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The impact of biologics on the management of autoimmune diseases: A comprehensive review for pharmacists

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***Abstract*---Background:** Biologics have emerged as a transformative approach in the treatment of Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD), systemic lupus erythematosus (SLE), asthma, and multiple sclerosis (MS), addressing the underlying pathophysiological mechanisms of these complex diseases. **Aim:** the main aim of this review is to explore the main biologics used for the treatment of SLE, IBD, MS, RA, and Asthma. **Methods:** An updated data were collected and analyzed using research original articles, and reviewed articles. **Results:** Biologics like belimumab and rituximab target B cells, offering limited yet significant improvements in patient

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outcomes. Other promising agents such as epratuzumab and low-dose IL-2 are under investigation, aiming to enhance treatment efficacy with improved safety profiles. In asthma management, monoclonal antibodies such as omalizumab, mepolizumab, and dupilumab target key cytokines involved in the inflammatory response, significantly reducing exacerbations and improving patient quality of life. Similarly, natalizumab represents a crucial advancement in MS therapy by inhibiting T cell migration into the central nervous system, effectively reducing disease activity. Despite their efficacy, the use of biologics is accompanied by challenges, including potential adverse effects and the need for personalized treatment strategies. **Conclusion:** Continued research and clinical trials are essential to refine these therapies and establish optimal treatment protocols for patients with SLE, asthma, and MS.

***Keywords*---**Biologics, Rheumatoid Arthritis, Lupus Erythematosus, Asthma, Inflammatory Bowel Disease, Autoimmune Disorders.

Introduction

In the United States, biologics are regulated mainly under the Public Health Service Act (PHSA), as opposed to solely under the Food, Drug, and Cosmetic Act (FDCA), with limited exceptions. This difference arises from their specific legislative and regulatory background [1]. The Biologics Control Act of 1902 initially regulated biologics, aiming to ensure the "safety, purity, and potency of vaccines, serums, toxins, antitoxins, and related products." This Act established regulatory protocols for biologics and their manufacturing sites, eventually becoming recodified in 1944 under the PHSA. Initially overseen by various government bodies, biologics shifted to FDA oversight from the National Institutes of Health (NIH) in 1972. This transition aimed to ensure the application of both PHSA and FDCA standards (safety, effectiveness, and protection against misbranding or adulteration) in biologic product approvals. The definition of "biologic" has expanded considerably. Today, over 250 biotechnology products, including healthcare products and vaccines, are commercially available worldwide (www.bio.org). According to the PHSA, a "biologic product" refers to "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (excluding chemically synthesized polypeptides), or analogous products, or arsphenamine or derivatives (or other trivalent organic arsenic compounds) applicable for preventing, treating, or curing diseases in humans" [2]. These products may comprise sugars, proteins, nucleic acids, or complex combinations of these substances and can include living entities, such as cells and tissues. Thus, this category encompasses cell and gene therapies, therapeutic viruses, and CAR-T therapies, in addition to terms like biopharmaceuticals, biologics, and therapeutic proteins—broadening well beyond blood products and vaccines. Biopharmaceuticals differ from traditional pharmaceuticals primarily in their manufacturing and processing methods. While biologics are typically produced in living organisms (e.g., bacteria, yeast, mammalian cells), traditional "small-molecule" drugs result from a series of chemical synthesis steps, although there are grey areas with chemically

synthesized peptides. Recombinant DNA technology is frequently employed to produce biotechnology products.

Various biologics subsets exist, categorized by FDA designations, though other regulatory frameworks also offer definitions. The International Council for Harmonization (ICH) initially defined biologics in its ICH S6 guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals, describing biopharmaceuticals as products derived from identified cells, including bacterial, yeast, insect, plant, and mammalian cells. These products can include proteins, peptides, and their derivatives or related components, such as cytokines, proteins, growth factors, fusion proteins, enzymes, receptors, hormones, and monoclonal antibodies (International Council for Harmonization, 1997c [3]. While the European Medicines Agency (EMA) largely aligns with the ICH's biologics definition, it also has a Committee for Advanced Therapies (CAT), which assesses advanced therapy medicinal products (ATMPs) defined as gene, cell, or tissue engineering-based human medicines [4]. As with traditional drugs, biologics can serve various purposes, from treating and preventing diseases to diagnosing conditions. Common examples of biologics today include vaccines, blood and blood products for transfusion or further manufacturing, allergenic extracts for diagnosis and treatment (e.g., allergy shots), human cells and tissues used for transplantation (e.g., tendons, ligaments, and bones), gene and cellular therapies, and tests for screening blood donors for infectious agents such as HIV [5].

Inflammatory arthritis, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), impose a considerable burden of morbidity and mortality on populations globally. A notable aspect of this burden is the two-fold increase in the risk of cardiovascular events (CVEs) [6], with evidence suggesting that this risk escalates with prolonged disease duration [7,8,9]. It has been posited that this association stems from inflammatory processes mediated by cytokines, particularly tumor necrosis factor (TNF). The high inflammatory load is thought to stimulate autoantibody production and induce apoptosis in endothelial cells, leading to vascular injury [10] and a pro-thrombotic state [11]. Consequently, the administration of TNF inhibitors may offer a means to mitigate cardiovascular risk by managing systemic inflammation. A recent investigation indicated that individuals with RA whose disease onset occurred after 2000 did not exhibit an elevated mortality risk relative to the general population; conversely, those whose disease began prior to 2000 faced an increased risk [12]. Multiple studies have shown that the treatment of inflammatory arthritis with TNF inhibitors correlates with improvements in surrogate markers of cardiovascular health, such as endothelial stiffness, biochemical lipid profiles, and carotid intima-media thickness [13-18].

