

Biologic therapies in non-rheumatic diseases: lessons for rheumatologists?

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Abstract | Biologic therapies have been licensed to treat rheumatic diseases for more than a decade. In parallel, they have gained acceptance in a variety of non-rheumatic diseases, where their impact has been no less revolutionary. In this Review, we examine the application of biologics in a number of non-rheumatic autoimmune and inflammatory disorders—psoriasis, inflammatory bowel disease, uveitis, asthma, diabetes, congestive cardiac failure and multiple sclerosis. In particular, we have sought information, or lessons, that could influence their application in rheumatic diseases. For example, we highlight the potential to stratify asthma into groups that might require different targeted approaches, and focus on some of the less common adverse events associated with biologic therapies in multiple sclerosis. Similarly, we examine type 1 diabetes mellitus in the context of potential therapeutic induction of immune tolerance. Working collaboratively, across specialties, there is significant synergy to be gained in regard to understanding how biologic therapies work, how best to use them, and the adverse effects we should be conscious of.

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Evaluate the use of biologic drugs for psoriasis.
- 2 Assess the efficacy and safety of biologic drugs in the treatment of Crohn disease.
- 3 Describe the use of biologic drugs in the treatment of asthma.
- 4 Assess the efficacy and safety of biologic drugs in the treatment of multiple sclerosis.

Introduction

More than 70 autoimmune diseases have been described. With our improved understanding of the immunological

Competing interests

J. D. Isaacs declares associations with the following companies: Abbott, Biogen Idec, GlaxoSmithKline, Pfizer, Roche, UCB. See the article online for full details of the relationships. The other authors, the journal Chief Editor J. Buckland and the CME questions author C. P. Vega declare no competing interests.

mechanisms underlying them, there has been a move away from traditional, chemically synthesized immunosuppressive drugs, such as azathioprine, to newer biologic agents derived from living cells. These 'biologics' target elements of the immune and inflammatory cascade more specifically than conventional immunosuppressives (Table 1). The apparent simplicity of this approach, however, belies significant underlying complexity in terms of the mode of action and therapeutic ratios of biologic agents.¹ In this Review, we examine their use in a variety of non-rheumatic autoimmune disorders for learning points that might be extrapolated to their use in rheumatology.

Psoriasis

Psoriasis is a chronic inflammatory skin condition that affects approximately 2–3% of the population. The commonest subtype, psoriasis vulgaris, is characterized by sharply demarcated scaly, salmon-pink plaques, with a tendency to occur on the extensor surfaces.

TNF blockade

Tumor necrosis factor (TNF) blockade has an established role in the management of psoriasis.² Two meta-analyses have attempted to indirectly compare the efficacy of biologic agents in this condition.^{3,4} The doses used can differ from those for rheumatoid arthritis (RA): etanercept can be commenced at a dose of 50 mg twice weekly for 12 weeks, and infliximab is administered at 5 mg/kg every 8 weeks. Adalimumab is used at the standard RA dosage (40 mg every other week). Using drug survival as a surrogate of efficacy, biologic registry data suggest that infliximab is inferior to etanercept in RA; however, in psoriasis—allowing for the dose variation outlined

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Key points

- Biologic therapies are increasingly used in non-rheumatic diseases
- As in rheumatic disease, biologics might provide a therapeutic option for otherwise refractory non-rheumatic disease
- These agents may also provide proof-of-concept for proposed mechanisms of immunopathology, such as IL-1 β blockade in type 2 diabetes mellitus
- In other situations their effects can be paradoxical, such as worsening of heart failure and occasional induction of psoriasis and uveitis during tumor necrosis factor blockade

Table 1 | Biologics licensed and in development for non-rheumatic diseases

Disease	Biologic agent	Mechanism of action
Psoriasis	Infliximab	Anti-TNF
	Adalimumab	Anti-TNF
	Etanercept	Neutralizes TNF
	Ustekinumab	Anti-IL-12/IL-23 (p40 subunit)
	Briakinumab (in development)	Anti-IL-12/IL-23 (p40 subunit)
Inflammatory bowel disease	Infliximab	Anti-TNF
	Adalimumab	Anti-TNF
Uveitis	Infliximab	Anti-TNF
	Adalimumab	Anti-TNF
Asthma	Omalizumab	Anti-IgE
	Mepolizumab (in development)	Anti-IL-5
Type 1 diabetes mellitus	Teplizumab (in development)	Non-activating anti-CD3
	Otelixizumab (in development)	Non-activating anti-CD3
Type 2 diabetes mellitus	Anakinra (in development)	Recombinant IL-1 receptor antagonist
Multiple sclerosis	Interferon β	Immunoregulatory
	Natalizumab	Anti- α 4 integrin
	Rituximab (in development)	B-cell depletion (anti-CD20)
	Alemtuzumab (in development)	Lymphocyte depletion (anti-CD52)

