Upon arrival, B-cells begin interacting with the T-cells, activating them. This activation leads to T-dependent activation, rather than just T-independent activation, leading to large populations of affected cells (204). Combined with autoantibody production, tissue damage, and inflammation are common in SS and are thought to both contribute to the elevated lymphoma risk seen in patients. Not only do these newly formed germinal centers cause long-term problems in the glands, but they can cause structural changes, leading to the symptoms that are most commonly associated with the disease (205). Overall, cytokines produced by B-cells lead to the migration of immune cells, leading to the symptoms of PSS spreading should the B-cells travel to other glands (206).

Multiple B-cell subtypes are necessary for SS to present in patients. Starting with MZ B-cells, studies show increased populations of these cells in patients with SS. Unlike in healthy populations, in SS, MZ B-cells have higher levels of CD21, but lower levels of CD23 and IgD.

This means that the cells have matured, and undergone class-switch recombination to produce a more efficient type of antibody (205). In SS, these antibodies are usually IgG or IgA. Another role MZ B-cells play in SS is their contribution to lymphoma development. In mouse models, mice without MZ B-cells that still has SS showed decreased development of lymphoma. In humans, lymphomas treated with rituximab (and anticancer medication) showed to have a positive outcome (203). This implies that the role of MZ B-cells and lymphoma development is important, if not well understood. MZ-B-cells may be hyperactivated by anti-Ro antibodies as well as IgG made nearby, leading to lymphoma but again, this isn't proven yet (207). Finally, in healthy individuals, MZ B-cells help guard against autoreactivity. Because of this change in SS patients, scientists believe that the selection process may be defective. This checkpoint disturbance would allow for the MZ B-cells that are autoreactive to survive. Whether this pathway is directed by BAFF present in the glands or through another mechanism is unclear (208).

Memory B-cells expressing CD70 migrate to the salivary glands in patients with SS, causing their populations elsewhere to decrease. This is most likely due to the high amounts of CD27 found in SS patients' salivary glands. Both the migration to an area filled with cytokines and naive B-cells cause these memory cells to begin stimulating other cells to become plasma cells. Because of this, there is an overall decrease in serum memory B-cells in SS patients. Also, due to higher CXCR4 and CXCR5 expression in the memory cells, more efficient infiltration of the glands takes place. This allows for the creation of germinal centers and structural damage to the glands discussed previously (208).

Antibody producing B-cells that make autoantibodies contribute to SS symptoms as well. These cells migrate to the glands and begin secreting IgG and IgA after being activated. In SS,

the autoantibodies anti-Ro and anti-La are very common among patients. These autoantibodies are against two different parts of a ribonucleoprotein (RNP). RNPs help to regulate mRNA, non-coding RNA, and keep the RNA more stable in mammalian cells. By creating antibodies to these RNPs, the risk of cancer increases in SS patients due to instability. Another problem in these antibody producing cells found in SS patients is that they were found to have a long-lived phenotype (207). Salivary gland epithelial cells in SS patients were found to secrete IL-6 and IL-17, and BAFF. Each of these cytokines induce the cells to stay alive longer, giving the B-cells more time to secrete more antibodies per generation. B-cells in SS patients were found to have increased CXCL12 expression, which allows cells to better interact with the cytokines and chemokines to keep them alive for longer. The type of immunoglobulin secreted from these cells can determine SS severity. Studies show that higher IgM expression in SS patients' salivary glands is correlated with longer lasting symptoms that are milder and is correlated with RF expression. Elevated IgG has been shown to be more prevalent in PSS patients and is usually correlated with more intense symptoms that spread to other glands (202). Finally, IgA levels are less understood, but are only found to be increased in some SS patients, usually those with PSS rather than SS. The variation in autoantibody production (not every patient has anti-RF and anti-Ro/La) highlights the need for further research in this area so scientists can better understand SS symptoms, progression and develop more effective treatments (207).

Genetics, specifically genes that effect B-cell populations and cytokines involved in SS are under observation. First, an abnormality in HLA-DR haplotypes in SS patients is thought to be present, as expression of HLA-DR has been found to have a stronger association to anti-Ro/anti-La antibodies than healthy counterparts. An abnormality here could possibly lead to increased presentation of these antibodies to T-cells in patients, furthering the autoimmune

reaction (204). Next, an 86bp mutation in IL-1 was observed in higher frequencies in SS patients. While this still needs further study to understand the extent of clinical significance, it is an area that researchers are looking into (209). Also, LINCOO487 is a gene that was found to be upregulated in the B-cells of SS patients. While scientists have confirmed it is needed for B-cell differentiation, the exact function of this gene is unknown (209). Finally, abnormalities in V_H genes have been found in B-cells located in the salivary glands of PSS patients. There are more mutational frequencies here than in the rest of the body and compared to healthy counterparts. These mutations could lead to autoimmunity occurring, but also could be why IgA levels aren't as high as IgG levels in SS patients (210). This switch could lead to the spreading of the disease to other glands as well, but each of these outcomes and the associated with these abnormalities has yet to be studied.

Treatment options for SS have changed greatly in the last few years. Originally, drinking more water and eyedrops were all that were recommended for SS patients. However, drugs like Belimumab and Bortezomib have been effective for PSS treatment (203, 211). Due to the failure of Rituximab treatments in completely eliminating symptoms, scientists turned to Belimumab, a BAFF targeting drug to combat the symptoms of SS. However, preliminary studies showed that this treatment didn't resolve symptoms in all patients. This could mean that there is another subtype in SS patients that hasn't been discovered yet. Trials are still ongoing (no data yet) on Belimumab's effects, but remission was seen to occur in most patients whose B-cell populations had been depleted (211). Bortezomib has been shown across multiple clinical studies to reduce symptoms of SS. This medication works by causing antibody secreting B-cells to undergo apoptosis by inhibiting the cell's protection mechanisms. This medication was found to be effective against long-lived B-cells as well, making it a frontrunner in SS treatment. Further

studies focused on eliminating long-lived B-cells have begun due to this medication's successes (203). Overall, many treatments for SS target those with PSS, rather than SSS. This is due to SSS being paired with other autoimmune diseases that require drugs that could have adverse effects combined with those for PSS. Due to this, more research is required to increase the effectiveness of these drugs in all patients.

Looking to the future, using CAR-T cells as a treatment for SS is a strong possibility. The effectiveness of this therapy hasn't been studied in animals yet, but there is a study being done to assess the safety and efficacy of using CART-T cells in SS patients. Furthermore, a study looking at the uses of CAR-T-cells to attack long-lived cells is another avenue to take to treat SS. The CAAR method would be used on NK cells and would attack anti-Ro/anti-La BCRs. While not tested in animals yet, this method has proven to be effective in the lab stages. Finally, another target for CAR-T cells would be BAFF. By no longer having access to this cytokine, symptoms of SS could be resolved, hopefully without damaging the healthy B-cell populations (212, 213).

