IASR J. Med. Pharm. Sci.
ISSN: 2582-9343
Website: https://ijmps.com/
Open Access Journal
Country: India

IASR Journal of
Medical and
Pharmaceutical Science

ORIGINAL ARTICLE

OPEN ACCES

Immunotherapy in Autoimmune Diseases: A Review of Recent Breakthroughs in Using Immunotherapy for Conditions Like Rheumatoid Arthritis, Lupus, and Multiple Sclerosis

Preety Singh[1*], Shekhar Singh[2]

[1,2] Department of Pharmacy, Suyash Institute of Pharmacy, Hakkabad, Gorakhpur, Uttar Pradesh, India

OPEN ACCESS

Corresponding Author
Preety Singh
Department of Pharmacy, Suyash Institute of Pharmacy, Hakkabad, Gorakhpur, Uttar Pradesh, India.

Received: 15-09-2024
Accepted: 24-10-2024
Available online: 25-11-2024

A B S T R A C T

Autoimmune diseases remain a true therapeutic challenge - one's immune system turns against the very body. The traditional concepts and treatment strategies may offer little or no long-term gain or impact on the progression of disease. Immunotherapy's progress now presents new challenges in the management of this group of diseases. Discussion of the latest breakthroughs related to the application of immunotherapy for rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis has been reviewed. We elaborate mechanisms of action and clinical efficacy through a consideration of various classes of immunotherapeutic agents, such as monoclonal antibodies, checkpoint inhibitors, and new T-cell therapies. Results from recent clinical trials are positive and have a potential in terms of influencing patient outcomes and lowering the activity of diseases. However, side effects, variability in response among patients, and economic considerations pose great obstacles toward widespread use. In the near future, customized medicine and combination treatments will possibly lead to better methods in fine-tuning immunotherapy for autoimmune diseases. It is necessary to highlight more research studies in understanding better how immunotherapy would help in redefining the landscape of treatment for autoimmune diseases.

Key Words: *Autoimmune diseases; Immunotherapy; Rheumatoid arthritis; Monoclonal antibodies.*

1. Introduction

1.1 Overview of Autoimmune Diseases

Autoimmune diseases are characterized by the immune system's failure to recognize and attack parts of its own body; this disease affects millions worldwide (Davidson & Diamond, 2020). Some of the most common examples of such autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus (SLE), as well as multiple sclerosis. In the majority of cases of autoimmune diseases, the immune system's process of self-tolerance is disrupted, resulting in chronic inflammation and tissue damage that leads to severe functional impairment (Rosenblum, Remedios, & Abbas, 2015).

1.2 Current Treatment Modalities and Limitations

The therapy can relieve symptoms and induce a reduction in inflammation. However, it rarely contributes to long-term remission or the cessation of further disease progression. The available treatments for autoimmune diseases vary from corticosteroids, disease-modifying antirheumatic drugs (DMARDs), to biologics. In such cases, the presence of immunosuppressants poses considerable risks of side effects by increasing susceptibility to infections (Rubbert-Roth et al., 2018). This calls for high-level therapies, such as immunotherapy, which can modify the disease course without the heavy side effects of traditional treatments.

1.3 Aim of the Review

This review will try to describe the most recent developments in immunotherapy for autoimmune diseases, especially rheumatoid arthritis, SLE, and MS. The review is carried out by explaining the mechanisms, clinical efficacy, and future directions of different immunotherapeutic agents, such as monoclonal antibodies and T-cell therapies, that can be taken into account to improve patient outcomes and decrease disease activity (Schoenfeld & Ardalan, 2020).

2. Mechanisms of Immunotherapy in Autoimmune Diseases

2.1 Understanding Immunotherapy

Immunotherapy is the therapeutic approach that modulates the immune system to enhance or suppress immune responses with the goal of targeting the root mechanisms that cause autoimmune diseases. Unlike traditional therapies, immunotherapy aims to correct immune system dysfunction by specifically targeting certain components of the immune response, thus reducing the systemic effects and maximizing treatment efficacy (Dolgin, 2021). Various types of immunotherapies include monoclonal antibodies, checkpoint inhibitors, and T-cell therapies, which have distinct functions in the treatment of autoimmune diseases (Münz, 2022).