Abbreviation: TNF, tumor necrosis factor.

above—the order appears reversed. Nonetheless, both drugs, along with adalimumab, are used to treat otherwise refractory disease. Furthermore, a study from the British Society for Rheumatology Biologics Registry (BSRBR) suggests no difference in efficacy between these three anti-TNF drugs in psoriatic arthritis, although infliximab was used at the lower dose of 3 mg/kg in this instance.⁵

Also of note are several reports of TNF blockade paradoxically inducing *de novo* or worsening psoriasis. Data from the BSRBR suggest an incidence of approximately one case per 1,000 patient years of treatment, with more cases attributed to adalimumab than to etanercept or infliximab.⁶ The psoriasis generally regresses on withdrawal of anti-TNF agents and, in some instances, upon switching to an alternative anti-TNF agent. Interferon α (IFN- α) has been implicated in the pathogenesis of psoriasis, and TNF inhibits its production by plasmacytoid dendritic cells. Hence, TNF blockade may result in enhanced IFN- α production leading to psoriasis induction, demonstrating how the complexities of cytokine networks can result in unanticipated consequences of their manipulation.⁷

The accessibility of skin assists with translational research, but, as with RA, the precise pharmacodynamics

of TNF blockade in psoriasis remain elusive. For example, one study suggested a delayed proapoptotic effect of TNF blockade with etanercept, but apoptosis was not seen in another study in which skin samples were obtained shortly after infliximab therapy.^{8,9}

Ustekinumab and briakinumab

In common with RA, evidence suggests that type 17 T-helper (T_H17) cells have a role in the pathogenesis of psoriasis. In health, T_H17 cells provoke a potent inflammatory response and differentiate in response to bacterial infections. Their development in humans is driven by the combination of transforming growth factor β (TGF- β) and a proinflammatory cytokine, such as IL-1 β or IL-6.¹⁰ Their stabilization requires IL-23, which comprises two subunits: p40, which it shares with IL-12; and p19, which is unique to IL-23 (Figure 1). IL-12 is similarly important for type 1 T-helper (T_H1) cell development. In psoriatic lesions, dendritic cells and keratinocytes produce IL-23 and encourage T_H17 cell development and subsequent production of IL-17, IL-22 and IL-23 itself. In mice, IL-23 causes epidermal hyperplasia and a psoriasis-like state,¹¹ and in an animal model of psoriasis, blocking IL-22 alleviates the condition.¹²

Treatments that target IL-23 have been developed, and two agents, ustekinumab and briakinumab, target the p40 subunit. The former, a fully human IgG1 monoclonal antibody, is licensed for the treatment of moderate-to-severe plaque psoriasis that has failed to respond to conventional treatments. It was shown to be effective and safe in two large trials, PHOENIX-1 and PHOENIX-2.^{13,14} Higher dosing schedules were given to non-responders in PHOENIX-2, resulting in clinical benefits. Subsequently, a head-to-head study of ustekinumab and etanercept demonstrated superiority of ustekinumab after 12 weeks: Psoriasis Area and Severity Index 75 (PASI75; approximating to a 75% improvement in terms of surface area affected and severity of erythema, induration and desquamation) was achieved in a significantly larger proportion of patients treated with ustekinumab 45 mg and 90 mg (67% and 74%, respectively) administered at weeks 0 and 4 compared with those receiving etanercept 25 mg twice weekly (57%; $P=0.01$ and $P=0.001$, respectively).¹⁵ Perhaps surprisingly, a clinical response was seen sooner with ustekinumab, and ustekinumab recipients also took longer to flare beyond 12 weeks. Approximately 50% of patients who failed to respond to etanercept subsequently responded to ustekinumab. There was no significant difference in safety between the agents.

Briakinumab (also a fully human IgG1 monoclonal antibody) similarly targets the p40 subunit of IL-12 and IL-23. It demonstrated efficacy over 12 weeks in a phase II placebo-controlled trial of 180 patients with moderate-to-severe chronic plaque psoriasis.¹⁶ Patients received 200 mg as a single dose, 100 mg every other week for 12 weeks, 200 mg weekly for 4 weeks, 200 mg every other week for 12 weeks, 200 mg weekly for 12 weeks, or placebo. The primary outcome measure was the proportion of patients achieving PASI75 at week 12. Study medication was then discontinued for 12 weeks, during which time responders

were monitored for loss of response (PASI50). Over 90% of patients receiving more than one briakinumab dose achieved PASI75 by 12 weeks, and over 85% maintained at least a PASI50 response at 24 weeks. Adverse events associated with briakinumab included injection site reactions (16.7%) and infections (34.7%, compared with 23.3% in the placebo group), but no serious infections or cardiovascular events were reported. Four phase III studies of briakinumab have now been completed. In one of these, there were seven major adverse cardiac events (out of 1,465 participants), all in patients with cardiovascular risk factors at baseline. The licensing application for briakinumab in psoriasis is currently suspended, pending further analysis of these data.¹⁷

Overall, these data demonstrate that targeting the cytokines that drive T-helper cell differentiation can be effective in T-cell-mediated autoimmunity, although they do not inform us of whether IL-12 or IL-23 is more pathogenic in psoriasis. Figure 1 summarizes the downstream effects of IL-12 and IL-23 that are of potential relevance to RA and psoriasis.