10. COMPARISON

There are many similarities between the autoimmune diseases covered in this paper. Specifically, similar cytokines, elevated BAFF, B-cell abnormalities, and certain genetic factors overlap. These similarities cause the overlap in symptoms such as inflammation and fatigue. The first of these similarities are the cytokines. IL-6 and L-21 are overexpressed in multiple autoimmune diseases while IL-10 is often less expressed (199). These cytokines allow for inflammation and cellular recruitment which is seen in many autoimmune diseases. By downregulating IL-10, regulatory B-cell function can be disrupted. When regulatory B-cells are disrupted, autoantigen producing cells remain unregulated, allowing them to keep producing the auto-IgG found in multiple autoimmune diseases. BAFF and BAFF receptors have been found in abundance in autoimmune diseases. While the exact mechanism used to cause problems is still unknown, BAFF can protect autoreactive B-cells from undergoing apoptosis, leading to long-lived cells found in a majority of the autoimmune diseases discussed in this paper.

Other cell surface molecules and their respective receptors are upregulated in many autoimmune diseases as well. These include CD20, CD27, CD40, CD80. CD20 allows for the differentiation into plasma cells that create antibodies that lead to self-tissue to be targeted. CD20 is a common target for drugs like rituximab that has shown to have some effect across diseases, though the extent of the aid differs. CD27 controls survival, and when overexpressed or when mutations occur, can lead to the long-lived B-cells found in autoimmune diseases. CD40 allows for isotype switching and affinity maturation to take place, leading to more effective autoantibodies in these autoimmune diseases. Finally, CD80 regulates how effectively the B-cells communicate with T-cells. In the case of autoimmune diseases, CD80 is upregulated,

allowing for more efficient crosstalk between branches of the immune system. This is aided by BCR upregulation found in the B-cells across autoimmune diseases.

Another interesting area of similarity is how hyper-stimulated MZ B-cells are. By acting as a starting point for many autoimmune diseases, these cells are an area that researchers are looking towards across autoimmune diseases as an area of future treatment. Also, by removing MZ B-cells in mouse models, many autoimmune diseases show improvement, thus highlighting their role in pathogenesis. It displays that MZ B-cells play as important of a role as antibody secreting cells do.

The differences seen in autoimmune diseases are most likely due to differences in genetic combinations and environmental factors. However, the most important difference is location. Where the immune reaction is taking place has a direct impact on which autoimmune condition will develop. Overall, researchers are still researching the exact mechanisms behind why these differences in autoimmune conditions occur.

REFERENCES

1.   Fairweather D, Rose NR. 2004. Women and Autoimmune Diseases1.

2.   Desai MK, Brinton RD. 2019. Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan. Front Endocrinol (Lausanne) 10:265.

3.   Moulton VR. 2018. Sex Hormones in Acquired Immunity and Autoimmune Disease. Front Immunol 9:2279.

4.   Greenfield J, Hudson M, Vinet E, Fortin PR, Bykerk V, Pineau CA, Wang M, Bernatsky S, Baron M. 2017. A comparison of health-related quality of life (HRQoL) across four systemic autoimmune rheumatic diseases (SARDs). PLoS One 12.

5.   Stojanovich L, Marisavljevich D. 2008. Stress as a trigger of autoimmune disease. Autoimmun Rev 7:209–213.

6.   Cojocaru M, Inimioara, Cojocaru M, Silosi I, Titu ". 2010. Multiple autoimmune syndrome. Mædica 5:132.

7.   Grimaldi CM, Jeganathan V, Diamond B. 2006. Hormonal Regulation of B Cell Development: 17β-Estradiol Impairs Negative Selection of High-Affinity DNA-Reactive B Cells at More Than One Developmental Checkpoint. J Immunol 176:2703–2710.

8.   Rodríguez-Pinto D. 2005. B cells as antigen presenting cells. Cell Immunol 238:67–75.

9.   Martin F, Oliver AM, Kearney JF. 2001. Marginal zone and B1 B cells unite in the early response against T-independent blood-borne particulate antigens. Immunity 14:617–629.

10.   Palm AKE, Kleinau S. 2021. Marginal zone B cells: From housekeeping function to autoimmunity? J Autoimmun 119:102627.

11. Cerutti A, Cols M, Puga I. 2013. Marginal zone B cells: virtues of innate-like antibody-producing lymphocytes. Nat Rev Immunol 2013 132 13:118–132.

12. Geva-Zatorsky N, Sefik E, Kua L, Pasman L, Tan TG, Ortiz-Lopez A, Yanortsang TB, Yang L, Jupp R, Mathis D, Benoist C, Kasper D. 2017. Mining the Human Gut Microbiota for Immunomodulatory Organisms. Cell 168.

13. Duan B, Morel L. 2006. Role of B-1a cells in autoimmunity. Autoimmun Rev 5:403–408.

14. Rothstein TL, Griffin DO, Holodick NE, Quach TD, Kaku H. 2013. Human B-1 cells take the stage. Ann N Y Acad Sci 1285:97.

15. Mauri C. 2012. Immune Regulatory Function of B Cells. Artic Annu Rev Immunol https://doi.org/10.1146/annurev-immunol-020711-074934.

16. Courtney AH, Bennett NR, Zwick DB, Hudon J, Kiessling LL. 2014. Synthetic Antigens Reveal Dynamics of BCR Endocytosis During Inhibitory Signaling. ACS Chem Biol 9:202.

17. den Haan JMM, Arens R, van Zelm MC. 2014. The activation of the adaptive immune system: Cross-talk between antigen-presenting cells, T cells and B cells. Immunol Lett 162:103–112.

18. Rubtsov A V., Rubtsova K, Kappler JW, Jacobelli J, Friedman RS, Marrack P. 2015. CD11c-Expressing B Cells Are Located at the T Cell/B Cell Border in Spleen and Are Potent APCs. J Immunol 195:71–79.

19. Lebien TW, Tedder TF. 2008. B lymphocytes: how they develop and function. Blood 112:1570–1580.

20. Manis JP, Tian M, Alt FW. 2002. Mechanism and control of class-switch recombination. Trends Immunol 23:31–39.

21. Pilzecker B, Jacobs H. 2019. Mutating for good: DNA damage responses during somatic hypermutation. Front Immunol 10:438.

22. Durandy A, Revy P, Fischer A. 2004. Human Models of Inherited Immunoglobulin Class Switch Recombination and Somatic Hypermutation Defects (Hyper-IgM Syndromes).

23. Fairlie-Clarke KJ, Shuker DM, Graham AL. 2009. Why do adaptive immune responses cross-react? Evol Appl 2:122.

24. Frank SA. 2002. Specificity and Cross-Reactivity.

25. Schmidt CW. 2011. Questions Persist: Environmental Factors in Autoimmune Disease. Environ Health Perspect 119:A248.

26. Schroeder KM, Gelwicks S, Naegeli AN, Heaton PC. 2019. Comparison Of Methods To Estimate Disease-Related Cost And Healthcare Resource Utilization For Autoimmune Diseases In Administrative Claims Databases. Clin Outcomes Res CEOR 11:713.

27. The Cost Burden of Autoimmune Disease: The Latest Front in the War on Healthcare Spending. 2000. *American Journal of Public Health* 90, 1463–1466.