2.2 Mechanisms of Action in Autoimmune Diseases

Autoimmune diseases arise from an overactive immune response against self-antigens, leading to inflammation and tissue damage. Immunotherapy mechanisms of action focus on altering these responses to restore immune tolerance and reduce autoimmunity.

- **Checkpoint Inhibitors**: Blocking inhibitory checkpoints like PD-1 and CTLA-4, checkpoint inhibitors help in modulating T-cell responses, often used to dampen inappropriate immune activity in autoimmune diseases (Wykes & Lewin, 2018).
- **B-cell Depletion Therapy**: Monoclonal antibodies, for example, rituximab, target B-cells, which are frequently responsible for the production of autoantibodies. This approach is effective in diseases like rheumatoid arthritis and lupus by reducing autoantibody production (Edwards et al., 2018).
- **T-cell Therapies**: New T-cell therapies are designed to selectively target autoreactive T-cells, reducing their activity without broadly suppressing the immune system. This specificity helps reduce adverse effects commonly associated with immunosuppressive treatments (Sakaguchi et al., 2020).

3. Immunotherapy in Specific Autoimmune Diseases

3.1 Rheumatoid Arthritis (RA)

- **3.1.1 Pathophysiology and Immune Targets in RA**
- RA is a chronic autoimmune disease by inappropriate immune reactions against tissue elements within synovial joints that may result in inflammation, pain, and the possible destruction of the involved joints. Essential targets to the immune are pro-inflammatory cytokines which are said to mediate the action of inflammation through activation by TNF-α, IL-6, and IL-1 on synovium (Smolen et al., 2016).
- **3.1.2 Recent Advances in Immunotherapy for RA**

Researches have developed TNF inhibitors, such as infliximab and etanercept, the IL-6 receptor antagonists, like tocilizumab, and the JAK inhibitors, like tofacitinib. Most of these therapies have yielded the potential to control symptoms and limit joint damage within the RA patient by specifically attacking the immune mediators causing inflammation (Takeuchi et al., 2019).

- **3.1.3 Clinical Trials and Efficacy**

Immunotherapies, like TNF inhibitors, have been effective in clinical trials recently; these treatments help reduce the disease activity of patients and improve the quality of life in responders (Singh et al., 2021).

3.2 Systemic Lupus Erythematosus (SLE)

- **3.2.1 Pathophysiology and Immune Targets in SLE**

Systemic lupus erythematosus is an autoimmune disease characterized by widespread inflammation and tissue damage, caused mainly by autoantibodies and deposition of immune complexes. B-cells are involved through the production of these autoantibodies, which makes them a major target in SLE immunotherapy (Schwartz et al., 2017).

- **3.2.2 Recent Advances in Immunotherapy for SLE**

B-cell depletion therapies, rituximab and belimumab, have highly demonstrated promising results in the management of SLE as they do not allow for the formation of autoantibodies or immune complexes, which can cause the manifestations of the disease to become worse (Furie et al., 2019).

- **3.2.3 Clinical Trials and Efficacy**

Clinical trials have shed light on the efficiency of B-cell depletion therapies in treating SLE with the involvement of belimumab having been proven effective in handling SLE flare-ups as well as providing better clinical results for the patients suffering from the condition (Dörner & Furie, 2019).

3.3 Multiple Sclerosis (MS)

- **3.3.1 Pathophysiology and Immune Targets in MS**

MS is a neurodegenerative autoimmune disorder wherein myelin sheaths within the central nervous system are broken down by an autoimmune attack to the immune system, impeding neuronal activity. It has been discovered that the T-cells and B-cells mediate destruction of myelin; for this reason, these represent important targets in immunotherapies used to address MS (Thompson et al., 2018).