Inflammatory bowel disease

A broad array of cytokines has been implicated in intestinal inflammation, including IL-1, 2, 6, 12, 17, 23, and TNF. TNF blockade has proved highly efficacious in inflammatory bowel disease (IBD), primarily for treatment of refractory and fistulizing Crohn's disease.^{18–22} As with psoriasis, the exact mechanism of action of TNF blockade in Crohn's disease is unclear, but there is no class effect because the fusion protein etanercept is ineffective.²³ Etanercept and the anti-TNF monoclonal antibodies differ in a number of ways, which could account for their differential efficacy in Crohn's disease. For example, etanercept neutralizes both lymphotoxin and TNF, and, although all TNF antagonists bind both soluble and membrane-bound TNF, etanercept is operationally monovalent compared to the bivalent monoclonal antibodies.²⁴ Etanercept is also a less potent inducer of complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity than the monoclonal antibodies, and it also transmits qualitatively different signals into the cell via transmembrane TNF ('inside-out' signaling).²⁵ In contrast, etanercept, infliximab and adalimumab each induce apoptosis of activated peripheral blood mononuclear cells, and apoptosis within the bowel mucosa may be an important mechanism of action of TNF blockade in Crohn's disease.^{25–27} Certolizumab pegol is a pegylated Fab fragment of a humanized anti-TNF antibody, and therefore lacks effector function; however, it remains effective in IBD.²² This agent mediates inside-out signaling to a similar degree to infliximab and adalimumab.²⁵ A reduced ability to mediate inside-out signaling could, therefore, explain the inefficacy of etanercept in patients with IBD. A recently proposed alternative hypothesis links TNF blockade efficacy in Crohn's disease to its granulomatous pathology.²⁴ Thus, etanercept has also shown inferior efficacy in Wegener's granulomatosis, sarcoidosis and some types of uveitis (see below), each of which is associated with

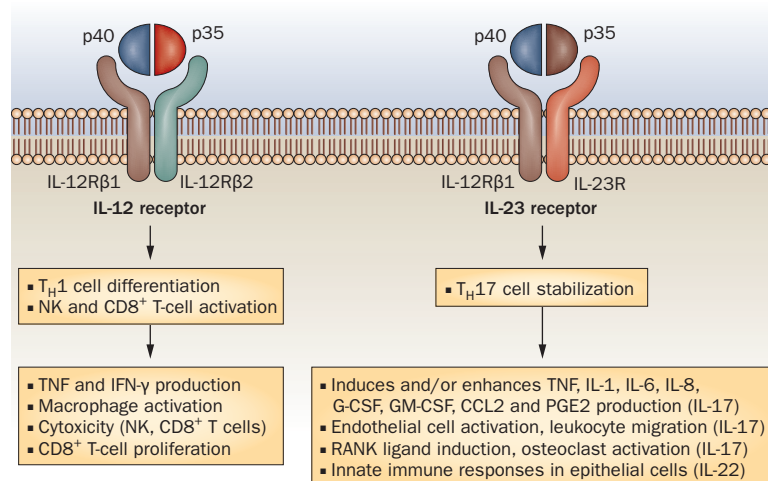


Figure 1 | The structure and function of the cytokines IL-12 and IL-23. IL-12 and IL-23 are heterodimers that share a common p40 subunit. Their downstream effects reflect the cells that express their respective receptors, which also share a common chain (IL-12Rβ1). IL-12 induces T cells to differentiate along the T_H1 pathway and also stimulates NK cells and CD8⁺ cytotoxic T cells. Its ultimate effects include macrophage activation, which is of clear importance in rheumatoid arthritis. IL-23 stabilizes T_H17 cells, leading to (via IL-17 and IL-22 secretion) proinflammatory cytokine induction, leukocyte migration (particularly polymorphonuclear leukocytes), and osteoclast and epithelial cell activation. The latter in particular might have an important role in psoriasis pathogenesis. Abbreviations: CCL2, CC-chemokine ligand 2; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN-γ, interferon γ; IL, interleukin; IL-12Rβ1, IL-12 receptor, β1 subunit; IL-12Rβ2, IL-12 receptor, β2 subunit; IL-23R, IL-23 receptor; NK, natural killer; PGE2, prostaglandin E2; RANK, receptor activator of nuclear factor κB; T_H1, type 1 T helper; T_H17, type 17 T helper; TNF, tumor necrosis factor.

granuloma formation. Etanercept is less able to disrupt granulomata, which also explains the reduced likelihood of tuberculosis reactivation with this drug.