28. Systemic Lupus Erythematosus (Lupus) - Who gets it? | NIAMS.

29. Study Underscores Economic Burden of Lupus in America | Lupus Foundation of America.

30.   Cohen-Solal JFG, Jeganathan V, Grimaldi CM, Peeva E, Diamond B. 2006. Sex hormones and SLE: influencing the fate of autoreactive B cells. Curr Top Microbiol Immunol 305:67–88.

31.   Foster MH. 2007. T cells and B cells in Lupus Nephritis. Semin Nephrol 27:47.

32.   Nashi E, Wang YH, Diamond B. 2010. The Role Of B Cells in Lupus Pathogenesis. Int J Biochem Cell Biol 42:543.

33.   Ezzat MHM, EL-Gammasy TMA, Shaheen KYA, Shokr ESM. 2011. Elevated production of serum B-cell-attracting chemokine-1 (BCA-1/CXCL13) is correlated with childhood-onset lupus disease activity, severity, and renal involvement. http://dx.doi.org/101177/0961203311398513 20:845–854.

34.   Clark EA, Giltiay N V. 2018. CD22: A Regulator of Innate and Adaptive B Cell Responses and Autoimmunity. Front Immunol 9:2235.

35.   Mundluru SN, Larson AR. 2018. Medical dermatologic conditions in transgender women. Int J Women's Dermatology 4:212.

36.   Grimaldi CM, Cleary J, Dagtas AS, Moussai D, Diamond B. 2002. Estrogen alters thresholds for B cell apoptosis and activation. J Clin Invest 109:1625.

37.   Ohl K, Tenbrock K. 2011. Inflammatory cytokines in systemic lupus erythematosus. J Biomed Biotechnol 2011.

38.   Davis LS, Hutcheson J, Mohan C. 2011. The Role of Cytokines in the Pathogenesis and Treatment of Systemic Lupus Erythematosus. J Interf Cytokine Res 31:781.

39.   Howe HS, Leung BPL. 2019. Anti-Cytokine Autoantibodies in Systemic Lupus Erythematosus. Cells 2020, Vol 9, Page 72 9:72.

40. Zhou Z, Niu H, Zheng YY, Morel L. 2011. Autoreactive marginal zone B cells enter the follicles and interact with CD4+T cells in lupus-prone mice. BMC Immunol 12:1–13.

41. Haas M. 1994. IgG subclass deposits in glomeruli of lupus and nonlupus membranous nephropathies. Am J Kidney Dis 23:358–364.

42. Tiller T, Tsuiji M, Yurasov S, Velinzon K, Nussenzweig MC, Wardemann H. 2007. Autoreactivity in Human IgG+ Memory B Cells. Immunity 26:205–213.

43. Mietzner B, Tsuiji M, Scheid J, Velinzon K, Tiller T, Abraham K, Gonzalez JB, Pascual V, Stichweh D, Wardemann H, Nussenzweig MC. 2008. Autoreactive IgG memory antibodies in patients with systemic lupus erythematosus arise from nonreactive and polyreactive precursors. Proc Natl Acad Sci U S A 105:9727–9732.

44. Mackay F, Browning JL. 2002. BAFF: A fundamental survival factor for B cells. Nat Rev Immunol 2002 27 2:465–475.

45. Fillatreau S, Manfroi B, Dörner T. 2020. Toll-like receptor signalling in B cells during systemic lupus erythematosus. Nat Rev Rheumatol 2020 172 17:98–108.

46. Chan OTM, Madaio MR, Shlomchik MJ, Chan OIM, Madaio MP, Shlomchik MJ. 1999. The central and multiple roles of B cells in lupus pathogenesis. Immunol Rev 169:107–121.

47. Multiple sclerosis - Diagnosis - NHS.

48. Dörner T, Giesecke C, Lipsky PE. 2011. Mechanisms of B cell autoimmunity in SLE. Arthritis Res Ther 13:1–12.

49. Karrar S, Cunninghame Graham DS. 2018. Abnormal B Cell Development in Systemic Lupus Erythematosus: What the Genetics Tell Us. Arthritis Rheumatol (Hoboken, N.j) 70:496.

50. Jang A, Sharp R, Wang JM, Feng Y, Wang J, Chen M. 2021. Dependence on Autophagy for Autoreactive Memory B Cells in the Development of Pristane-Induced Lupus. Front Immunol 12:2858.

51. Medications used to treat lupus | Lupus Foundation of America.

52. Taylor EB, Ryan MJ. 2017. Immunosuppression with mycophenolate mofetil attenuates hypertension in an experimental model of autoimmune disease. J Am Heart Assoc 6.

53. Jayne D. 2010. Role of rituximab therapy in glomerulonephritis. J Am Soc Nephrol 21:14–17.

54. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, Maciuca R, Zhang D, Garg JP, Brunetta P, Appel G, LUNAR Investigator Group. 2012. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 64:1215–1226.

55. Lightstone L. 2012. The landscape after LUNAR: rituximab's crater-filled path. Arthritis Rheum 64:962–965.

56. The Lancet Rheumatology. 2022. 2022: a banner year for systemic lupus erythematosus? Lancet Rheumatol 4:e451.

57. Hasni SA, Gupta S, Davis M, Poncio E, Temesgen-Oyelakin Y, Carlucci PM, Wang X, Naqi M, Playford MP, Goel RR, Li X, Biehl AJ, Ochoa-Navas I, Manna Z, Shi Y, Thomas D, Chen J, Biancotto A, Apps R, Cheung F, Kotliarov Y, Babyak AL, Zhou H, Shi R,

Stagliano K, Tsai WL, Vian L, Gazaniga N, Giudice V, Lu S, Brooks SR, MacKay M, Gregersen P, Mehta NN, Remaley AT, Diamond B, Shea JJO, Gadina M, Kaplan MJ. 2021. Phase 1 double-blind randomized safety trial of the Janus kinase inhibitor tofacitinib in systemic lupus erythematosus. Nat Commun 12.

58.   Yamamoto Y, Kanayama N, Nakayama Y, Matsushima N. 2022. Current Status, Issues and Future Prospects of Personalized Medicine for Each Disease. J Pers Med 12.

59.   Baker DJ, June CH. 2022. CAR T therapy extends its reach to autoimmune diseases. Cell 185:4471–4473.

60.   Multiple Sclerosis MSJ Journal https://doi.org/10.1177/1352458514521888.

61.   Bebo, B., Cintina, I., LaRocca, N., Ritter, L., Talente, B., Hartung, D., Ngorsuraches, S., Wallin, M. & Yang, G.(2022). Economic burden of MS projected to reach $105 billion by 2039. *Neurology*.

62.   Rodriguez-Rincon D, Leach B, Pollard J, Parkinson S, Gkousis E, Lichten C, Sussex J, Manville C. 2019. Exploring the societal burden of multiple sclerosis: A study into the non-clinical impact of the disease, including changes with progression.