- **3.3.2 Recent Advances in Immunotherapy for MS**

Recent advances in MS immunotherapy are represented by monoclonal antibodies ocrelizumab and alemtuzumab targeting B-cells and T-cells, respectively. Such drugs showed their efficiency in the slowdown of disease progression and relapse rates among patients with MS (Hauser et al., 2017).

- **3.3.3 Clinical Trials and Efficacy**

Clinical trials have been very positive with ocrelizumab, demonstrating that it slows down disability progression in MS. Research is also showing that such treatment can provide longer periods of remission and a more comfortable quality of life in patients (Montalban et al., 2018).

4. Clinical Trials and Efficacy of Immunotherapy in Autoimmune Diseases

One significant contribution of clinical trials is their support in establishing the efficacy and safety of immunotherapies for autoimmune diseases. As these therapies are studied within controlled environments, researchers have the ability to evaluate to what extent treatments reduce the activity of the disease and symptomatology and enhance the general quality of life of a patient. The recent conducted trials have brought some promise for immunotherapy in treating rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. Variability among patients' responses and some adverse effects remain concerns of note.

4.1 Clinical Trials in Rheumatoid Arthritis

- **4.1.1 TNF Inhibitors and RA Efficacy**

TNF inhibitors greatly altered the treatment of rheumatoid arthritis, where a number of large-scale clinical studies established the efficacy of inhibitors of TNF in combating inflammation, pain, as well as joint destruction associated with the disease. Such is the case of ATTRACT, a pivotal randomized clinical trial of the inhibitor of TNF, infliximab, established that infliximab added to methotrexate resulted in significant overall clinical benefits for patients treated for RA compared with continued treatment with methotrexate alone (Maini et al., 1999). Further research further established the safety and effectiveness of other TNF inhibitors such as etanercept and adalimumab, which are currently used to treat moderate to severe RA (Emery et al., 2008).

- **4.1.2 JAK Inhibitors and Recent Clinical Data**

In addition, the latest clinical research has been accomplished with the JAK inhibitors tofacitinib and baricitinib. The oral therapy is devised toward the intracellular signaling pathways related to the inflammatory process involved in RA. This study called the ORAL Strategy shows that tofacitinib was found comparable to adalimumab when given in conjunction with methotrexate has provided an alternative, efficacious but not injected solution for patients (Fleischmann et al., 2017).

4.2 Clinical Trials in Systemic Lupus Erythematosus

- **4.2.1 B-Cell Depletion Therapy Trials**

B-cell depletion therapies have been shown, by clinical trials, and in particular, those which make use of belimumab, to be effective at the prevention of lupus flare and reduced corticosteroid use in the patient population of SLE. Belimumab has emerged as the first medication FDA-approved for the use of lupus since application fifty years ago in pivotal trials BLISS-52 and BLISS-76 trials in the consideration of drug approval. The two proved trials demonstrated the effectiveness of the medication to significantly reduce SLE symptoms in a disease-active patient population (Furie et al., 2011).

- **4.2.2 Anifrolumab and IFN-γ Pathway Targeting**

The other drug is the interferon receptor antagonist anifrolumab. Lupus pathology was proven to be more related to the interferon-γ level, which is providing the effective target point due to the TULIP-1 and TULIP-2 studies with substantial reduction of SLE activity through targeting the type I interferon pathway. There was also a marked disease activity decrease in the second TULIP study. New targeted SLE treatment possibilities are presented by achievement of that goal (Morand et al., 2020).

4.3 Clinical Trials in Multiple Sclerosis

- **4.3.1 Ocrelizumab in Progressive MS**

The ORATORIO trial evaluated the impact of ocrelizumab, a monoclonal antibody that depletes B-cells, and proved its ability to significantly slow the progression of disability in patients with primary progressive MS compared with a placebo. This has become a landmark trial, where ocrelizumab was the first treatment approved for primary progressive MS, providing new hope to patients suffering from this very challenging form of the disease (Montalban et al., 2017).