Unlike the situation in RA, Crohn's disease is not associated with an enhanced baseline risk of infectious morbidity or lymphomas, which should simplify the risk assessment for the use of biologic drugs in this condition.²⁸ However, conventional immunosuppressants used in Crohn's disease (such as corticosteroids, azathioprine and 6-mercaptopurine) increase the risk of both infectious and malignant morbidity. Systematic reviews and meta-analyses have not detected an enhanced risk of serious infections with TNF blockade in Crohn's disease over that associated with conventional immunosuppression, apart from tuberculosis and granulomatous infections.²⁸ Nonetheless, increased incidences of malignancies in association with TNF blockade in Crohn's disease have been reported. For example, the US FDA identified 48 malignancies in children and adolescents receiving anti-TNF therapy for a variety of indications, including Crohn's disease.²⁹ Approximately 50% were lymphomas, including unusual subtypes, such as the otherwise rare hepatosplenic T-cell lymphoma. Infliximab was most commonly incriminated, in association with various prior or concurrent immunosuppressive drugs. As a consequence, the FDA mandated a specific warning on the Summary of Product Characteristics relating to these observations, although

it remains impossible to separate the risk from that of concurrent or historical immunosuppressants.³⁰ This is important, because uncertainty remains as to whether immunosuppressants enhance the efficacy of anti-TNF therapy in Crohn's disease,³¹ although they may reduce the incidence of antiglobulin responses, particularly in the case of infliximab. Immunogenicity is increased with intermittent dosing regimes, which are often used in Crohn's disease.¹

Uveitis

Uveitis is inflammation of the uveal tract, which comprises the iris, ciliary body and choroid. It is associated with a number of autoimmune diseases, including the seronegative spondyloarthropathies, juvenile idiopathic arthritis (JIA), IBD, sarcoidosis, Wegener's granulomatosis and Behçet's disease. There is evidence that TNF has a key role in the pathogenesis of uveitis. For example, in experimental autoimmune uveitis, a model in which mice are immunized against ocular proteins, anti-TNF treatment reduced end-organ damage by reducing T_H1 effector function³² and preventing NO production by macrophages.³³

TNF blockade has been used to good effect in studies of various types of uveitis, particularly in cases refractory to conventional immunosuppression. These are mostly small, noncontrolled studies and case series, but the results are promising, with complete remission rates of 71–100%.³⁴ Furthermore, in uveitis-associated conditions in which TNF blockade is licensed for use, such as ankylosing spondylitis, the rate and severity of uveitis flares is significantly reduced following its commencement.^{35,36} In JIA, TNF blockade also seems beneficial for treating uveitis.³⁷

In contrast, some reports suggest that TNF blockade might actually promote uveitis under certain circumstances, particularly with etanercept. Several case reports have highlighted new cases of uveitis occurring after the commencement of etanercept in a variety of disorders, despite control of the underlying inflammation, and an analysis of a national biologics registry supports these observations.³⁸ A population-based study estimated the prevalence of uveitis in the general population at 52 cases per 100,000 person-years, and it is conceivable that etanercept is simply the least effective anti-TNF therapy for preventing new-onset disease. However, in at least one case uveitis settled following etanercept withdrawal and recurred with rechallenge.³⁹

Without head-to-head studies, it remains difficult to directly compare different anti-TNF therapies. However, psoriasis, IBD and uveitis are overlapping seronegative disorders that frequently occur in association with one another, and it is intriguing that, unlike in RA, etanercept may be less effective (psoriasis, uveitis) or even ineffective (Crohn's disease) in these conditions, raising the possibility of a common pharmacodynamic explanation.

Asthma

The pathogenesis of asthma is incompletely understood, but certain inhaled antigens provoke a type 2 T-helper

(T_H2)-cell-deviated immune response. However, asthma has a broad definition—reversible airflow obstruction in the presence of symptoms—resulting in significant heterogeneity, with various classifications.⁴⁰ Amongst these groups there are overlaps and associations: for example, those with early-onset disease have better long-term lung function⁴¹ and carry different genetic predisposition⁴² compared to those with late-onset disease. Only one biologic drug is currently licensed for asthma (omalizumab), but the disease provides an example of how 'stratified medicine' may develop in other conditions.