63.   Stampanoni Bassi M, Iezzi E, Drulovic J, Pekmezovic T, Gilio L, Furlan R, Finardi A, Marfia GA, Sica F, Centonze D, Buttari F. 2020. IL-6 in the Cerebrospinal Fluid Signals Disease Activity in Multiple Sclerosis. Front Cell Neurosci 14:120.

64.   Maeda K, Mehta H, Drevets DA, Coggeshall KM. 2010. IL-6 increases B-cell IgG production in a feed-forward proinflammatory mechanism to skew hematopoiesis and elevate myeloid production. Blood 115:4699.

65. Li R, Rezk A, Miyazaki Y, Hilgenberg E, Touil H, Shen P, Moore CS, Michel L, Althekair F, Rajasekharan S, Gommerman JL, Prat A, Fillatreau S, Bar-Or A. 2015. Proinflammatory GM-CSF-producing B cells in multiple sclerosis and B cell depletion therapy. Sci Transl Med 7.

66. Bar-Or A, Fawaz L, Fan B, Darlington PJ, Rieger A, Ghorayeb C, Calabresi PA, Waubant E, Hauser SL, Zhang J, Smith CH. 2010. Abnormal B-cell cytokine responses a trigger of T-cell–mediated disease in MS? Ann Neurol 67:452–461.

67. Matejčíková Z, Mareš J, Sládková V, Svrčinová T, Vysloužilová J, Zapletalová J, Kaňovský P. 2017. Cerebrospinal fluid and serum levels of interleukin-8 in patients with multiple sclerosis and its correlation with Q-albumin. Mult Scler Relat Disord 14:12–15.

68. Fevang B, Yndestad A, Damås JK, Halvorsen B, Holm AM, Beiske K, Aukrust P, Frøland SS. 2009. Chemokines and common variable immunodeficiency; possible contribution of CCL19, CCL21 and CCR7 to immune dysregulation. Clin Exp Immunol 158:237.

69. Bielecki B, Jatczak-Pawlik I, Wolinski P, Bednarek A, Glabinski A. 2015. Central Nervous System and Peripheral Expression of CCL19, CCL21 and Their Receptor CCR7 in Experimental Model of Multiple Sclerosis. Arch Immunol Ther Exp (Warsz) 63:367.

70. Sellam J, Rouanet S, Hendel-Chavez H, Miceli-Richard C, Combe B, Sibilia J, Le Loët X, Tebib J, Jourdan R, Dougados M, Taoufik Y, Mariette X. 2013. CCL19, a B cell chemokine, is related to the decrease of blood memory B cells and predicts the clinical response to rituximab in patients with rheumatoid arthritis. Arthritis Rheum 65:2253–2261.

71.   Muñoz Ú, Sebal C, Escudero E, García Sánchez MI, Urcelay E, Jayo A, Arroyo R, García-Martínez MA, Álvarez-Lafuente R, Sádaba MC. 2022. High prevalence of intrathecal IgA synthesis in multiple sclerosis patients. Sci Rep 12:4247.

72.   Pröbstel AK, Zhou X, Baumann R, Wischnewski S, Kutza M, Rojas OL, Sellrie K, Bischof A, Kim K, Ramesh A, Dandekar R, Greenfield AL, Schubert RD, Bisanz JE, Vistnes S, Khaleghi K, Landefeld J, Kirkish G, Liesche-Starnecker F, Ramaglia V, Singh S, Tran EB, Barba P, Zorn K, Oechtering J, Forsberg K, Shiow LR, Henry RG, Graves J, Cree BAC, Hauser SL, Kuhle J, Gelfand JM, Andersen PM, Schlegel J, Turnbaugh PJ, Seeberger PH, Gommerman JL, Wilson MR, Schirmer L, Baranzini SE. 2020. Gut microbiota–specific iga+ B cells traffic to the CNS in active multiple sclerosis. Sci Immunol 5.

73.   Arneth BM. 2019. Impact of B cells to the pathophysiology of multiple sclerosis. J Neuroinflammation 16:1–9.

74.   von Büdingen HC, Gulati M, Kuenzle S, Fischer K, Rupprecht TA, Goebels N. 2010. Clonally expanded plasma cells in the cerebrospinal fluid of patients with central nervous system autoimmune demyelination produce "oligoclonal bands." J Neuroimmunol 218:134–139.

75.   van Langelaar J, Rijvers L, Smolders J, van Luijn MM. 2020. B and T Cells Driving Multiple Sclerosis: Identity, Mechanisms and Potential Triggers. Front Immunol 11:760.

76.   Disanto G, Morahan JM, Barnett MH, Giovannoni G, Ramagopalan S V. 2012. The evidence for a role of B cells in multiple sclerosis. Neurology 78:823–832.

77.   Jelcic I, Al Nimer F, Wang J, Lentsch V, Planas R, Jelcic I, Madjovski A, Ruhrmann S, Faigle W, Frauenknecht K, Pinilla C, Santos R, Hammer C, Ortiz Y, Opitz L, Grönlund H, Rogler G, Boyman O, Reynolds R, Lutterotti A, Khademi M, Olsson T, Piehl F, Sospedra M, Martin R. 2018. Memory B Cells Activate Brain-Homing, Autoreactive CD4+ T Cells in Multiple Sclerosis. Cell 175:85-100.e23.

78.   Wang J, Jelcic I, Mühlenbruch L, Haunerdinger V, Toussaint NC, Zhao Y, Cruciani C, Faigle W, Naghavian R, Foege M, Binder TMC, Eiermann T, Opitz L, Fuentes-Font L, Reynolds R, Kwok WW, Nguyen JT, Lee JH, Lutterotti A, Münz C, Rammensee HG, Hauri-Hohl M, Sospedra M, Stevanovic S, Martin R. 2020. HLA-DR15 Molecules Jointly Shape an Autoreactive T Cell Repertoire in Multiple Sclerosis. Cell 183:1264-1281.e20.

79.   Soldan SS, Lieberman PM. 2022. Epstein–Barr virus and multiple sclerosis. Nat Rev Microbiol 2022 211 21:51–64.

80.   Milo R. 2019. Therapies for multiple sclerosis targeting B cells. Croat Med J 60:87.

81.   Lehmann-Horn K, C. Kronsbein H, S. Weber M. 2013. Targeting B cells in the treatment of multiple sclerosis: recent advances and remaining challenges. Ther Adv Neurol Disord 6:161–173.

82.   Torkildsen O, Myhr KM, Bø L. 2016. Disease-modifying treatments for multiple sclerosis – a review of approved medications. Eur J Neurol 23:18–27.

83.   Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, Vollmer T, Agius MA, Kappos L, Stites T, Li B, Cappiello L, Von Rosenstiel P, Lublin FD. 2014. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis

(FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 13:545–556.

84. Allende ML, Tuymetova G, Lee BG, Bonifacino E, Wu YP, Proia RL. 2010. S1P1 receptor directs the release of immature B cells from bone marrow into blood. J Exp Med 207:1113.

85. Tolebrutinib in MS | Experimental MS Treatments | Multiple Sclerosis News Today.

86. Crofford LJ, Nyhoff LE, Sheehan JH, Kendall PL. 2016. The role of Bruton's tyrosine kinase in autoimmunity and implications for therapy. Expert Rev Clin Immunol 12:763–773.

