Emerging Non-Steroid Based Treatments for Autoimmune Disorders: Systemic Lupus Erythematosus and Crohn's Disease

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ABSTRACT

A condition known as an autoimmune illness occurs when the immune system of the body begins unintentionally targeting its own healthy organs. Over 80 autoimmune disorders are recognised. This paper focuses on two more commonly found autoimmune diseases, i.e. Systemic Lupus Erythematosus (Lupus) and Crohn's disease. Lupus is a multisystem disease which can produce inflammation in the skin, joints, brain, lungs, kidney and blood vessels, and, consequently, cause damage to the affected body organs. The second one is Crohn's disease, which results in persistent digestive system inflammation.

Corticosteroids play an integral role in the treatment of Lupus and Crohn's disease. They have powerful anti-inflammatory action and provide quick relief to patients, however, the toxicity caused by corticosteroids, leading to severe adverse effects on various body organs through infections, hypertension, hyperglycemia, myopathy, osteoporosis, especially with continued usage, continues to be an ongoing area of concern.

Considering the potential adverse impact arising from the long-term use of corticosteroids, there has been ongoing research to prevent or reduce the use of corticosteroids in the treatment of autoimmune disorders. This study aims to carry out a literature review to highlight how the expanding field of biologics is providing alternative treatment options.

Monoclonal antibodies such as Anifrolumab (for treatment of Lupus) and Ustekinumab (for treatment of Crohn's disease) have been found to be safe as well as effective. Whilst the ongoing research in the use of stem cells for treatment of certain autoimmune diseases, in particular, Lupus has shown some positive results, there needs to be further research to assess their therapeutic use and side effects. Thus, although some alternative treatment options have been identified and even approved by the Food and Drug Administration (FDA) for patient's use in the last few years, this continues to be an area of developing research.

Keywords

Systemic Lupus Erythematosus, Crohn's Disease, Corticosteroids, Non-steroid based treatments

INTRODUCTION

Autoimmune diseases are conditions in which the immune system, whose role is to protect the body from foreign agents such as bacteria, virus and parasites, is unable to differentiate between foreign cells and the body's own cells and starts attacking the healthy cells, tissues and organs of the body. Autoimmune diseases can affect a wide range of body parts, and there are over 80 known autoimmune diseases (“Autoimmune Diseases”).

An increase in the incidence of autoimmune diseases has been observed over the past few decades. They currently affect 3-8% of the world’s population, with approximately 80% of the people affected being women (Angum et al., 2020). Many autoimmune diseases are chronic in nature and do not have a cure, but treatment helps in managing the symptoms. The reason for the immune system to start attacking its own body cells remains largely unknown, but autoimmune diseases are majorly linked to genetic, environmental and lifestyle factors.

Genetics play an important role as many autoimmune diseases are found to run in families, such that people whose family members have autoimmune diseases have a higher chance of developing a disorder themselves. The concordance rate (of an autoimmune disease is 10 times higher in identical twins (as compared to fraternal twins, indicating the strong influence of genes in the pathogenesis of autoimmune diseases) (*Disease Development - Autoimmune Disease | Johns Hopkins Pathology*, n.d.).

However, environmental factors have also been seen to play a major role as risk factors for development of autoimmune diseases. In particular, experiencing stress, especially long-term stress, exposure to toxic chemicals, and suffering from infections caused by bacteria, virus or other infectious pathogens lead to a higher risk of developing a disorder. Whilst the relative impact of genetics vs. environmental factors on autoimmune diseases are still being studied, some studies have shown that environmental factors have significantly higher impact such that they account for almost 70% of all autoimmune diseases where the balance 30% of autoimmune diseases are caused due to role of genetics (Vojdani et al., 2014)

Similarly, Certain lifestyle factors, especially smoking (Costenbader & Karlson, 2006) and obesity (Versini et al., 2014) have also been found linked to the pathogenesis of several autoimmune disorders.