Omalizumab

Omalizumab is a humanized monoclonal antibody that binds the constant region of IgE, preventing its interaction with FcεRI and FcεRII on inflammatory cells (Figure 2a).⁴³ It is licensed for use in patients with raised serum IgE levels or a positive radioallergen sorbent test, and has proven effective at reducing steroid requirements and flares of severe asthma.^{44,45} A recent randomized controlled trial demonstrated the efficacy of omalizumab in a population with uncontrolled allergic asthma and heavy exposure to allergens due to city living.⁴⁶ Because raised IgE levels are not a specific marker for allergic asthma, however, omalizumab could be more broadly effective, but robust evidence is currently lacking.

Mepolizumab

Eosinophils are important players in the pathogenesis of asthma.^{47,48} IL-5 is critical for eosinophil differentiation⁴⁹ and release into the peripheral circulation.⁵⁰ Mepolizumab, a humanized anti-IL-5 monoclonal antibody, depletes the serum, airways and sputum of eosinophils (Figure 2a).⁵¹ Despite this biological effect, early trials were disappointing in terms of outcomes such as FEV1 (forced expiratory volume in 1 s), quality of life scores, use of β₂-adrenergic agonists and airway hyper-responsiveness.^{52,53} However, not all asthmatic inflammation is eosinophilic: inflammation of the airways has been broadly subdivided into eosinophilic, neutrophilic, both or neither, and each has certain clinical associations. Eosinophilic asthma tends to be adult-onset and more symptomatic, with frequent exacerbations and persistent airflow limitation.^{54,55} In an example of 'stratified medicine', two further studies re-examined the use of mepolizumab in patients specifically with persistent eosinophilic airways inflammation despite treatment with prednisolone. In this situation, mepolizumab was effective as a steroid-sparing agent, and reduced exacerbation rates.^{56,57}

TNF blockade

The TNF axis is upregulated in refractory, corticosteroid-resistant asthma,⁵⁸ in which the airways contain more neutrophils and fewer eosinophils than in steroid-responsive asthma (Figure 2b).^{59,60} Early studies suggested a benefit of TNF blockade in corticosteroid-resistant asthma, but this was not confirmed by a larger study, in which treatment was also associated with a

greater incidence of serious adverse events (including serious infections and malignancies) compared with placebo.^{61–63} However, on post-hoc analysis of the latter study, patients with an older age of onset, bronchodilator reversibility at study entry and a history of sinusitis were more likely to respond. A prospective study would be required to confirm this suggestion. IL-17 (Figure 1 and Figure 2b) also drives neutrophilic inflammation, suggesting a further potential therapeutic target in this asthma subtype.⁶⁴

Overall, the use of biologics in asthma has not shown the same success as in RA. However, it is clear that there are distinct subtypes in both conditions that exhibit differential responsiveness to the available drugs (Figure 2). In RA, for example, rituximab is more effective in patients who test positive for rheumatoid factor or anti-CCP (cyclic citrullinated peptide) autoantibodies, although this is the only robust example of differential biologic responsiveness identified to date.⁶⁵

Type 1 diabetes mellitus

Anti-CD3 therapy for tolerance induction

Like RA, type 1 diabetes mellitus (T1DM) is also a T-cell-mediated autoimmune disease. It is characterized by destruction of insulin-secreting pancreatic islet beta cells and the requirement for insulin replacement, but there is also a pre-clinical phase characterized by progressive loss of beta cells. Prevention of beta-cell destruction and maintenance of endogenous insulin production may be achievable through the induction of immune tolerance. Anti-CD3 monoclonal antibodies were initially studied in transplant rejection, but, with the development of safer products that are less likely to provoke first-dose cytokine storms, they have been more recently studied in autoimmunity. At least in preclinical models, tolerance induction reflects the death of effector T cells followed by the induction of regulatory T cells.⁶⁶ Non-obese diabetic (NOD) mice, a murine model of T1DM, regained long-lasting normoglycemia after 5 days of treatment with anti-CD3 monoclonal antibodies, suggesting the presence of significant residual beta-cell mass at presentation of hyperglycemia. Their immune response was otherwise intact, excluding long-lived immune suppression as an explanation for this effect.⁶⁷

Two clinical trials in T1DM have studied humanized, FcγR-non-binding anti-CD3 monoclonal antibodies. The first compared 14 days of teplizumab treatment with placebo in 24 patients (aged 7–30 years) with new-onset T1DM. Disease progression, as measured by the C-peptide response (a measure of endogenous insulin secretion), was halted by teplizumab for up to 5 years.^{68–70} In the second trial, 80 patients received oteplizumab for 6 days. Active treatment preserved beta-cell function at 6, 12 and 18 months compared to placebo. Furthermore, 75% of patients with above-median beta-cell mass at baseline were clinically insulin independent at 18 months.⁷¹ After 36 months, residual beta-cell function in the treatment group was 80% higher than in the placebo group. From 24 to 48 months, mean insulin requirement increased progressively in the active treatment arm, but