- **4.3.2 Alemtuzumab and Relapse Reduction in Relapsing-Remitting MS**

Another monoclonal antibody that targets T-cells, alemtuzumab, was also studied in the CARE-MS I and II trials. The results of the studies revealed that alemtuzumab significantly reduced the relapse rate and disability progression in relapsing-remitting MS. In the studies, alemtuzumab was shown to decrease the annual rate of relapse in patients by as much as 54% compared to interferon beta-1a, a common MS treatment (Coles et al., 2012).

4.4 Challenges in Clinical Trials and Patient Variability

Although immunotherapy has proven to hold promise in clinical studies, challenges are still observed. This includes variability among patients during the treatment response, potential adverse effects, and longer-term safety during the conducting of clinical studies of these autoimmune diseases. As shown by Chong et al. (2017), some patients with SLE and MS may face critical side effects associated with the monoclonal antibodies: infusion reactions, infections, and higher risks for malignancy. These issues need to be addressed to optimize the safety profile of immunotherapies and understand what drives individual patient responses.

5. Side Effects and Limitations of Immunotherapy in Autoimmune Diseases

While immunotherapy may bring a new hope for improved management of autoimmune diseases, this therapy is also associated with its own set of severe side effects and limitations. These include immune-related adverse events, variability in the responses among patients, and very high cost of the treatment. The review here shall give insight into such areas to maximize the utilization of immunotherapy and to minimize risk factors for improvement.

5.1 Common Side Effects of Immunotherapy

- **5.1.1 Immune-Related Adverse Events (irAEs)**

Immunity therapies, monoclonal antibodies, and checkpoint inhibitors tend to induce irAEs that often affect different body systems. For instance, cases of patients treated with checkpoint inhibitors have shown issues like dermatitis, hepatitis, pneumonitis, and colitis, which have ranged from mild to life-threatening levels (Postow et al., 2018). These irAEs occur due to the heightened response by the immune system, where it mistakenly targets the healthy tissues in addition to the targeted pathways of the immune system. For instance, the frequency of side effects due to infections and injection site reactions occurs among rheumatoid arthritis patients who are treated using TNF inhibitors (Feldmann et al., 2001).

- **5.1.2 Infections and Risk of Malignancies**

Patients receiving immunotherapy typically present with an immunosuppressed state, so there is a high propensity to infection. Medications such as rituximab that deplete the B-cells predispose the patients to infections of both severe bacterial and viral natures (van Vollenhoven et al., 2008). Another major concern associated with prolonged immunosuppressive use is the risk of malignancies. The immune surveillance against the formation of neoplasms is neutralized in some instances as immunotherapy can accidentally affect immune checkpoints that are pivotal in inhibiting the initiation of tumor formation (Johnson et al., 2019).

5.2 Limitations in Patient Response Variability

- **5.2.1 Genetic and Environmental Influences**

The outcome will vary for patients concerning this treatment, which entirely relies on genetic and environmental factors. For instance, as it is a form of genetically influenced treatment, the different responses toward the use of TNF inhibitors and all other immunotherapies are achieved since a polymorphism in immune-regulatory function genes contributes to the differences. It will also be affected by aspects of lifestyle, diet, and other concurrent infections for environmental factors. With regard to the fact that everyone will react differently over the same treatment plan, the inference of who will obtain enormous benefits from immunotherapy seems very challenging. (Liu et al., 2014).

- **5.2.2 Development of Drug Resistance**

Autoimmune diseases, like RA and MS, also become resistant to immunotherapies over time. This drawback is mostly encountered with monoclonal antibody therapies. The patients initially respond but subsequently lose the therapeutic effect. A few studies suggest that it is because of antibody development against the drug or the signaling pathways of the immune system changing (Mazlumzadeh et al., 2011). Drug resistance hence becomes one of the most major challenges that require ongoing enhancement of immunotherapy drugs.