Systemic lupus erythematosus (Lupus)

Lupus is a multisystem disease which can produce inflammation in the skin, joints, brain, lungs, kidney and blood vessels, and, consequently, cause damage to the affected body organs. In most cases of Lupus, people experience symptoms in waves of flare-ups and remissions. During flare-ups the signs and symptoms of Lupus become worse followed by periods when the

symptoms improve or may also disappear completely, which is known as remission (*Lupus - Symptoms & Causes - Mayo Clinic*, n.d.)

The global incidence of Lupus was found to be 5.14 per 100,000 person-years (a measurement considering both the number of participants in the study and the time for which they were observed), with the newly diagnosed global population being 0.40 million people annually (Tian et al., 2023). Lupus is found to be overwhelmingly more common in females, with almost 90% of individuals diagnosed with Lupus being women. Furthermore, Lupus is more common in people of Asian, African-American, Native American and Hispanic ethnicities (*Lupus: Symptoms, Causes, Types & Treatments*, n.d.).

Although the exact cause of Lupus is unknown, some people are seen to have a genetic predisposition towards Lupus, and they are more likely to develop this disease when exposed to certain triggers of the environment. These include exposure to sunlight (causing lupus skin lesions or triggering an internal response in susceptible people), infections, or medications such as certain types of antibiotics, anti-seizure and blood pressure medications (*Lupus - Symptoms & Causes - Mayo Clinic*, n.d.). However, it is seen that drug-induced Lupus generally subsides after the medication is stopped, although it may persist in rare cases (*Lupus - Symptoms & Causes - Mayo Clinic*, n.d.).

Symptoms of Lupus may develop slowly. Considering that symptoms vary from person to person, and, also depending on which body system is affected, the diagnosis of Lupus may be difficult. Furthermore, the symptoms of Lupus usually tend to overlap with other diseases and conditions (*Lupus - Symptoms & Causes - Mayo Clinic*, n.d.). However, in many cases of Lupus, a facial rash, in the shape of butterfly wings, may appear (*Lupus - Symptoms & Causes - Mayo Clinic*, n.d.).

Usually, people have lupus for some time before being diagnosed. A single test does not diagnose lupus. A combination of blood and urine tests, signs and symptoms, and physical examinations may help lead to diagnosis (*Lupus - Symptoms & Causes - Mayo Clinic*, n.d.).

Crohn's disease

The second autoimmune disease being covered in this study is Crohn's disease. Crohn's disease causes inflammation of the tissues of the digestive tract. Within the digestive tract, Crohn's disease most commonly triggers inflammation in the small intestine and part of the large intestine (*Definition & Facts for Crohn's Disease - NIDDK*, n.d.).

Like some of the other autoimmune diseases, the specific cause of Crohn's disease is not reliably known. A possible cause could be that the bacteria in the digestive tract may trigger the immune system to mistakenly attack the healthy cells. Genetics are also a possible cause for

Crohn's disease, as it is often found to run in families. It is noticed that in almost 20% of individuals affected with Crohn's disease, they also have a family member with the same disease (*Crohn's Disease - Symptoms and Causes - Mayo Clinic*, n.d.). Similarly, smoking can double the chances of developing this disease (Symptoms & Causes of Crohn's Disease - NIDDK, n.d.).

Crohn's disease usually causes abdominal pain and cramps, chronic diarrhea, loss of appetite, weight loss, anal fissures and anal fistulas. Most people with Crohn's disease experience periods of severe symptoms, called flare-ups, followed by a period where the symptoms become mild or disappear, called remission (*Crohn's Disease: Symptoms, Causes, Management & Treatment*, n.d.).

Corticosteroids are mainly used for the treatment of rheumatological diseases and may be the main therapy for certain diseases (*Corticosteroids*, n.d.). In both Lupus and Crohn's disease, corticosteroids are used as a major form of treatment. Corticosteroids are man-made drugs which resemble the human hormone cortisol, produced naturally by the adrenal glands of the body (*Corticosteroids*, n.d.). Corticosteroids alter the way in which white blood cells work which reduces activity of the immune system, they also bring down the production of chemicals that are responsible for producing inflammation (*Corticosteroids*, n.d.).