Conflicting evidence exists concerning clinical cardiovascular endpoints, including the rates of myocardial infarction, stroke, and cardiovascular-related mortality following treatment with biologics in RA patients. Some studies indicate a reduced risk of CVEs [19, 20], while others report no significant differences [21, 22]. Research examining cardiovascular risk in RA has been conducted in various regions, including North America [23-25], Britain [26], and Sweden [27]. However, to date, no studies have been conducted within the Australian context, where access to biologic therapy is governed by stringent criteria. Additionally, there has

been limited investigation into the impact of biologics on CVE rates for inflammatory arthritis beyond RA. Therefore, more extensive research is necessary across diverse arthritic conditions to determine whether biologic therapy provides benefits that extend beyond the direct management of arthritis in these patients.

Biologics and Inflammatory Bowel Diseases:
TNF-α Inhibitors:

TNF-α inhibitors, such as adalimumab (Humira®) and certolizumab pegol (Cimzia®), are widely used in treating inflammatory diseases, particularly Crohn's disease (CD) and rheumatoid arthritis (RA). Adalimumab, approved by the FDA in 2002, is a fully human monoclonal antibody that inhibits TNF-α, a cytokine involved in inflammation and immune responses (28, 29). Adalimumab specifically blocks interactions between TNF-α and its cell receptors, effectively reducing inflammatory symptoms without affecting TNF-β (30). Its indications include moderate-to-severe RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and CD, among others (31, 32). Adalimumab's efficacy in CD has been demonstrated through various clinical trials, such as CLASSIC-I and CLASSIC-II, which showed dose-dependent remission in moderate-to-severe CD patients (33, 34). Furthermore, in the CHARM and GAIN trials, long-term clinical remission was observed in both TNF-α inhibitor-naive and infliximab-intolerant patients, underscoring adalimumab's versatility (35, 36). The recommended adalimumab dosing for CD starts with an initial 160 mg, followed by 80 mg on day 15, and 40 mg biweekly from day 29 for up to a year. Pediatric use is supported by IMAgINE 1 and 2 trials, which reported sustained remission in children with CD unresponsive to other therapies, with comparable safety profiles to adults (37, 38). Adalimumab is also effective in ulcerative colitis (UC), with a meta-analysis showing higher remission and response rates compared to placebo (39, 40). Common side effects include injection pain, infections, and increased cancer risk, although incidence rates are consistent with age-matched populations (40, 42). It is categorized as pregnancy-safe in animals but should be cautiously prescribed for breastfeeding and elderly patients.

Certolizumab pegol, FDA-approved in 2008, is a TNF-α inhibitor with unique properties due to its polyethylene glycol (PEG) conjugation, which improves bioavailability and stability (43). It lacks an Fc region, eliminating complement activation, making it safer in certain contexts (43). Indications for certolizumab include moderate-to-severe CD, RA, and psoriatic arthritis (42). In the PRECiSE trials, certolizumab showed superior clinical response and remission rates over placebo for CD management, with significant maintenance of remission in long-term studies (44, 45). The recommended dosing in CD starts with 400 mg at weeks 0, 2, and 4, with a maintenance dose every four weeks (42). PRECiSE-3, a long-term study, demonstrated over 68% remission rates annually (46). The safety profile of certolizumab is favorable, with no significant risk of malignancies or tuberculosis reactivation in clinical trials. Adverse effects are generally mild, with gastrointestinal and injection-site reactions being the most common (43). Both adalimumab and certolizumab pegol thus represent vital tools in managing inflammatory conditions, offering effective, well-studied options for patients across various age groups and disease profiles.

Integrin Receptor Antagonists:

Integrin receptor antagonists such as vedolizumab and natalizumab offer targeted therapeutic approaches for inflammatory conditions like Crohn's disease (CD) and ulcerative colitis (UC). Vedolizumab, a humanized monoclonal antibody (MAb) approved by the FDA in 2014, targets the α4β7 integrin receptor, blocking the binding of Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1) and inhibiting T-cell adhesion to reduce inflammation specifically in the gut epithelium, where these receptors are predominantly located (47). Vedolizumab is currently indicated for moderate-to-severe CD and UC and is available as a 300 mg dose in a lyophilized form for reconstitution (48, 51). Clinical trials in pediatric populations have been ongoing since 2017, indicating potential broader applications for this treatment (49, 50). Vedolizumab has a complex pharmacokinetic profile, with a half-life of approximately 25 days and nonlinear elimination at lower concentrations but a more predictable, linear elimination at higher therapeutic levels (51).