87. Nair K V. 2022. Role of the Bruton tyrosine kinase pathway in multiple sclerosis. Am J Manag Care 28:S323–S328.

88. Hartkamp LM, Radstake TRDJ, Reedquist KA. 2015. Bruton's tyrosine kinase in chronic inflammation: from pathophysiology to therapy. Int J Interf Cytokine Mediat Res 7:27–34.

89. Botox & Multiple Sclerosis Treatment.

90. Critchfield JMD. 2002. Considering the Immune Response to Botulinum Toxin. Clin J Pain 18:S133–S141.

91. Boffa G, Signori A, Massacesi L, Mariottini A, Sbragia E, Cottone S, Amato MP, Gasperini C, Moiola L, Meletti S, Repice AM, Morra VB, Salemi G, Patti F, Filippi M, De Luca G, Lus G, Zaffaroni M, Sola P, Conte A, Nistri R, Aguglia U, Granella F, Galgani S, Caniatti LM, Lugaresi A, Romano S, Iaffaldano P, Cocco E, Saccardi R, Angelucci E, Trojano M, Mancardi GL, Sormani MP, Inglese M. 2022. Hematopoietic

Stem Cell Transplantation in People With Active Secondary Progressive Multiple Sclerosis. Neurology 10.1212/WNL.0000000000206750.

92.   Researchers from Italy Report Long-Term Outcomes from Bone Marrow Transplants (aHSCT) to Treat MS | National Multiple Sclerosis Society.

93.   Boffa G, Massacesi L, Inglese M, Mariottini A, Capobianco M, Moiola L, Amato MP, Cottone S, Gualandi F, de Gobbi M, Greco R, Scimè R, Frau J, Zimatore GB, Bertolotto A, Comi G, Uccelli A, Signori A, Angelucci E, Innocenti C, Ciceri F, Repice AM, Sormani MP, Saccardi R, Mancardi G. 2021. Long-term clinical outcomes of hematopoietic stem cell transplantation in multiple sclerosis. Neurology 96:E1215–E1226.

94.   What is RA?: Rheumatoid arthritis explained | NRAS.

95.   Rheumatoid arthritis - Symptoms and causes - Mayo Clinic.

96.   Rheumatoid Arthritis (RA) | Arthritis | CDC.

97.   Rheumatoid Arthritis: Symptoms, Diagnosis, and Treatment | Arthritis Foundation.

98.   rheumatoid arthritis autoimmune in young adults - Google Search.

99.   Codd Y, Stapleton T, Veale DJ, FitzGerald O, Bresnihan B. 2020. Everyday life with rheumatoid arthritis. Int J Ther Rehabil 17:24–32.

100. Hsieh PH, Wu O, Geue C, McIntosh E, McInnes IB, Siebert S. 2020. Economic burden of rheumatoid arthritis: a systematic review of literature in biologic era. Ann Rheum Dis 79:S771–S777.

101. Silverman GJ, Carson DA. 2003. Roles of B cells in rheumatoid arthritis. Arthritis Res Ther 2003 54 5:1–6.

102. Dörner TM, Burmester GRM. 2003. The role of B cells in rheumatoid arthritis mechanisms and therapeutic targets. Curr Opin Rheumatol 15:246–252.

103. Wu F, Gao J, Kang J, Wang X, Niu Q, Liu J, Zhang L. 2021. B Cells in Rheumatoid Arthritis：Pathogenic Mechanisms and Treatment Prospects. Front Immunol 12:3987.

104. Yap HY, Tee SZY, Wong MMT, Chow SK, Peh SC, Teow SY. 2018. Pathogenic Role of Immune Cells in Rheumatoid Arthritis: Implications in Clinical Treatment and Biomarker Development. Cells 7.

105. Edwards JCW, Szczepa´nski S, Szechi´nski S, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T. 2004. Efficacy of B-Cell–Targeted Therapy with Rituximab in Patients with Rheumatoid Arthritis. https://doi.org/101056/NEJMoa032534 350:2572–2581.

106. De Vita S, Zaja F, Sacco S, De Candia A, Fanin R, Ferraccioli G. 2002. Efficacy of Selective B Cell Blockade in the Treatment of Rheumatoid Arthritis Evidence for a Pathogenetic Role of B Cells. ARTHRITIS Rheum 46:2029–2033.

107. Choy E. 2012. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology 51:v3–v11.

108. Jennings F, Lambert E, Fredericson M. 2008. Rheumatic diseases presenting as sports-related injuries. Sport Med 38:917–930.

109. Brawer AE, Goel N. 2016. The onset of rheumatoid arthritis following trauma. Open Access Rheumatol Res Rev 8:77.

110. Van Vollenhoven RF, Emery P, Bingham CO, Keystone EC, Fleischmann RM, Furst DE, Tyson N, Collinson N, Lehane PB. 2013. Long-term safety of rituximab in rheumatoid

arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis 72:1496–1502.

111. Mok CC. 2014. Rituximab for the treatment of rheumatoid arthritis: an update. Drug Des Devel Ther 8:87.

112. Rituximab: Principles of use and adverse effects in rheumatoid arthritis - UpToDate.

113. What is inflammatory bowel disease (IBD)? | IBD.

114. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. 2017. Crohn's disease. Lancet 389:1741–1755.

115. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. 2017. Ulcerative colitis. Lancet 389:1756–1770.

116. Kuenzig ME, Benchimol EI, Lee L, Targownik LE, Singh H, Kaplan GG, Bernstein CN, Bitton A, Nguyen GC, Lee Mba K, Cooke-Lauder J, Murthy SK. 2019. The Impact of Inflammatory Bowel Disease in Canada 2018: Direct Costs and Health Services Utilization. J Can Assoc Gastroenterol 2:17–33.

117. Lichtenstein GR, Shahabi A, Seabury SA, Lakdawalla DN, Espinosa OD, Green S, Brauer M, Baldassano RN. 2020. Lifetime Economic Burden of Crohn's Disease and Ulcerative Colitis by Age at Diagnosis. Clin Gastroenterol Hepatol 18:889-897.e10.

118. Shimomura Y, Mizoguchi E, Sugimoto K, Kibe R, Benno Y, Mizoguchi A, Bhan AK. 2008. Regulatory role of B-1 B cells in chronic colitis. Int Immunol 20:729–737.

119. Pararasa C, Zhang N, Tull TJ, Chong MHA, Siu JHY, Guesdon W, Chavele KM, Sanderson JD, Langmead L, Kok K, Spencer J, Vossenkamper A. 2019. Reduced

CD27−IgD− B cells in blood and raised CD27−IgD− B cells in gut-associated lymphoid tissue in inflammatory bowel disease. Front Immunol 10:361.

120. Castro-Dopico T, Clatworthy MR. 2019. IgG and Fcγ receptors in intestinal immunity and inflammation. Front Immunol 10:805.

121. Mann ER, Li X. 2014. Intestinal antigen-presenting cells in mucosal immune homeostasis: Crosstalk between dendritic cells, macrophages and B-cells. World J Gastroenterol 20:9653.