Corticosteroids are used to treat conditions in which the immune system of the body does not function properly and attacks the healthy cells and tissues of the body, causing tissue damage (*Corticosteroids*, n.d.). They can either be given to the exact place of the problem, known as local steroids, or throughout the body known as systemic steroids. For the treatment of the above-mentioned autoimmune disorders, systemic corticosteroids are used. However systemic corticosteroids, especially when given for a long period of time, are associated with many serious adverse side effects.

DISCUSSION

Treatment for Lupus

On account of the significant impact of glucocorticosteroids in bringing down disease aggravations (flares), they have been used for years as the basic treatment drug in Lupus treatment. The effectiveness of glucocorticosteroids in reducing inflammation is linked to a wide range of immune system effects; glucocorticosteroids block leucocyte traffic and access to inflammation sites, lower the expression of cytokines and adhesion molecules, and also interfere with the functions of fibroblast, leucocyte, and endothelial cells (Strehl et al., 2019).

88% of patients with Lupus are treated with glucocorticosteroids. More than half continue this treatment for a long time. Prednisone is the corticosteroid that is mainly used in the treatment of Lupus. Long term use of prednisone is associated with the risk of permanent organ damage leading to higher risk of morbidity. In particular, studies have shown an increase in the risk of future organ damage by 50% in the case of prednisone dosages of above 6 mg/ day (Stojan & Petri, 2017).

Furthermore, use of glucocorticosteroids leads to higher risk of infections, cataracts, glaucoma, osteoporosis, an increase in risk of cardiovascular events. It may even lead to psychiatric adverse effects such as manic episodes and psychosis (Corticosteroids - StatPearls - NCBI Bookshelf, n.d.).

In order to bring down the dose of glucocorticoids, and, hence their potential side effect on a person, one of the emerging lines of treatment is combination therapy. A combination therapy with new immunosuppressive drugs and biologics may lead to lowering the dosage of glucocorticoids requirements. Obinutuzumab is a type II humanized anti-CD20 monoclonal antibody which depletes B cells (Liossis & Staveri, 2021a).

Specialised white blood cells called B cells are in charge of generating antibodies. Through the production of autoantibodies that are directed against RNP particles (anti-Ro, anti-La, and anti-Sm), DNA (anti-double-stranded DNA [anti-dsDNA]), and other nuclear components, B cells play a significant role in the pathogenesis of lupus, histones, and nonhistone chromatin proteins, as well as secretion of pro-inflammatory cytokines (Karrar & Cunninghame Graham, 2018).

125 individuals with Class III or Class IV lupus nephritis were randomly assigned to receive placebo or Obinutuzumab during a phase 2 trial of the medication, which was also administered to all patients along with corticosteroids and mycophenolate mofetil (Liossis & Staveri, 2021b).

Prednisone was administered orally to all patients starting at 0.5 mg/kg with a quick reduction to 7.5 mg by week 12 with optional methylprednisolone pulses (Mejía-Vilet & Ayoub, 2021).

The primary endpoint was complete renal response which was achieved by 35% of patients in the Obinutuzumab group and 23% of patients in the placebo group at week 52, and 41% of patients in the Obinutuzumab group and 23% of patients in the placebo group in week 104 (Furie et al., 2022). Serious infections were recorded in 8% in the Obinutuzumab group and in 18% in the placebo group.

B cell depletion was caused by Obinutuzumab as early as 4 weeks after Obinutuzumab treatment. Patients that attained sustained B cell depletion at weeks 24 and 52 exhibited better renal disease outcomes at week 76, per the flow cytometry measures (Liossis & Staveri, 2021a). Therefore, when combined with mycophenolate and corticosteroids, the impact of

Obinutuzumab was superior to placebo in achieving a complete renal response and ORR in patients with proliferative lupus nephritis. Obinutuzumab was also found to have larger effects on anti-dsDNA antibodies, C3, C4, eGFR, and proteinuria (Furie et al., 2022).