The standard dosing regimen for both UC and CD involves an initial phase of 300 mg IV infusions at weeks 0, 2, and 6, followed by maintenance infusions every eight weeks. If there is no clinical improvement, treatment is generally discontinued (51). In clinical trials, such as the GEMINI I, significant rates of clinical response and remission were observed at week 6, with 47% of UC patients responding to treatment versus 26% receiving placebo, and remission rates reaching 17% compared to 5% with placebo ($P<0.001$) (52). The GEMINI II and III trials, conducted for CD, yielded mixed results; while the response rates were generally favorable, statistical significance was not achieved for all endpoints. However, GEMINI II showed that among responders to induction therapy, long-term remission rates at week 52 were significantly higher in the vedolizumab groups compared to placebo (53, 54). Common adverse reactions associated with vedolizumab include infusion reactions and infections due to its immunomodulatory effect (54). Long-term safety data indicate a low malignancy rate (0.4%) but suggest a potential for immunogenicity, with 13% of patients developing anti-vedolizumab antibodies by week 24 (57). Pediatric safety and efficacy have not been established, although no age-related differences have been observed in geriatric populations. The drug is rated as a Category B medication in pregnancy, with animal studies showing no fetal harm, though caution is advised for nursing mothers due to possible transfer into breast milk (57).

Natalizumab, also a humanized IgG4 MAb, was the first integrin receptor antagonist approved by the FDA in 2004 (55, 56). Unlike vedolizumab, natalizumab acts on both α4β1 (VLA-4) and α4β7 integrins, affecting leukocyte translocation across blood vessel membranes (57). This dual mechanism makes natalizumab suitable for treating multiple sclerosis and CD. Natalizumab is administered as a 300 mg IV infusion every four weeks, with a steady-state concentration reached at approximately 24 weeks. Unlike vedolizumab, natalizumab should not be used in combination with other immunosuppressants or TNF-α inhibitors due to an increased risk of adverse effects (58). The ENACT-1 and ENCORE trials demonstrated natalizumab's efficacy in CD, with clinical responses observed in 56% of patients receiving the drug versus 49% with placebo by week 10, though remission rates did not reach statistical significance

(59). The ENCORE trial, which focused on maintenance, found clinical responses sustained in 61% of natalizumab-treated patients versus 28% for placebo (P<0.0001) (60). While natalizumab's side effects are similar to vedolizumab's, the FDA has flagged the risk of progressive multifocal leukoencephalopathy (PML) due to John Cunningham virus reactivation as a severe adverse effect (61). Like vedolizumab, natalizumab is classified as a Category B drug in pregnancy, with limited data on its safety in breastfeeding and elderly populations.

IL-12 and IL-23 Antagonists:

Ustekinumab (Stelara®) is a monoclonal antibody (MAb) targeting the p40 subunit common to interleukin (IL)-12 and IL-23, cytokines involved in immune regulation and inflammatory pathways. Approved initially in Canada in 2008 and by the FDA in 2009, ustekinumab is primarily indicated for chronic inflammatory diseases, such as plaque psoriasis, psoriatic arthritis, and Crohn's disease (CD), by inhibiting IL-12 and IL-23-mediated activation of natural killer cells and CD4+ T lymphocytes (62, 63). Available as both intravenous (IV) and subcutaneous (SC) formulations, ustekinumab is formulated for flexibility across conditions; IV administration is indicated for weight-based CD induction, while SC doses offer maintenance options (64). Mechanistically, ustekinumab reduces the expression of IL-12 and IL-23 mRNA, achieving a steady-state concentration by week 28, with an elimination half-life of approximately 15 to 45.5 days (64).

For CD, the dosing regimen begins with a single, weight-based IV induction dose (260 mg for patients ≤55 kg, 390 mg for 55-85 kg, and 520 mg for >85 kg), followed by an SC maintenance dose of 90 mg administered every eight weeks (64). Clinical efficacy for CD was confirmed in UNITI-1 and UNITI-2 trials, where ustekinumab demonstrated significant improvements over placebo in clinical response and remission rates. Specifically, UNITI-1 (n=741) showed a week-6 clinical response rate of 33.7% for ustekinumab versus 21.5% for placebo (P<0.01), while week-8 remission rates reached 20.9% compared to 7.3% (P<0.001) (71). UNITI-2 (n=628) showed even higher response and remission rates at week 6 and 8, with 55.5% versus 28.7% (P<0.001) for response and 40.2% versus 19.6% (P<0.001) for remission, favoring ustekinumab (65). The IM-UNITI trial further demonstrated the maintenance of remission with ustekinumab at 8-week and 12-week intervals, achieving remission in 53.1% and 48.8% of patients at week 44, respectively, as compared to 35.9% for placebo (P=0.005 and P=0.04) (66).

Side effects most frequently associated with ustekinumab include nasopharyngitis, injection site erythema, and vulvovaginal candidiasis, as well as serious infections like anal abscess, gastroenteritis, and pneumonia (63). Additionally, 0.2% of patients treated with ustekinumab developed nonmelanoma skin cancer (NMSC) and other malignancies, with none reported in placebo recipients (64). Immunogenicity rates differ slightly between conditions; 6% of psoriasis patients developed anti-ustekinumab antibodies, while only 3% did so among CD patients (64). Post-marketing data have reported hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, and though limited, human pregnancy data show no evidence of adverse fetal effects at doses exceeding 100 times the recommended human dose (64). Animal studies have

found the presence of ustekinumab in milk in lactating monkeys, but not in human milk. Ustekinumab's safety and efficacy in the pediatric population remain unestablished, and there are insufficient data among the elderly to confirm differences from adults (64).