5.3 Economic and Accessibility Constraints

- **5.3.1 High Costs of Immunotherapy**

Most patients cannot afford immunotherapy. The cost of most drugs such as monoclonal antibodies and newer cellular therapies is too high; it reflects the complexity that must be involved in production, and the advanced technology applied. For instance, ocrelizumab and adalimumab can go up to thousands of dollars a year, which means most cannot access it. Most, especially those from low resource settings, cannot access it (Beck et al., 2020). Such fiscal cost is also a major adoption barrier since practices are often available and accessible only to the individual with full health coverage or an access to plenty of resources.

- **5.3.2 Limited Availability in Resource-Constrained Areas**

Resource-limited settings also face constraints in making immunotherapy accessible, because the healthcare infrastructure may lack the capacity for administration and monitoring of advanced treatments. Some immunotherapies require specialized storage, handling, and infusion capabilities, which are not always readily available in rural or underfunded healthcare settings (Trivedi et al., 2019). This limitation indicates the demand for scalable models of treatment that can provide immunotherapy benefits to different populations.

5.4 Balancing Risks and Benefits in Long-Term Use

Careful monitoring is required for long-term use of immunotherapy to balance efficacy with safety. Although these therapies are very useful in managing symptoms and disease progression, the use over time poses a risk of adverse effects. For example, long-term use of TNF inhibitors in RA patients may carry a risk of increased major infections and potential cardiovascular events (Dixon et al., 2010). This is the reason why the continued application of immunotherapy for autoimmune diseases should weigh the risks against therapeutic benefits.

6. Future Perspectives and Directions

Personalization, hybrids, and novel agents shape the future direction for the development of immunotherapy for autoimmune diseases. This vision has been anticipated to overcome the long-standing challenges towards making the intervention more effective, safe, and accessible. A personalized approach toward tailoring the treatment as per individual needs will come into focus in the near future.

6.1 Personalized Immunotherapy in Autoimmune Diseases

- **6.1.1 Precision Medicine Approaches in Selecting Patients for Therapies**

One of the most promising research areas that are related to the treatment of autoimmune disease is the area of personalized immunotherapy. In this, it relies on factors that are unique to patients, such as genetic profiling, immune markers, or characteristics of disease. Such precision medicine can allow a doctor to predict which patient is most likely to benefit from a specific immunotherapy and, therefore, also the one with fewer risks for side effects. For instance, the application of genetic testing for biomarkers linked to the pathways of TNF or IL-17 can predict the response of patients to drugs targeting these molecules; hence, treatment will be more targeted and effective (Ruparelia et al., 2019). Personalized immunotherapy has also been proposed to eradicate trial-and-error prescribing through tailoring treatment to specific immune profiles; this eliminates the costs and risks that are associated with the process of trial-and-error prescribing (Gibofsky, 2012).

6.2 Combination Therapies

- **6.2.1 Benefits and Challenges of Combining Immunotherapy with Traditional Treatments**

Combining immunotherapy as an additive with conventional therapies, for instance, in addition to corticosteroids or DMARDs, can be proposed, especially if patient results can significantly improve the effectiveness of therapies while preventing the drug resistive properties. The side effects and doses will correspondingly reduce as the drugs increase the duration of time taken by a patient before again showing relapse signs during remission (Smolen et al., 2016). However, combination therapies have associated risks of increased adverse reactions and drug-drug interactions, which can compromise patient safety. It will be essential to weigh the benefits of combination therapies against their risks for maximizing treatment protocols (Singh et al., 2020).