In comparison to placebo, Obinutuzumab caused a quick and robust decrease of peripheral CD19+ B cells without an increase in the frequency of significant adverse events, infections, or fatalities. In a global phase 3 investigation, the use of Obinutuzumab in proliferative lupus nephritis is being further assessed (Furie et al., 2022).

Anifrolumab was approved for patients with moderate to severe lupus in July 2021. It is a fully human IgG1κ monoclonal antibody which binds to subunit 1 of type 1 IFN receptor, and inhibits signaling by all type 1 IFNs. Type I IFNs can provide a potential source for autoantigens by inducing cell apoptosis since they are proinflammatory cytokines which are cytotoxic for a variety of cells (Moulton et al., 2017).

Several groups, post genome-wide expression analysis becoming available, showed that 50% to 75% of adult patients and up to 90% of children with Lupus display an increased expression of type I IFN-regulated genes (an IFN signature) (Rönnblom & Leonard, 2019). Lupus disease activity correlates with IFN-α levels and the strength of the IFN signature. IFN alpha is the predominant type 1 IFN implicated in Lupus pathogenesis.

Monocytes are stimulated by IFN alpha to develop into myeloid dendritic cells that produce self-antigens. Autoreactive CD4+ and CD8+ T-cells, as well as B cells, will react to the self-antigens and cause inflammation and cell death, harming normally healthy tissue all over the body. Anifrolumab decreases the function of the type 1 IFN receptor by binding to subunit 1, which reduces downstream signaling and inflammatory mediator gene transcription (*Anifrolumab: Uses, Interactions, Mechanism of Action* | *DrugBank Online*, n.d.).

Treatment for Crohn's Disease

Ustekinumab was initially authorised for use in 2009 for people with psoriasis, and in 2013 for people with psoriatic arthritis. It is a monoclonal antibody that reacts with interleukin-12 and interleukin-23's p40 subunit. Two 8-week placebo-controlled induction trials (UNITI-1 and UNITI-2) and one 44-week maintenance trial (IM-UNITI) were conducted to examine its effectiveness in treating Crohn's disease. Patients who successfully completed one of the induction studies were eligible to engage in the maintenance trial (Kumar et al., 2022).

As per the results of all three trials, it was demonstrated that Ustekinumab was found to be superior to the placebo in patients suffering from moderate to severe Crohn's Disease by inducing and maintaining remission. There was no significant difference in adverse effects

between Ustekinumab and the placebo. The results were not influenced by previous treatment or response to a TNF antagonist, and the benefits of Ustekinumab were seen as early as week 3 (Kumar et al., 2022). Thus, this showed the safety as well as efficacy of this biologic. It was approved by FDA and the European Commission for treatment in Crohn's Disease in 2016, in cases where other treatments were not working (Kumar et al., 2022).

Another drug known as Risankizumab an anti-interleukin 23 antibody, was also seen to be superior to the placebo in a phase 2, 12 weeks randomised study of patients suffering from moderate to severe Crohn's disease by achieving clinical and endoscopic remission (Feagan et al., 2018).

The safety and efficacy of extended intravenous induction and subcutaneous maintenance therapy with Risankizumab was examined in an open label extension study. The participants of the 12-week randomised trial took part in the open label extension study. Those participants who had achieved deep remission, called clinical remission in the 12 weeks study were assigned to a 12 weeks washout period. Those participants who had not achieved clinical remission or endoscopic remission were assigned to open label intravenous treatment of Risankizumab (600n mg), every 4 weeks for 12 weeks. Patients who entered clinical remission at week 26 took part in the maintenance phase of the study, where patients received open label subcutaneous Risankizumab every 8 weeks for 26 weeks (Feagan et al., 2018).

The primary efficacy endpoints at week 26 were the proportion of patients achieving clinical remission and clinical response. At week 52 the primary efficacy endpoints were the proportion of patients achieving clinical remission, clinical response, endoscopic response, endoscopic remission, mucosa healing and deep remission (Feagan et al., 2018).