Biologics in Rheumatoid Arthritis:

Roughly 40% of newly diagnosed patients with rheumatoid arthritis (RA) fail to achieve disease remission or low disease activity using conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) due to inadequate efficacy or dose-related intolerance. Although some patients achieve initial remission, long-term treatment often sees a reduction in efficacy, even with csDMARDs and corticosteroids. In these cases, biologic DMARDs (bDMARDs) become essential and are frequently effective in reaching the desired treatment targets. If the response diminishes over time, switching to another bDMARD is often beneficial. In the UK, five tumour necrosis factor-α inhibitors (TNFis) are licensed for RA treatment, with biosimilars available for two of them. Additionally, bDMARDs with three distinct mechanisms of action are also approved. These drugs demonstrate effectiveness for RA patients who did not respond to methotrexate (MTX), showing clinical, structural, and functional benefits through randomized controlled trials. Trials typically compare bDMARDs in combination with MTX against a placebo plus MTX, with key results compiled in research summaries.

First-line biologic use of bDMARDs generally yields American College of Rheumatology (ACR) response rates of 20% (ACR20), 50% (ACR50), and 70% (ACR70) in patients inadequately responding to MTX. On a broad scale, bDMARDs of differing actions perform similarly in first-line treatment. While co-administration with MTX enhances efficacy, poor MTX tolerance leads about a third of patients to use bDMARDs with other csDMARDs or as monotherapy. Notably, the ADACTA and MONARCH trials showed that anti-interleukin-6 receptor antibodies (e.g., tocilizumab and sarilumab) as monotherapies outperformed adalimumab monotherapy in patients who had inadequate responses to MTX. In second-line biologic use, bDMARD response rates generally decrease compared to first-line treatments, with response rates being similar across all bDMARD classes. However, patients switching from a TNFi to a biologic with a different mechanism of action often respond better than those who switch within the TNFi class. Assessing drug levels of some TNFis aids in determining whether to use another TNFi or a different bDMARD. Comparative studies of bDMARDs have shown no superiority within the TNFi class, as demonstrated by the EXXELERATE trial, which found no efficacy difference between certolizumab and adalimumab. Between-class trials also show comparable results, with the ORBIT study demonstrating rituximab's non-inferiority to TNFi, and the AMPLE trial showing similar outcomes between adalimumab and abatacept for early RA. Other studies, such as RA-BEAM and ORAL, support the efficacy of targeted synthetic DMARDs (tsDMARDs) like baricitinib and tofacitinib as comparable or superior to TNFis in MTX-inadequate responders.

The introduction of bDMARDs has transformed RA management, significantly reduced erosive damage and preserved function. However, access to bDMARDs remains uneven, often restricted by cost-based eligibility criteria, as seen in

England and Wales, where a Disease Activity Score (DAS28) threshold of 5.1 is required for reimbursement. This threshold excludes patients with moderate disease activity (DAS28 scores above 3.2 but below 5.1), who typically fare poorly with csDMARDs alone, facing risks of functional impairment and joint destruction. While efficacy among bDMARDs appears similar at the group level, certain stratifiers support more tailored use in individual cases. For instance, TNFis are generally avoided in patients with interstitial lung disease, cardiac failure, or multiple sclerosis, where safer alternatives like rituximab and abatacept are preferred. Tocilizumab is not advised for patients with diverticular disease, while TNFis require screening for latent tuberculosis and hepatitis B before rituximab use due to increased risks. Rituximab is also recommended for patients with recent lymphoma histories, given the limited evidence linking TNFis to cancer, except non-melanoma skin cancer.

Certain biomarkers also guide bDMARD selection. Sero-positivity for rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) enhances responses to rituximab and abatacept, though not to tocilizumab or TNFis. Smoking adversely affects responses to TNFis and abatacept but does not significantly impact rituximab or tocilizumab efficacy. Obesity further complicates treatment outcomes, especially with fixed-dose TNFi injections, whereas drugs dosed by weight, like intravenous golimumab, are effective in patients over 100 kg. Although fixed-dose subcutaneous tocilizumab and abatacept match the efficacy of their intravenous counterparts across body mass indices, response rates remain lower in patients over 100 kg, a limitation not observed with rituximab. Patients experiencing diminished efficacy or tolerance loss with a bDMARD often switch to another. Across studies, subsequent responses to a second or third bDMARD are lower than with initial treatment, reflecting the challenge of matching patients to the most effective mechanism of action without predictive biomarkers for individual outcomes. Therapeutic drug levels of adalimumab and certolizumab can help guide treatment adjustments, as therapeutic levels suggest that the lack of response likely stems from inadequate TNF inhibition. Conversely, low drug levels may indicate non-adherence or anti-drug antibodies, suggesting that switching within the TNFi class may still be effective. Dose reduction has also become common in patients achieving sustained remission (typically over a year). Many patients with supratherapeutic TNFi levels maintain remission after reducing bDMARD doses by extending intervals or administering lower doses, such as 25 mg of etanercept where available. The future of RA treatment may shift toward precision medicine, aiming to optimize drug choice and dosing from the outset to improve outcomes and minimize trial-and-error adjustments.