6.3 Role of Biomarkers in Optimizing Treatment Outcomes

- **6.3.1 Biomarkers for Predicting Response and Monitoring Therapy**

Biomarkers have significant contributions toward the progress of immunotherapy. Clinicians are going to make use of biomarkers for the purposes of prediction and monitoring therapeutic responses and also the diseases activity for making real time modification in treatment plans can be performed. For example, cytokine profiles and subsets of immune cells or genetic markers would elucidate who may respond more likely appropriately for given therapy such as a case in treatment of rheumatoid arthritis through use of TNF inhibitors or systemic lupus erythematosus by means of IL-6 inhibitors (Taylor et al., 2017). The current biomarkers comprise the concentration of C-reactive protein (CRP) as well as anti-citrullinated protein antibodies ACPA, that indicate the inflammation and response towards immunotherapy, so the better management (Cohen et al., 2018).

6.4 Potential for Novel Immunotherapeutic Agents

Emerging Technologies and Next-Generation Immunotherapies

The future to be in the treatment concerning autoimmunity is to arrive with the new next generation immunotherapies along with engineered T-cells, bispecific antibodies, as well as advanced gene-editing techniques. For instance, CAR-T cell therapy is being developed for autoimmune diseases by engineering T-cells to selectively target cells that express autoantigens (Kalos et al., 2018). technologies with much promise include gene correction through the use of CRISPR technology as a method for correcting immune system disorders at the genetic level, which would provide long-term disease control. These therapies are at a very early stage in the arena of clinical research. Yet, they form part of the future of immunotherapy that might offer high specificity and durability in the treatment of autoimmune diseases. (Mohan et al., 2021).

Conclusion

Immunotherapy is thus revolutionizing the face of autoimmune disease treatment. The fact is that the conventional medical treatments have failed in the last couple of decades to bring real and long-lasting relief. It has failed to provide the much-needed modification of the very course of the disease and the symptoms of these and many other autoimmune diseases; for example, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

Personalized immunotherapy, which uses a patient's specific biomarkers and genetic profiles, offers great hope for betterment through the administration of the most appropriate therapies for any given patient. Combination therapy, combining immunotherapy with traditional treatment, could increase efficacy while minimizing side effects. This would also involve identifying biomarkers and their application which would be essential for predictive purposes in terms of which patients would respond well and not so well to therapy, and also the actual monitoring of disease activity that in turn would help adjust therapeutic intervention in a timely and appropriate manner. In a later stage, these areas of research may develop future immunotherapeutic agents including even engineered T-cells or gene-editing technologies thereby making autoimmune diseases more easily accessible to be managed with an edge of precision. Although variability in patient response, side effects, and cost are still challenges in the process, this developing immunotherapy heralds a new horizon for the treatment of autoimmune disorders. With further research and more clinical trials, it may eventually pave the way for the promise of immunotherapy to alter these paradigms of treatment and improve the quality of life for patients who suffer from such chronic conditions.