122. Park SC, Jeen YT. 2019. Genetic Studies of Inflammatory Bowel Disease-Focusing on Asian Patients. Cells 8.

123. Uzzan M, Martin JC, Mesin L, Livanos AE, Castro-Dopico T, Huang R, Petralia F, Magri G, Kumar S, Zhao Q, Rosenstein AK, Tokuyama M, Sharma K, Ungaro R, Kosoy R, Jha D, Fischer J, Singh H, Keir ME, Ramamoorthi N, Gorman WEO, Cohen BL, Rahman A, Cossarini F, Seki A, Leyre L, Vaquero ST, Gurunathan S, Grasset EK, Losic B, Dubinsky M, Greenstein AJ, Gottlieb Z, Legnani P, George J, Irizar H, Stojmirovic A, Brodmerkel C, Kasarkis A, Sands BE, Furtado G, Lira SA, Tuong ZK, Ko HM, Cerutti A, Elson CO, Clatworthy MR, Merad M, Suárez-Fariñas M, Argmann C, Hackney JA, Victora GD, Randolph GJ, Kenigsberg E, Colombel JF, Mehandru S. 2022. Ulcerative colitis is characterized by a plasmablast-skewed humoral response associated with disease activity. Nat Med 2022 284 28:766–779.

124. Mizoguchi A, Bhan AK. 2017. Immunobiology of B cells in inflammatory bowel disease. Crohn's Dis Ulcerative Colitis From Epidemiol Immunobiol to a Ration Diagnostic Ther Approach Second Ed 111–116.

125. Oka A, Ishihara S, Mishima Y, Tada Y, Kusunoki R, Fukuba N, Yuki T, Kawashima K, Matsumoto S, Kinoshita Y. 2014. Role of Regulatory B Cells in Chronic Intestinal Inflammation: Association with Pathogenesis of Crohn's Disease. Inflamm Bowel Dis 20:315–328.

126. Kumric M, Zivkovic PM, Kurir TT, Vrdoljak J, Vilovic M, Martinovic D, Bratanic A, Lizatovic IK, Bozic J. 2022. Role of B-Cell Activating Factor (BAFF) in Inflammatory Bowel Disease. Diagnostics 12.

127. McDonnell M, Liang Y, Noronha A, Coukos J, Kasper DL, Farraye FA, Ganley-Leal LM. 2011. Systemic toll-like receptor ligands modify B-cell responses in human inflammatory bowel disease. Inflamm Bowel Dis 17:298–307.

128. Noronha AM, Liang Y, Hetzel JT, Hasturk H, Kantarci A, Stucchi A, Zhang Y, Nikolajczyk BS, Farraye FA, Ganley-Leal LM. 2009. Hyperactivated B cells in human inflammatory bowel disease. J Leukoc Biol 86:1007–1016.

129. Defendenti C, Sarzi-Puttini P, Grosso S, Croce A, Senesi O, Saibeni S, Bollani S, Almasio PL, Bruno S, Atzeni F. 2011. B Lymphocyte intestinal homing in inflammatory bowel disease. BMC Immunol 12:1–6.

130. Dalwadi H, Wei B, Schrage M, Su TT, Rawlings DJ, Braun J. 2003. B Cell Developmental Requirement for the Gαi2 Gene. J Immunol 170:1707–1715.

131. Yamamoto S, Ma X. 2009. Role of Nod2 in the development of Crohn's disease. Microbes Infect 11:912.

132. Duchmann R, Kaiser I, Hermann E, Mayet W, Ewe K, Meyer Zum Buschenfelde KH. 1995. Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD). Clin Exp Immunol 102:448.

133. Rabe H, Malmquist M, Barkman C, Östman S, Gjertsson I, Saalman R, Wold AE. 2019. Distinct patterns of naive, activated and memory T and B cells in blood of patients with ulcerative colitis or Crohn's disease. Clin Exp Immunol 197:111–129.

134. Wei B, Velazquez P, Turovskaya O, Spricher K, Aranda R, Kronenberg M, Birnbaumer L, Braun J. 2005. Mesenteric B cells centrally inhibit CD4+ T cell colitis through interaction with regulatory T cell subsets. Proc Natl Acad Sci U S A 102:2010–2015.

135. Giessen J van der, Huang VW, Woude CJ van der, Fuhler GM. 2019. Modulatory Effects of Pregnancy on Inflammatory Bowel Disease. Clin Transl Gastroenterol 10:e00009.

136.   C. difficile infection - Symptoms and causes - Mayo Clinic.

137. Guh AY, Mu Y, Winston LG, Johnston H, Olson D, Farley MM, Wilson LE, Holzbauer SM, Phipps EC, Dumyati GK, Beldavs ZG, Kainer MA, Karlsson M, Gerding DN, McDonald LC. 2020. Trends in U.S. Burden of Clostridioides difficile Infection and Outcomes . N Engl J Med 382:1320–1330.

138. Nitzan O, Elias M, Chazan B, Raz R, Saliba W. 2013. Clostridium difficile and inflammatory bowel disease: Role in pathogenesis and implications in treatment. World J Gastroenterol 19:7577.

139. Fordtran JS. 2006. Colitis due to Clostridium difficile toxins: underdiagnosed, highly virulent, and nosocomial. Proc (Bayl Univ Med Cent) 19:3.

140. Hirohata S, Ohshima N, Yanagida T, Aramaki K. 2002. Regulation of human B cell function by sulfasalazine and its metabolites. Int Immunopharmacol 2:631–640.

141. Parashette KR, Makam CR, Cuffari C. 2010. Infliximab therapy in pediatric Crohn's disease: a review. Clin Exp Gastroenterol 3:57.

142. Steenholdt C, Svenson M, Bendtzen K, Thomsen OA, Brynskov J, Ainsworth MA. 2011. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. Aliment Pharmacol Ther 34:51–58.

143. Timmermans WMC, Van Laar JAM, Van Der Houwen TB, Kamphuis LSJ, Bartol SJW, Lam KH, Ouwendijk RJ, Sparrow MP, Gibson PR, Van Hagen PM, Van Zelm MC. 2016. B-Cell Dysregulation in Crohn's Disease Is Partially Restored with Infliximab Therapy. PLoS One 11:e0160103.

144. Castro-Dopico T, Colombel JF, Mehandru S. 2020. Targeting B cells for inflammatory bowel disease treatment: back to the future. Curr Opin Pharmacol 55:90–98.

145. Nakashima J, Preuss C V. 2022. Mesalamine (USAN). StatPearls.

146. Nielsen OH. 1982. Sulfasalazine intolerance. A retrospective survey of the reasons for discontinuing treatment with sulfasalazine in patients with chronic inflammatory bowel disease. Scand J Gastroenterol 17:389–393.

147. Giles A, Foushee J, Lantz E, Gumina G. 2019. Sulfonamide Allergies. Pharm J Pharm Educ Pract 7:132.

148. Wu X, Mu Y, Yao J, Lin F, Wu D, Ma Z. 2022. Adipose-Derived Stem Cells From Patients With Ulcerative Colitis Exhibit Impaired Immunosuppressive Function. Front Cell Dev Biol 10:155.