Biologics and Lupus Erythematosus:

Because of the disease's variability and lack of a defined treatment plan, managing active systemic lupus erythematosus (SLE) is extremely difficult. Corticosteroids and immunosuppressants are the mainstays of current treatment strategies [67]. Complete remission is still uncommon in clinical practice, despite being the desired result for SLE care [268]. The effectiveness of standard therapy regimens using corticosteroids and immunosuppressants varies, helping only a small percentage of patients while also causing serious side effects like infections, osteoporosis, and cardiovascular problems [69-71]. As a result, treatments with

increased effectiveness and a lower profile of adverse effects are desperately needed. The development of targeted biologics, which try to modify specific components of immune responses, has increased due to advances in understanding the pathogenic mechanisms of SLE. Targeting B cells, T cells, cytokines, and other immunological mediators, new treatment medicines are being developed for SLE, and ongoing phase II and III trials are showing encouraging results.

Belimumab and rituximab are two B cell-targeted treatments that have seen clinical success. For the treatment of SLE, belimumab, a fully humanized monoclonal antibody against B-cell activating factor (BAFF), has been approved by regulators in both Europe and the USA. Nevertheless, belimumab has only been shown to provide a slight improvement in clinical trials, with a 14% greater response rate at 52 weeks when compared to a placebo (SRI = 58%). Rituximab, a CD20-targeting medication, has been thoroughly investigated and may be used as a treatment [72-74]. For example, rituximab has shown promise efficacy in lowering corticosteroid reliance, according to a prospective study [75]. However, the major goals of the LUNAR study for lupus nephritis and the EXPLORER study for nonrenal SLE were not met [76, 77]. Despite rituximab's effectiveness in SLE, treatment outcomes may be improved by grouping patients according to their clinical traits. Furthermore, in phase II EMBLEM studies, the anti-CD22 antibody epratuzumab demonstrated positive clinical responses and reduced CD19+ B cell numbers with good tolerability [78]. However, as compared to placebo, the phase III EMBODY studies did not show a statistically significant increase in response rates (39.8% vs. 34.1%) [79]. To evaluate the effectiveness of anti-CD22 treatments in SLE, more investigation is necessary. CD40L inhibitors are another possible treatment; they block the generation of high-affinity autoantibodies by preventing IgG class switching when they bind to CD40 on B cells. A phase I trial with dapirolizumab pegol, an anti-CD40L Fab fragment, recently showed that 46% of patients achieved BICLA with no significant side effects; however, due to the small sample size, additional evaluation is required [80]. Low-dose IL-2 showed effectiveness and tolerability in patients with active SLE in a recent proof-of-concept study [81]. By week 12, 89.5% of subjects had experienced an SRI response, with improvements in proteinuria and autoantibody titers, increased C3 and C4 levels, and decreases in clinical symptoms such rash, alopecia, arthritis, fever, leukopenia, and thrombocytopenia. By increasing Treg activity and decreasing pathogenic responses linked to Tfh and Th17 cells, low-dose IL-2 seems to alter immunological balance [82-85]. Additionally, this strategy increases the activity of CD8 T cells and NK cells, which may improve SLE patients' immunological responses to infections.

Furthermore, patients with active SLE frequently exhibit higher serum IFNα levels and IFN gene expression profiles [86-87]. Phase II and III trials have shown promising results for drugs such as sifalimumab (anti-IFNα mAb), rontalizumab (humanized IgG1 anti-IFNα antibody), and anifrolumab (anti-interferon receptor 1 (IFNAR1)) [88-92]. Although very slightly so, a phase II trial of sifalimumab showed a statistically improved SRI-4 response in treatment groups (56.5–58.3%) as compared to placebo (45.4%). Patients who received the experimental medication had higher infection rates [89]. Phase III trials are currently being conducted to assess the effectiveness and safety of this strategy. Additionally,

ustekinumab has been shown to be effective in inhibiting the IL12/23 pathway, which is associated in the pathophysiology of SLE. In a phase II research, the SRI-4 response rate after 24 weeks was 60%, compared to 31% for a placebo [93]. A CTLA-4-Ig fusion protein called abatacept, which inhibits T-cell activity and has demonstrated disease-modifying potential in murine models of lupus nephritis, has attracted a lot of attention [94-96]. No significant clinical improvements have been noted in SLE patients despite abatacept's evaluation [97-101]. Although primary goals were not met, abatacept has shown biologic action, such as decreasing anti-dsDNA antibodies and raising C3 levels, with tolerability in patients with active lupus nephritis [101]. Lastly, therapeutic approaches that use T cell vaccines (TCVs) and mesenchymal stem cells (MSCs) have demonstrated safety and efficacy in SLE, and they may be promising future therapy choices [102-104]. In conclusion, therapies that target anti-CD22, IFN-α, CTLA-4-Ig, and other biologics are undergoing clinical trials, whereas treatments that target anti-Blys, anti-CD20, low-dose IL-2, MSCs, and TCVs are currently in clinical usage for SLE. Researcher-rheumatologist cooperation seem to be ushering in a new era of tailored SLE therapy.