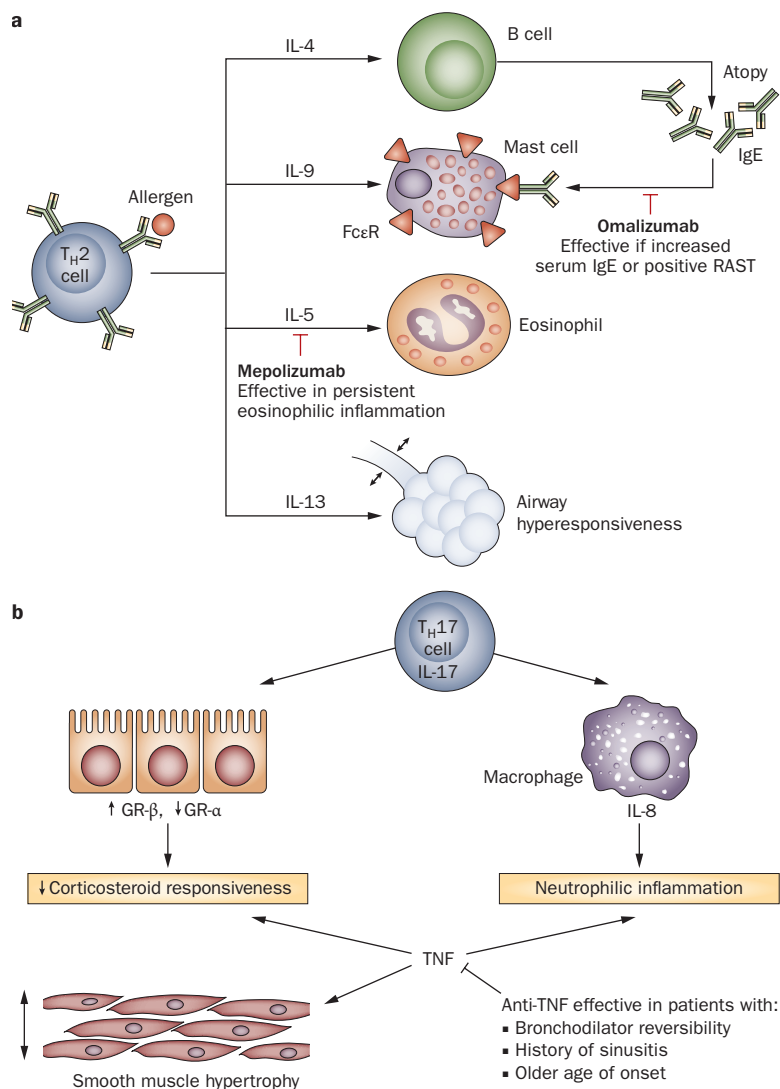


Figure 2 | Pathogenesis of asthma and the potential role of biologics. **a** | In atopic patients, the initial response to allergen results in the generation of a Th₂ immune response. On further exposure to allergen, primed Th₂ cells release cytokines such as IL-4, IL-5, IL-9 and IL-13, which drive the pathological features of asthma. Blockade of mediators such as IgE (preventing its binding to FcεR on mast cells) or IL-5 (reducing eosinophil counts) have both demonstrated efficacy in specific subtypes of asthma. Omalizumab (anti-IgE) has shown efficacy in patients with raised serum IgE levels and/or a positive RAST. Mepolizumab (anti-IL-5) has shown efficacy in steroid-refractory eosinophilic airway inflammation. **b** | Refractory asthma is a pathologically distinct entity, with features including corticosteroid hyporesponsiveness, smooth muscle hypertrophy and neutrophilic inflammation, and both IL-17 and TNF are implicated in its development. Numbers of Th₁₇ cells in the peripheral blood and levels of IL-17 and IL-8 mRNA in the sputum are increased in asthmatics in proportion to the severity of their disease. IL-17 promotes neutrophilic inflammation via the release of the chemokine IL-8 and decreases steroid responsiveness by upregulating the inhibitory corticosteroid receptor GR-β. TNF is overexpressed in refractory asthma, and has been directly implicated in many of its pathological features, including corticosteroid hyporesponsiveness, smooth muscle hypertrophy and neutrophilic inflammation. Abbreviations: GR-α, glucocorticoid receptor α; GR-β, glucocorticoid receptor β; IL, interleukin; RAST, radioallergosorbent test; Th₂, type 2 T helper; Th₁₇, type 17 T helper; TNF, tumor necrosis factor.

still remained 40–64% lower than in the placebo group.⁷² Whether re-treatment at intervals would prevent this slow disease progression remains to be studied. Apart