149. Graves' disease - Symptoms and causes - Mayo Clinic.

150. Elfenbein DM, Schneider DF, Havlena J, Chen H, Sippel RS. 2015. Clinical and Socioeconomic Factors influence treatment decisions in Graves' Disease. Ann Surg Oncol 22:1196.

151. Douglas RS, Naik V, Hwang CJ, Afifiyan NF, Gianoukakis AG, Sand D, Kamat S, Smith TJ. 2008. B Cells from Patients with Graves' Disease Aberrantly Express the IGF-1 Receptor: Implications for Disease Pathogenesis. J Immunol 181:5768–5774.

152. Fan JL, Desai RK, Dallas JS, Wagle NM, Seetharamaiah GS, Prabhakar BS. 1994. High frequency of B cells capable of producing anti-thyrotropin receptor antibodies in patients with graves' disease. Clin Immunol Immunopathol 71:69–74.

153. Grubczak K, Starosz A, Stożek K, Bossowski F, Moniuszko M, Bossowski A. 2021. Regulatory B cells involvement in autoimmune phenomena occurring in pediatric graves' disease patients. Int J Mol Sci 22:10926.

154. Jiang X, Wang Y, Li X, He L, Yang Q, Wang W, Liu J, Zha B. 2020. Microarray profile of B cells from Graves' disease patients reveals biomarkers of proliferation. Endocr Connect 9:405–417.

155. Cao Y, Zhao X, You R, Zhang Y, Qu C, Huang Y, Yu Y, Gong Y, Cong T, Zhao E, Zhang L, Gao Y, Zhang J. 2022. CD11c+ B Cells Participate in the Pathogenesis of

Graves' Disease by Secreting Thyroid Autoantibodies and Cytokines. Front Immunol 13:1116.

156. Rydzewska M, Jaromin M, Pasierowska IE, Stozek K, Bossowski A. 2018. Role of the T and B lymphocytes in pathogenesis of autoimmune thyroid diseases. Thyroid Res 11.

157. Gianoukakis AG, Khadavi N, Smith TJ. 2008. Cytokines, Graves' Disease, and Thyroid-Associated Ophthalmopathy. Thyroid 18:953.

158. Smith MJ, Rihanek M, Coleman BM, Gottlieb PA, Sarapura VD, Cambier JC. 2018. Activation of thyroid antigen-reactive B cells in recent onset autoimmune thyroid disease patients. J Autoimmun 89:82.

159. Su HW, Baker JR. 2006. Targeting B Cells in Graves' Disease. Endocrinology 147:4559–4560.

160. Salvi M, Vannucchi G, Campi I, Rossi S, Bonara P, Sbrozzi F, Guastella C, Avignone S, Pirola G, Ratiglia R, Beck-Peccoz P. 2006. Efficacy of rituximab treatment for thyroid-associated ophthalmopathy as a result of intraorbital B-cell depletion in one patient unresponsive to steroid immunosuppression. Eur J Endocrinol 154:511–517.

161. Cole M, Hynes AM, Howel D, Hall L, Abinun M, Allahabadia A, Barrett T, Boelaert K, Drake AJ, Dimitri P, Kirk J, Zammitt N, Pearce S, Cheetham T. 2019. Adjuvant rituximab, a potential treatment for the young patient with Graves' hyperthyroidism (RiGD): study protocol for a single-arm, single-stage, phase II trial. BMJ Open 9:e024705.

162. Del Mar Montesinos M, Pellizas C. 2019. Thyroid hormone action on innate immunity. Front Endocrinol (Lausanne) 10:350.

163. El Fassi D, Nielsen CH, Hasselbalch HC, Hegedüs L. 2006. The rationale for B lymphocyte depletion in Graves' disease. Monoclonal anti-CD20 antibody therapy as a novel treatment option. Eur J Endocrinol 154:623–632.

164. El Fassi D, Banga JP, Gilbert JA, Padoa C, Hegedüs L, Nielsen CH. 2009. Treatment of Graves' disease with rituximab specifically reduces the production of thyroid stimulating autoantibodies. Clin Immunol 130:252–258.

165. Ostrowski RA, Bussey MR, Shayesteh Y, Jay WM. 2015. Rituximab in the Treatment of Thyroid Eye Disease: A Review. Neuro-Ophthalmology 39:109.

166. Ueki I, Abiru N, Kobayashi M, Nakahara M, Ichikawa T, Eguchi K, Nagayama Y. 2011. B cell-targeted therapy with anti-CD20 monoclonal antibody in a mouse model of Graves' hyperthyroidism. Clin Exp Immunol 163:309–317.

167. Gilbert JA, Kalled SL, Moorhead J, Hess DM, Rennert P, Li Z, Khan MZ, Banga JP. 2006. Treatment of Autoimmune Hyperthyroidism in a Murine Model of Graves' Disease with Tumor Necrosis Factor-Family Ligand Inhibitors Suggests a Key Role for B Cell Activating Factor in Disease Pathology. Endocrinology 147:4561–4568.

168. Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR, Patrizio A, Camastra S, Miccoli M, Cavallini G, Benvenga S, Antonelli A. 2021. Cytokines as Targets of Novel Therapies for Graves' Ophthalmopathy. Front Endocrinol (Lausanne) 12:1.

169. Hashimoto's Thyroiditis | Johns Hopkins Medicine.

170. Hashimoto's Disease - NIDDK.

171. Hashimoto's disease - Diagnosis and treatment - Mayo Clinic.

172. Hepp Z, Lage MJ, Espaillat R, Gossain V V. 2021. The direct and indirect economic burden of hypothyroidism in the United States: a retrospective claims database study https://doi.org/10.1080/13696998.2021.1900202.

173. Ben-Skowronek I, Szewczyk L, Kulik-Rechberger B, Korobowicz E. 2013. The differences in T and B cell subsets in thyroid of children with Graves' disease and Hashimoto's thyroiditis. World J Pediatr 9:245–250.

174. Ramos-Leví AM, Marazuela M. 2016. Pathogenesis of thyroid autoimmune disease: the role of cellular mechanisms. Endocrinol y Nutr 63:421–429.

175. Kawashima ST, Tagami T, Nakao K, Nanba K, Tamanaha T, Usui T, Naruse M, Minamiguchi S, Mori Y, Tsuji J, Tanaka I, Shimatsu A. 2014. Serum levels of IgG and IgG4 in Hashimoto thyroiditis. Endocrine 45:236–243.

176. Vanderpump MPJ. 2011. The epidemiology of thyroid disease. Br Med Bull 99:39–51.

177. McGregor AM, Ibbertson HK, Smith BR, Hall R. 1980. Carbimazole and autoantibody synthesis in Hashimoto's thyroiditis. Br Med J 281:968–969.

178. Chen P, Xia Y, Lei W, Zhong S, Jiang H, Ren L, Qian W, Liu H. 2022. Case report: Hashimoto's thyroiditis after CD19 chimeric antigen receptor T-cell therapy. Front Immunol 13:6270.