Biologics and Asthma:

Inhaled allergens activate B lymphocytes, prompting them to differentiate into plasma cells that produce immunoglobulin E (IgE) antibodies. These antibodies circulate in the bloodstream and bind to high-affinity IgE receptors on mast cells and basophils. When allergens re-enter the body, they bind to these IgE-bound receptors, triggering the release of inflammatory mediators like histamines and leukotrienes, which cause bronchoconstriction typical in asthma exacerbations. Omalizumab, the first monoclonal antibody approved for asthma management, interferes by binding to IgE, inhibiting its binding to high-affinity receptors on mast cells and basophils. This blockade reduces the release of allergic response mediators, significantly lowering asthma exacerbations in patients with poorly controlled allergic asthma despite inhaled corticosteroids. Studies highlight omalizumab’s efficacy, particularly in patients exhibiting type 2 inflammation, as indicated by elevated blood eosinophils, periostin, or nitric oxide levels (105). Although well tolerated, omalizumab can cause local pain at injection sites and occasionally hypersensitivity reactions, making it unsuitable for chronic obstructive pulmonary disease (COPD) (106-108).

Interleukin-5 (IL-5), a cytokine, plays a vital role in eosinophil proliferation, maturation, and functioning. This cytokine, primarily produced by Th2 lymphocytes, natural killer cells, and eosinophils, is elevated in asthma, especially with allergen exposure. Eosinophils, associated with inflammation in asthma and COPD, release granular proteins through IL-5–mediated pathways, which intensify airway inflammation. IL-5, therefore, has become a major target for treating eosinophilic asthma and COPD (10). Among IL-5-targeted biologics, mepolizumab, a monoclonal antibody targeting IL-5, demonstrated decreased exacerbations in patients with high eosinophil levels even under corticosteroid treatments. Cleared in 2015 for eosinophilic asthma patients over 12 years old, mepolizumab offers significant relief (109-111). Another monoclonal antibody, reslizumab, administered intravenously, reduces asthma symptoms and improves lung function. Approved in 2016 for adult eosinophilic asthma, it has shown

efficacy in lung function and symptom improvement (112). Benralizumab, targeting the IL-5 receptor, not only inhibits IL-5 binding but also attracts natural killer cells, aiding in eosinophil depletion and further improving asthma control. Cleared for eosinophilic asthma in 2017, benralizumab allows dosing every eight weeks after initial monthly administration, demonstrating long-term efficacy and a reduction in corticosteroid use (113-116).

However, anti–IL-5 therapies have not yet received FDA approval for COPD treatment. Mepolizumab phase 3 trials in COPD patients with an eosinophilic phenotype did indicate a decrease in exacerbations in the METREX study but inconclusive results in the METREO trial, suggesting further research is needed to explore eosinophil roles in COPD (117). Although reslizumab has not been evaluated formally for COPD, early benralizumab trials in COPD patients with eosinophilic phenotypes yielded mixed results, warranting additional studies to clarify its benefits in COPD management (118). Newer therapeutic targets have emerged, such as interleukin-4 (IL-4) and interleukin-13 (IL-13), cytokines elevated in asthma patients. IL-4 facilitates Th2 cell development and B-cell isotype switching, while IL-13 impacts smooth airway muscle and promotes allergic responses. Dupilumab, a monoclonal antibody blocking IL-4 and IL-13, showed promising results in reducing exacerbations and improving lung function in asthma. Initial trials of IL-13-targeting antibodies, lebrikizumab and tralokinumab, demonstrated limited benefits in asthma and are currently not pursued further (119-122). These cytokine-focused therapies highlight ongoing advances in targeted asthma treatments, but further studies are necessary for COPD applications.

Biologics in Multiple Sclerosis:

A humanized IgG4 monoclonal antibody (mAb), natalizumab (NTZ) exclusively targets the vascular adhesion protein VLA-4, more especially its alpha-4 subunit, which is found on T cell membranes. Natalizumab efficiently blocks its interaction with VCAM-1, which is expressed on the surface of endothelial cells, by binding to VLA-4 (123). By stopping T cells from sticking to the endothelium and then moving into the central nervous system (CNS), this blockade lowers inflammation in this vital region. Natalizumab has been used as a second-line treatment for patients with relapsing-remitting multiple sclerosis (RRMS) since it was approved in 2006. In addition to considerably lowering MRI indications of disease activity, it has shown extraordinary efficacy, reducing recurrence rates and the buildup of impairment (124-125). Natalizumab administration carries several hazards despite its advantages. Progressive multifocal leukoencephalopathy (PML), which has an incidence rate of roughly 1 in 1,000, is one serious side effect linked to its use. The reactivation of the John Cunningham virus (JCV) causes PML, a demyelinating disorder of the central nervous system that can be deadly and destroy oligodendrocytes. JCV is unique to humans and species-specific. The virus can remain dormant in different organs since the initial infection usually happens in early childhood and is frequently asymptomatic (126-127). Individuals taking natalizumab for more than 24 months or those who have previously had immunosuppressive treatments are more likely to acquire PML (128-129). According to recent research, individuals receiving natalizumab medication may be at additional risk for PML if their blood anti-JCV antibody levels are elevated

(130). It is recommended to stop natalizumab treatment in such cases. When natalizumab is stopped, the disease activity may return to what it was before treatment. However, the immunological reconstitution inflammatory syndrome (IRIS) can cause serious clinical and radiological decline in certain patients. With a 20% fatality rate, this illness usually appears days to weeks after natalizumab therapy is stopped. Significant lymphocytic infiltration in the brain and an increased immune response to viral antigens are characteristics of IRIS, which causes damaging inflammation that affects glial cells and both healthy and infected neurons (131-132).