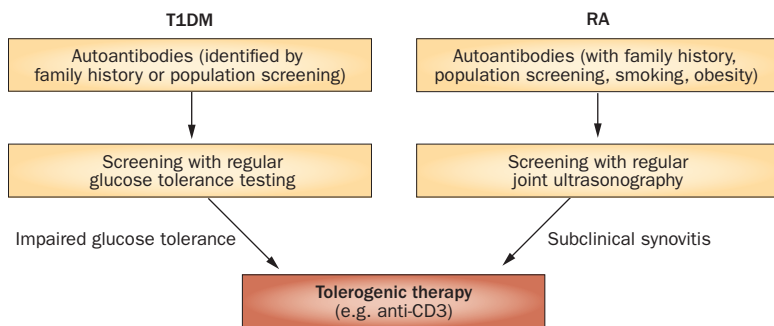


Figure 3 | The potential for tolerogenic therapy in practice. Although not yet definitively demonstrated in human autoimmunity, tolerogenic therapy is likely to be most effective in the earliest stages of disease. The heritability of T1DM is high, and relatives of patients can be screened for autoantibodies, such as anti-GAD and anti-insulin antibodies. Autoantibody-positive patients can then undergo regular glucose tolerance tests until signs of impaired glucose homeostasis are detected and tolerogenic therapy administered. Such strategies have already been adopted in phase II studies of anti-CD3 monoclonal antibodies in T1DM. RA has lower heritability than T1DM, and population screening with the use of serology and, potentially, genetic markers, especially in high-risk populations such as heavy smokers, should give a higher yield of ACPA-positive individuals than simply screening relatives. ACPA-positive patients could undergo, for example, regular joint ultrasonography until subclinical inflammation is detected, at which stage tolerogenic therapy would be administered. In both diseases, a tolerogenic therapy that is safe could theoretically be administered to autoantibody-positive patients without signs of subclinical disease in order to maximize the likelihood of tolerance induction. Abbreviations: ACPA, anti-citrullinated peptide/protein autoantibodies; GAD, glutamate decarboxylase; RA, rheumatoid arthritis; T1DM, type 1 diabetes mellitus.

from transient reactivation of Epstein–Barr virus following treatment and mild cytokine-release symptoms at the time of infusion, the therapy seems safe.⁷³

Despite these encouraging phase II data, both teplizumab and oteplizumab have recently been the subject of negative phase III studies.^{74,75} Whether these results represent an inappropriate choice of primary outcome or suboptimal dosing remains to be seen. A phase I trial of oteplizumab is currently underway in patients with established RA, although, as with T1DM, treatment is more likely to demonstrate efficacy at or before clinical disease onset (Figure 3).⁷⁶ Again, as with T1DM, it may ultimately prove possible to identify such ‘pre-RA’ patients using a combination of family history, genotyping, circulating autoantibodies and demographic factors, such as smoking history.⁷⁷

Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) occurs when beta-cell function cannot compensate for insulin resistance. In turn, hyperglycemia has adverse effects on pancreatic beta-cell function, a concept known as glucotoxicity. Hyperglycemia enhances IL-1 β secretion by beta cells, which subsequently impairs beta-cell function and induces apoptosis. In human islets, IL-1 β has been shown to inhibit insulin release and to induce Fas expression. This potential ‘vicious circle’ of hyperglycemia-induced IL-1 β secretion and beta-cell damage suggested the potential of IL-1 β as a therapeutic target in T2DM to preserve beta-cell mass and function.⁷⁸

Anakinra, a recombinant IL-1 receptor antagonist, improved glucose tolerance and insulin secretion when

administered to C57BL/6J mice fed a high-fat diet.⁷⁹ In humans, a clinical trial compared anakinra 100 mg daily for 13 weeks with placebo in patients with T2DM.⁸⁰ The primary outcome was the change in glycosylated hemoglobin level between baseline and 13 weeks, which fell significantly more in the anakinra group. Additionally, beta-cell function, as assessed by stimulated C-peptide secretion, improved with anakinra, which, apart from injection-site reactions, was well tolerated. This proof-of-concept study suggests a potential role for IL-1 β blockade in T2DM. Additional studies are underway in T2DM and T1DM.⁸¹

Congestive cardiac failure

Circulating TNF levels are raised in patients with severe congestive cardiac failure (CCF), and increase in association with progressive clinical signs and symptoms. In addition, TNF is associated with ventricular remodeling, interstitial fibrosis and cardiomyocyte apoptosis. Multiple preclinical studies have suggested a beneficial effect of anti-TNF therapy in CCF, and a phase I study suggested a benefit of etanercept in patients with heart failure in terms of both improved ejection fraction and functional outcomes.⁸² This early success was not, however, matched in later-phase trials. For example, in the ATTACH trial, 150 patients with stable, New York Heart Association (NYHA) class III or IV heart failure and ventricular ejection fraction $\leq 35\%$ were randomly assigned to receive placebo or infliximab (5 mg/kg or 10 mg/kg) at 0, 2 and 6 weeks.⁸³ The primary end point of the study was change in clinical status, assessed by a clinical composite score, which worsened in the 10 mg/kg infliximab group at both 14 and 28 weeks compared with the other two groups. This group also experienced statistically significant increases in mortality and hospitalization rates, including for worsening heart failure.