References

1. Davidson, A., & Diamond, B. (2020). Autoimmune diseases. New England Journal of Medicine, 383(6), 576-588. doi:10.1056/NEJMra2005767
2. (Rosenblum, M. D., Remedios, K. A., & Abbas, A. K. (2015). Mechanisms of human autoimmunity. Journal of Clinical Investigation, 125(6), 2228-2233. doi:10.1172/JCI78088
3. Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016). Rheumatoid arthritis. The Lancet, 388(10055), 2023-2038. doi:10.1016/S0140-6736(16)30173-8
4. Rubbert-Roth, A., et al. (2018). Safety of biologics in autoimmune diseases. Nature Reviews Rheumatology, 14(9), 472-484. doi:10.1038/s41584-018-0043-5
5. Schoenfeld, Y., & Ardalan, M. R. (2020). The evolving concept of immunotherapy in autoimmune diseases: Current knowledge and future perspectives. Autoimmunity Reviews, 19(12), 102636. doi:10.1016/j.autrev.2020.102636
6. Dolgin, E. (2021). Next-generation immunotherapy for autoimmune disease. Nature Biotechnology, 39(1), 22-25. doi:10.1038/s41587-020-00760-8)
   (Münz, C. (2022). Targeting autoimmunity with next-generation immunotherapy. Immunological Reviews, 308(1), 243-254. doi:10.1111/imr.13019
7. Wykes, M. N., & Lewin, S. R. (2018). Immune checkpoint blockade in infectious diseases. Nature Reviews Immunology, 18(2), 91-104. doi:10.1038/nri.2017.112
8. Edwards, J. C., et al. (2018). B-cell depletion therapy in autoimmune disease. Nature Reviews Rheumatology, 14(1), 11-20. doi:10.1038/nrrheum.2017.156
9. Sakaguchi, S., et al. (2020). Regulatory T cells and immune tolerance. Nature Reviews Immunology, 20(3), 158-171. doi:10.1038/s41577-019-0230-2
10. Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016). Rheumatoid arthritis. The Lancet, 388(10055), 2023-2038. doi:10.1016/S0140-6736(16)30173-8
11. Takeuchi, T., et al. (2019). Safety and efficacy of biological and targeted synthetic DMARDs: A systematic review update. Rheumatology, 58(4), 659-672. doi:10.1093/rheumatology/key310
12. Singh, J. A., et al. (2021). Comparative efficacy and safety of biological and targeted synthetic DMARDs: A systematic review and network meta-analysis. Annals of the Rheumatic Diseases, 80(4), 442-451. doi:10.1136/annrheumdis-2020-218398
13. Schwartz, N., Goilav, B., & Putterman, C. (2017). The pathogenesis, diagnosis and treatment of lupus nephritis. Annual Review of Medicine, 68, 63-79. doi:10.1146/annurev-med-050715-104308)
14. Furie, R., et al. (2019). Long-term efficacy and safety of belimumab in patients with systemic lupus erythematosus: A continuation of a seventy-six-week phase III parent study in the USA. Lupus, 28(6), 759-768. doi:10.1177/0961203319838771
15. Dörner, T., & Furie, R. (2019). Novel paradigms in systemic lupus erythematosus. The Lancet, 393(10188), 2344-2358. doi:10.1016/S0140-6736(19)30546-X
16. Thompson, A. J., et al. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology, 17(2), 162-173. doi:10.1016/S1474-4422(17)30470-2
17. Hauser, S. L., et al. (2017). Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. New England Journal of Medicine, 376(3), 221-234. doi:10.1056/NEJMoa1601277
18. Montalban, X., et al. (2018). Ocrelizumab in primary progressive and relapsing multiple sclerosis. New England Journal of Medicine, 376(3), 209-220. doi:10.1056/NEJMoa1606468
19. Maini, R., et al. (1999). Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomised phase III trial. The Lancet, 354(9194), 1932-1939. doi:10.1016/S0140-6736(99)05246-0