179. Chiovato L, Magri F, Carlé A. 2019. Hypothyroidism in Context: Where We've Been and Where We're Going. Adv Ther 36:47–58.

180. What Is Type 1 Diabetes? | CDC.

181. Type 1 Diabetes - NIDDK.

182.   Type 1 Diabetes Facts - JDRF.

183.   Kawasaki E. 2014. Type 1 Diabetes and Autoimmunity. Clin Pediatr Endocrinol 23:99.

184.   Mental Health: Living with Type 1 | ADA.

185.   Sussman M, Benner J, Haller MJ, Rewers M, Griffiths R. 2020. Estimated Lifetime Economic Burden of Type 1 Diabetes. Diabetes Technol Ther 22:121–130.

186.   Hinman RM, Smith MJ, Cambier JC. 2014. B cells and type 1 diabetes …in mice and men. Immunol Lett 160:128.

187.   Hanley P, Sutter JA, Goodman NG, Du Y, Sekiguchi DR, Meng W, Rickels MR, Naji A, Luning Prak ET. 2017. Circulating B cells in type 1 diabetics exhibit fewer maturation-associated phenotypes. Clin Immunol 183:336–343.

188.   Wong FS, Wen L. 2005. B Cells in Autoimmune Diabetes. Rev Diabet Stud 2:121.

189.   Noorchashm H, Noorchashm N, Kern J, Rostami SY, Barker CF, Naji A. 1997. B-Cells Are Required for the Initiation of Insulitis and Sialitis in Nonobese Diabetic Mice. Diabetes 46:941–946.

190.   Rolf J, Motta V, Duarte N, Lundholm M, Berntman E, Bergman M-L, Sorokin L, Cardell SL, Holmberg D. 2005. The Enlarged Population of Marginal Zone/CD1dhigh B Lymphocytes in Nonobese Diabetic Mice Maps to Diabetes Susceptibility Region Idd11. J Immunol 174:4821–4827.

191.   Mariño E, Batten M, Groom J, Walters S, Liuwantara D, Mackay F, Grey ST. 2008. Marginal-Zone B-Cells of Nonobese Diabetic Mice Expand With Diabetes Onset, Invade the Pancreatic Lymph Nodes, and Present Autoantigen to Diabetogenic T-Cells. Diabetes 57:395–404.

192. Ben Nasr M, Usuelli V, Seelam AJ, D'Addio F, Abdi R, Markmann JF, Fiorina P. 2021. Regulatory B Cells in Autoimmune Diabetes. J Immunol 206:1117–1125.

193. Boldison J, Wong FS. 2021. Regulatory B Cells: Role in Type 1 Diabetes. Front Immunol 12:3824.

194. Felton JL, Maseda D, Bonami RH, Hulbert C, Thomas JW. 2018. Anti-Insulin B Cells Are Poised for Antigen Presentation in Type 1 Diabetes. J Immunol 201:861–873.

195. Pescovitz MD, Greenbaum CJ, Bundy B, Becker DJ, Gitelman SE, Goland R, Gottlieb PA, Marks JB, Moran A, Raskin P, Rodriguez H, Schatz DA, Wherrett DK, Wilson DM, Krischer JP, Skyler JS. 2014. B-Lymphocyte Depletion With Rituximab and β-Cell Function: Two-Year Results. Diabetes Care 37:453–459.

196. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, Gottlieb PA, Marks JB, McGee PF, Moran AM, Raskin P, Rodriguez H, Schatz DA, Wherrett D, Wilson DM, Lachin JM, Skyler JS. 2009. Rituximab, B-Lymphocyte Depletion, and Preservation of Beta-Cell Function. N Engl J Med 361:2143–2152.

197. Mariño E, Silveira PA, Stolp J, Grey ST. 2011. B cell-directed therapies in type 1 diabetes. Trends Immunol 32:287–294.

198. Sjögren's Syndrome Risk Factors | Johns Hopkins Medicine.

199. Sjogren's syndrome - Symptoms and causes - Mayo Clinic.

200. Sjögren's Syndrome | National Institute of Dental and Craniofacial Research.

201. Sjögren's syndrome - NHS.

202. Groom J, Kalled SL, Cutler AH, Olson C, Woodcock SA, Schneider P, Tschopp J, Cachero TG, Batten M, Wheway J, Mauri D, Cavill D, Gordon TP, Mackay CR, Mackay F. 2002. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjögren's syndrome. J Clin Invest 109:59–68.

203. Cornec D, Devauchelle-Pensec V, Tobón GJ, Pers JO, Jousse-Joulin S, Saraux A. 2012. B cells in Sjögren's syndrome: From pathophysiology to diagnosis and treatment. J Autoimmun 39:161–167.

204. Rischmueller M, Lester S, Chen Z, Champion G, Van Den Berg R, Beer R, Coates T, McCluskey J, Gordon T. 1998. HLA class II phenotype controls diversification of the autoantibody response in primary Sjögren's syndrome (pSS). Clin Exp Immunol 111:365.

205. Ambrus JL, Suresh L, Peck A. 2016. Multiple Roles for B-Lymphocytes in Sjogren's Syndrome. J Clin Med 2016, Vol 5, Page 87 5:87.

206. Ibrahem HM. 2019. B cell dysregulation in primary Sjögren's syndrome: A review. Jpn Dent Sci Rev 55:139.

207. Broeren MGA, Wang JJ, Balzaretti G, Groenen PJTA, Van Schaik BDC, Chataway T, Kaffa C, Bervoets S, Hebeda KM, Bounova G, Pruijn GJM, Gordon TP, De Vries N, Thurlings RM. 2022. Proteogenomic analysis of the autoreactive B cell repertoire in blood and tissues of patients with Sjögren's syndrome. Ann Rheum Dis 81:644–652.

208. Hansen A, Lipsky PE, Dörner T. 2007. B cells in Sjögren's syndrome: Indications for disturbed selection and differentiation in ectopic lymphoid tissue. Arthritis Res Ther 9:1–12.

209. Inamo J, Suzuki K, Takeshita M, Kassai Y, Takiguchi M, Kurisu R, Okuzono Y, Tasaki S, Tasaki S, Yoshimura A, Takeuchi T. 2020. Identification of novel genes associated with dysregulation of B cells in patients with primary Sjögren's syndrome. Arthritis Res Ther 22:1–11.

210. Hernández-Molina G, Leal-Alegre G, Michel-Peregrina M. 2011. The meaning of anti-Ro and anti-La antibodies in primary Sjögren's syndrome. Autoimmun Rev 10:123–125.

211. Skarlis C, Marketos N, Mavragani CP. 2019. Biologics in Sjögren's syndrome. Pharmacol Res 147:104389.

212. A Study of CD19/BCMA Chimeric Antigen Receptor T Cells Therapy for Patients With Refractory Sjogren's Syndrome - Full Text View - ClinicalTrials.gov.

213. Oh S, Payne AS. 2022. Engineering Cell Therapies for Autoimmune Diseases: From Preclinical to Clinical Proof of Concept. Immune Netw 22.