Clinicians may decide to stop natalizumab therapy for a number of reasons, such as insufficient efficacy, tolerability issues, or patient preferences for oral drugs, in addition to the risk of PML. However, discontinuing medication might cause a recurrence of the illness in some people, which frequently manifests more strongly than the usual relapses seen in those who have never had treatment. This occurrence, referred to as "rebound" activity, most likely results from the blood-brain barrier being more permeable, which allows activated lymphocytes from the periphery to enter the central nervous system. According to several studies, the rebound rate varies between 10% and 30% of patients and usually happens three to six months after stopping natalizumab (133). Another oral disease-modifying drug for RRMS is tingolimod (FTY720), which is categorized as a second-line treatment. In 2010, it was first approved in the United States, and in 2011, it was also approved in Europe and Japan. Sphingosine-1-phosphate (S1P), a naturally occurring phospholipid that controls several vital physiological functions such as cellular survival, cytoskeletal organization, and motility, shares structural similarities with tingolimod, a chemical derivative of myriocin obtained from the fungus Isaria sinclairii (134). S1P binds to its particular receptors (S1P1-S1P5) to produce its effects. To respond to the high levels of S1P in blood and other body fluids, for instance, S1P1 is necessary for lymphocyte egress from the thymus and secondary lymphoid organs (135). Sphingosine kinases cause fingolimod to become phosphorylated; the phosphorylated version, known as fingolimod-P, functions as an agonist on four of the five known S1P receptors, with the exception of S1P2 (134). Fingolimod-P binds to S1P1 inside lymphocytes, causing it to internalize irreversibly and preventing activated T cells from leaving secondary lymphoid organs. Thus, fingolimod therapy prevents inflammatory cells from migrating to sites of inflammation by selectively and reversibly sequestering T cells from the spleen and circulation into secondary lymphoid organs (136).

Because the chemokine receptor CCR7 is expressed, naïve T and B lymphocytes settle in peripheral lymphoid organs. The efficient migration of T and B cells via high endothelial venules (HEV) into lymph nodes depends on the interaction between CCR7 and its ligands, CCL19 and CCL21, which are expressed on HEV. CCR7 (CCR7+CD45RA-) is also expressed by central memory T cells (TCM). Fingolimod-P preserves CCR7-negative effector memory T cells (TEM), a unique subpopulation of T cells crucial for immunological surveillance, while blocking the outflow of CCR7-positive naïve T cells and TCM from lymph nodes (137). Similarly, B cells express CCR7 and S1P receptors. B cell egress from lymph nodes is dependent on S1P1. Through receptor internalization, tingolimod decreases S1P receptor expression on B cells, which may alter how B cells exit lymph nodes and the spleen. But compared to B cells, it seems to affect CD4+ T

cells more strongly (138-139). The blood-brain barrier (BBB) is easily crossed by tingolimod, which may affect CNS cell activity there. According to recent research, fingolimod may have direct effects on the central nervous system, and these non-immune processes could help stop the progression of MS (140). Since sphingosine-1-phosphate receptors are present in a wide variety of tissues, fingolimod may have negative effects on different organs and tissues (141). Headache, exhaustion, bradycardia, and atrioventricular (AV) block are the most commonly reported adverse effects; skin cancer and macular edema have also been observed (142-143). There have been reports of infections, such as disseminated herpes zoster virus infection (VZV), herpes simplex virus encephalitis, and B cell lymphoma linked to Epstein-Barr virus (EBV) infection, despite the fact that fingolimod has no effect on the function of effector memory T cells (TEM), suggesting that patients shouldn't be more susceptible to infections (144-145).

Although PML can happen to patients using fingolimod, its frequency (1:10,000) is much lower than that of natalizumab (146). Notably, during the course of two decades, widespread usage of glatiramer acetate and interferon-β has not been linked to any recorded cases of PML. Like natalizumab, stopping fingolimod can cause exacerbations in the radiological and clinical manifestations, which are linked to the emergence of immune reconstitution inflammatory syndrome (147-148). When IFN-β or glatiramer acetate treatment is ineffective for individuals with active multiple sclerosis, doctors frequently think about switching to natalizumab or fingolimod. However, other research suggests that natalizumab may be a better option than fingolimod for reducing relapse rates and short-term disability loads (149). Researchers have successfully studied novel small compounds that overcome the negative effects of fingolimod while maintaining its advantageous qualities. Ozanimod, a novel oral selective small drug that targets S1P1 and S1P5, is one intriguing possibility. Ozanimod does not require phosphorylation to function, in contrast to fingolimod. Ozanimod has a 19-hour half-life, which permits once-daily dosage and causes a dose-dependent decrease in the number of circulating lymphocytes. However, because of its short half-life, it promotes a quick recovery of lymphocytes when therapy stops. In phase II clinical studies, ozanimod was well tolerated (150), and no serious side events related to the heart, lungs, eyes, infections, or cancer were documented, including no cases of macular edema. Building on these encouraging results, phase III trials, like the RADIANCE trial, started in December 2013 and are expected to yield results in the upcoming year (150).