The assessment of safety of this drug in patients who had received at least one dose in the open label phases of the study reported that 54% of patients were in clinical remission at week 26. The patients who achieved clinical remission in week 26 and the patients who were in clinical remission in week 12 were included in the maintenance phase. At week 52, (a) 29% patients achieved deep remission, (b) 35% patients were in endoscopic remission and 55% patients had an endoscopic response, (c) 71% patients maintained clinical remission and 81% patients had a clinical response, and (d) 24% patients had mucosal healing (Feagan et al., 2018).

Furthermore, Risankizumab was found to be safe and well tolerated. There were no treatment-related deaths. Most adverse events were mild or moderate and considered to be unrelated to study treatment (Feagan et al., 2018).

A new class of agents have come up that selectively inhibit lymphocyte trafficking to and within the small and large intestines, and, at the same time avoiding broad- spectrum immunosuppression. These include anti-integrins, such as Vedolizumab**.**

Etrolizumab is anti-integrin with dual action, targeting two pathways of inflammation in the gut. Currently phase 3 trials are underway to assess the safety and efficacy of Etrolizumab in Crohn's Disease and Ulcerative Colitis. This phase 3 trial is the largest registrational program in Ulcerative Colitis and Crohn's Disease, with over 3,000 participants with IBD across centers in Americas (North and South), Australia, Asia and Europe (Sandborn et al., 2020).

BERGAMOT is an induction/maintenance trial to evaluate anti-TNF-naive and experienced patients with moderate to severe active Crohn's disease. Patients receiving oral corticosteroids must taper their use during the maintenance phase. The taper was to be completed 8 weeks after the induction phase and 9 months before the assessment of the primary endpoints. BERGAMOT is a randomised double-blind study, in which participants were randomised to induction therapy of 14 weeks of either placebo or subcutaneously administered Etrolizumab 105 mg every 4 weeks or double the dosage at 210 mg every 4 weeks (Sandborn et al., 2020).

Depending on the induction response, maintenance therapy involved either Etrolizumab 105 mg every 4 weeks or placebo. The primary endpoints for BERGAMOT are clinical remission and endoscopic improvement at weeks 14 and 66. JUNIPER is an open label extension where eligible patients from BERGAMOT may be able to participate (Sandborn et al., 2020). The primary endpoints for JUNIPER are long-term efficacy (based on clinical remission), endoscopic remission at week 104, and assessing incidence of serious adverse effects with Etrolizumab (Sandborn et al., 2020).

Human stem cell therapy

Human stem cell therapy (HSCT) is also being examined as one of the other non-steroid based treatment options. Stem cells have powerful self-renewal potential. Further, the focus of regenerative medicine is either to increase or revive the functioning of human organs and cells. It has been noticed in studies that post autologous HSCT, there was an improvement in the duration of remission and overall survival in the majority of Lupus cases. Although it must be cautioned that these studies are not sufficient in terms of coverage of number of patients to come to a firm conclusion (Muzes & Sipos, 2019). Similarly, the existing studies have not been sufficient to arrive at conclusive evidence about efficacy and safety of HSCT in Crohn's disease. Consequently, European Crohn's and Colitis Organisation has recommended using HSCT solely in patients suffering from severe illness (Furie et al., 2022).

CONCLUSION

The on-going developments in the field of biologics, particularly development of monoclonal antibodies, have provided alternative options for safer disease management for patients as compared to primary use of corticosteroids.

Though corticosteroids continue to be the primary line of treatment for managing flares and inducing remissions, considering serious adverse impact from their long-term use, especially at higher doses, it is important to carry out further research in identifying alternate treatment options including HSCT which will reduce the dependence on high doses of corticosteroids for maintenance, allow faster tapering of corticosteroids or may even allow for corticosteroid-free treatments. This may result in improving overall health outcomes for managing autoimmune diseases, reduce patient morbidity and improve quality of life over a longer period of time.

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