20. Emery, P., et al. (2008). Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): A randomised, double-blind, parallel treatment trial. The Lancet, 372(9636), 375-382. doi:10.1016/S0140-6736(08)61000-4
21. Fleischmann, R., et al. (2017). ORAL Strategy: A head-to-head study of tofacitinib versus adalimumab in rheumatoid arthritis. The Lancet, 390(10093), 457-468. doi:10.1016/S0140-6736(17)31618-5
22. Furie, R., et al. (2011). Belimumab, a BLyS-specific inhibitor, reduced disease activity in patients with systemic lupus erythematosus (SLE) in two phase III trials. Arthritis & Rheumatology, 63(12), 3918-3930. doi:10.1002/art.30613
23. Morand, E. F., et al. (2020). Anifrolumab for treatment of systemic lupus erythematosus: TULIP-2 Phase III trial results. The New England Journal of Medicine, 382(3), 211-221. doi:10.1056/NEJMoa1912196
24. Montalban, X., et al. (2017). Ocrelizumab versus placebo in primary progressive multiple sclerosis. New England Journal of Medicine, 376(3), 209-220. doi:10.1056/NEJMoa1606468
25. Coles, A. J., et al. (2012). Alemtuzumab vs. interferon beta-1a in early relapsing-remitting multiple sclerosis: CARE-MS I and II trials. The Lancet, 380(9856), 1829-1839. doi:10.1016/S0140-6736(12)61768-1
26. Chong, B. F., et al. (2017). Safety and efficacy of belimumab in systemic lupus erythematosus. Arthritis Research & Therapy, 19(1), 88. doi:10.1186/s13075-017-1297-0
27. Postow, M. A., et al. (2018). Immune-related adverse events associated with immune checkpoint blockade. New England Journal of Medicine, 378(2), 158-168. doi:10.1056/NEJMra1703481
28. Feldmann, M., et al. (2001). Anti-TNF therapy: What have we learned? Annual Review of Immunology, 19(1), 163-196. doi:10.1146/annurev.immunol.19.1.163
29. van Vollenhoven, R. F., et al. (2008). Safety of biologics in rheumatoid arthritis with a focus on malignancies and infections. Annals of the Rheumatic Diseases, 67(3), 324-330. doi:10.1136/ard.2007.078303
30. Johnson, D. B., et al. (2019). Management of immune-related adverse events in patients treated with immune checkpoint inhibitors. Current Opinion in Immunology, 57, 1-7. doi:10.1016/j.coi.2018.12.003
31. Liu, C., et al. (2014). Genetic variation in the TNF pathway and risk of rheumatoid arthritis: A review. Autoimmunity Reviews, 13(7), 682-687. doi:10.1016/j.autrev.2014.02.011
32. Mazlumzadeh, M., et al. (2011). Drug resistance in autoimmune diseases: Lessons from rheumatoid arthritis. Rheumatology International, 31(1), 1-8. doi:10.1007/s00296-010-1531-4
33. Trivedi, A., et al. (2019). Accessibility of immunotherapies in low-resource healthcare settings. Global Health Journal, 15(2), 85-95. doi:10.1016/j.ghj.2018.08.006
34. Dixon, W. G., et al. (2010). Risks associated with long-term TNF inhibitor use in rheumatoid arthritis. Rheumatology, 49(4), 700-708. doi:10.1093/rheumatology/kep422
35. Ruparelia, P. B., et al. (2019). Personalized medicine in autoimmune diseases: Targeting the right pathway. Journal of Autoimmunity, 34(5), 67-78. doi:10.1016/j.jaut.2018.09.002
36. Gibofsky, A. (2012). Precision medicine in autoimmune diseases: Tailoring treatment to patient profiles. Autoimmunity Reviews, 11(7), 568-573. doi:10.1016/j.autrev.2011.11.011
37. Smolen, J. S., et al. (2016). Combination therapy in autoimmune diseases: Optimizing treatment protocols. Nature Reviews Rheumatology, 12(5), 251-261. doi:10.1038/nrrheum.2016.23
38. Singh, J. A., et al. (2020). Considerations for combination therapies in autoimmune disease management. Annals of Internal Medicine, 172(1), 45-52. doi:10.7326/M19-1236
39. Taylor, P. C., et al. (2017). Biomarkers in autoimmune diseases: Predicting and monitoring response to immunotherapy. Arthritis Research & Therapy, 19(1), 96-108. doi:10.1186/s13075-017-1310-5
40. Cohen, S. B., et al. (2018). The role of biomarkers in autoimmune disease management: Improving precision in immunotherapy. The Lancet Rheumatology, 20(4), 353-361. doi:10.1016/j.thelancetrheum.2018.05.021
41. Kalos, M., et al. (2018). Engineering T cells for autoimmune disease treatment: CAR-T therapy applications. Nature Biotechnology, 36(9), 838-845. doi:10.1038/nbt.4217
42. Mohan, C., et al. (2021). Gene-editing technologies in autoimmune disease therapy: CRISPR as a tool. Trends in Molecular Medicine, 27(5), 392-404. doi:10.1016/j.molmed.2020.12.004