Apart from fingolimod, two other drugs that are taken orally have surfaced: cladribine and dimethyl fumarate (DMF). In 2013, the FDA and EMA approved dimethyl fumarate, the methyl ester of fumaric acid, for the treatment of relapse multiple sclerosis. DMF is now one of the most commonly prescribed disease-modifying drugs in both the US and Europe due to its good safety record. Memory vs naïve, conventional versus regulatory T cell subsets, and CD8+ versus CD4+ cells are all affected more by DMF's induction of apoptosis in T cells (151). DMF also affects dendritic cells, which results in less IL-12 and IL-23 being synthesized. This decrease in myeloid antigen-presenting cells therefore increases the production of the Th2 cytokine IL-4 and decreases the development of CD4+ T cells into pro-inflammatory Th1 and Th17 subtypes (151). DMF has been shown

to have a possible neuroprotective effect, which is most likely due to its influence on the nuclear factor NRF-2 in neurons, oligodendrocytes, and astrocytes. Numerous neuroprotective genes, including those involved in heme oxygenase-1 production, have been demonstrated to have their transcription facilitated by NRF-2 binding to the antioxidant response element (ARE) (151). As a short-term therapy, cladribine, a purine nucleoside analog, is given. Rapidly dividing lymphocytes are specifically targeted by its immunosuppressive qualities, which deplete T and B cells while leaving resting cells—including memory T and B cells—unaffected. Cladribine has a special mode of action that uses the depletion of adenosine triphosphate (ATP) to cause programmed cell death (151). However, patients are continuously watched for the reactivation of latent infections, especially with the JC virus, as well as other opportunistic infections, because it might cause persistent lymphopenia. The long-term ramifications of cladribine treatment are yet unknown, despite its similar efficacy to fingolimod and comparatively low incidence of treatment-related side events (151).

Conclusion

The development of biologics has significantly altered the therapeutic landscape for systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, asthma, and multiple sclerosis, offering targeted interventions that address specific immunological pathways. In SLE, while agents like belimumab and rituximab have shown moderate success, ongoing research into novel biologics such as anti-CD22 and anti-IFNα therapies could further improve treatment outcomes. In asthma, the introduction of IL-5 and IL-4 inhibitors has provided new avenues for managing severe forms of the disease, though further studies are needed to assess their role in chronic obstructive pulmonary disease (COPD). For multiple sclerosis, natalizumab demonstrates profound efficacy in managing relapsing forms of the disease, albeit with a risk of serious side effects like progressive multifocal leukoencephalopathy (PML). As our understanding of these diseases continues to evolve, personalized medicine approaches that consider individual patient profiles will be crucial in optimizing the use of biologics, minimizing adverse effects, and enhancing overall treatment efficacy. The collaboration between researchers and clinicians will be pivotal in advancing the development of these targeted therapies and addressing the unmet needs in the management of SLE, asthma, and MS.

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الملخص:

الخلفية :برزت العلاجات البيولوجية كنهج تحولي في علاج التهاب المفاصل الروماتويدي (RA) ، ومرض الأمعاء الالتهابي (IBD) ، والذئبة الحمراء (SLE) ، والربو ، والتصلب المتعدد (MS) ، من خلال معالجة الآليات الفسيولوجية المرضية الأساسية لهذه الأمراض المعقدة.

الهدف :الهدف الرئيسي من هذه المراجعة هو استكشاف العلاجات البيولوجية الرئيسية المستخدمة في علاج الذئبة الحمراء، ومرض الأمعاء الالتهابي، والتصلب المتعدد، والتهاب المفاصل الروماتويدي، والربو.

الطرق :تم جمع وتحليل بيانات محدثة باستخدام المقالات الأصلية البحثية والمقالات المراجعة.

النتائج :تستهدف العلاجات البيولوجية مثل بليموماب وريتوكسيماب خلاياB ، مما يوفر تحسينات محدودة لكنها ملحوظة في نتائج المرضى. كما أن هناك عوامل واعدة أخرى مثل إبراتوزوماب و IL-2بجرعات منخفضة قيد التحقيق، بهدف تعزيز فعالية العلاج مع تحسين السلامة. في إدارة الربو، تستهدف الأجسام المضادة أحادية النسيلة مثل أومالیزوماب ومابوليزوماب ودوبيلوماب السيتوكينات الرئيسية المشاركة في الاستجابة الالتهابية، مما يقلل بشكل كبير من حدوث النوبات ويعزز نوعية حياة المرضى. بالمثل، يمثل ناتاليزوماب تقدمًا حاسمًا في علاج التصلب المتعدد من خلال تثبيط هجرة خلايا T إلى الجهاز العصبي المركزي، مما يقلل بشكل فعال من نشاط المرض. على الرغم من فعاليتها، فإن استخدام العلاجات البيولوجية يرافقه تحديات، بما في ذلك الآثار الجانبية المحتملة والحاجة إلى استراتيجيات علاج شخصية.

الخلاصة :تظل الأبحاث والتجارب السريرية المستمرة ضرورية لتحسين هذه العلاجات وإرساء بروتوكولات العلاج المثلى للمرضى المصابين بالذئبة الحمراء والربو والتصلب المتعدد.

الكلمات المفتاحية :العلاجات البيولوجية، التهاب المفاصل الروماتويدي، الذئبة الحمراء، الربو، مرض الأمعاء الالتهابي، الاضطرابات المناعية الذاتية.