The RECOVER and RENAISSANCE studies also demonstrated a lack of efficacy of TNF blockade in heart failure.⁸⁴ These double-blind, randomized, placebo-controlled multicenter clinical trials studied patients with NYHA class II–IV heart failure and a left ventricular ejection fraction $\leq 30\%$. The trials differed only in etanercept dose: in RECOVER, the patients were randomized to placebo or etanercept 25 mg subcutaneously once or twice weekly, whereas in RENAISSANCE, patients received etanercept 25 mg twice or thrice weekly. The primary end point for each study was change in clinical status up to 24 weeks, but both were terminated prematurely due to a lack of benefit of active treatment. In RENAISSANCE, a higher proportion of patients receiving etanercept twice weekly had symptomatic deterioration compared with placebo. However, there was no increase in mortality or hospitalization due to chronic heart failure in a prespecified, combined analysis of patients from both trials receiving etanercept twice or thrice weekly compared to placebo (the RENEWAL study).

Thus, despite the evidence from preclinical studies and our knowledge of TNF pathophysiology, TNF blockade showed no benefit in phase III trials in CCF,

with a suggestion that treatment even resulted in clinical deterioration. Whether this paradoxical outcome reflects the characteristics of patients recruited to the large-scale trials (entry criteria allowed NYHA class IV heart failure compared to a maximum of class III in the smaller studies), inappropriate dosing of anti-TNF treatment, or simply a poor understanding of cytokine networks in heart failure, has not been resolved. However, the data are reminiscent of those in multiple sclerosis (MS) trials in which TNF blockade also led to paradoxical worsening of symptoms. The results of these studies have limited the prescribing of anti-TNF agents to patients with inflammatory disease and coexisting heart failure, although one analysis suggests that the net effect of TNF blockade in RA patients with coexisting heart failure is more likely to be beneficial than harmful.⁸⁵

Multiple sclerosis

MS is a chronic demyelinating disease of the central nervous system (CNS). The majority of patients present initially with relapsing-remitting MS (RRMS), characterized by inflammation and occasional demyelinating events. In contrast, progressive MS is distinguished by marked demyelination and neurodegeneration. Most therapies are directed towards RRMS, although effective treatments have proved more elusive than in RA, and some therapies used in other autoimmune conditions have not transferred successfully to MS. For example, as with heart failure, TNF blockade was associated with worsening of existing demyelination as well as development of *de novo* demyelination,¹ which may reflect disordered repair of spontaneous demyelination events.⁸⁶

IFN- β and glatiramer acetate

Both IFN- β and glatiramer acetate have been used in the treatment of MS for over 10 years. There are two licensed forms of IFN- β : IFN- β 1a and IFN- β 1b. Their precise modes of action is unclear, but IFN- β has multiple immunomodulatory effects, reduces the relapse rate (by about a third) and slows disability.⁸⁷ Glatiramer acetate is a random polymer of glutamic acid, lysine, alanine and tyrosine that may deviate the anti-self immune response towards a T_H2 phenotype by binding to MHC class II molecules.⁸⁸

Natalizumab

The most recently licensed biologic agent for use in MS is natalizumab, a humanized monoclonal antibody against the α 4 integrin chain that inhibits the adhesion of activated lymphocytes to endothelium. In the 2-year AFFIRM study, natalizumab monotherapy significantly reduced the risk of disability progression and increased the proportion of patients who were free of disease activity according to clinical, radiological and combined criteria.⁸⁹

The serious and usually fatal brain condition, progressive multifocal leucoencephalopathy (PML), has occurred in three clinical trial patients receiving natalizumab. Two were in the RRMS SENTINEL study, which compared the combination of natalizumab and IFN- β 1a

Box 1 | Lessons learnt from biologic use in non-rheumatic diseases

- The pharmacodynamics of most biologics is incompletely understood; for example, etanercept is ineffective in Crohn's disease, whereas other anti-tumor necrosis factor (TNF) drugs are highly potent.
- Cytokines are pleiotropic and may have distinct acute and chronic effects, potentially explaining unexpected adverse events such as demyelination and exacerbation of heart failure with TNF blockade.
- Induction of immune tolerance may be achievable in the early stages of autoimmunity, particularly in preclinical disease.
- Biologic therapies have occasionally been associated with reactivation of latent viruses such as Epstein-Barr virus and JC virus. This may be inseparable from their mode of action, and highlights the need for careful post-marketing surveillance.
- Many inflammatory diseases exist as several phenotypes, which respond differently to therapy. As highlighted by asthma studies, it is essential to identify and consider these factors during clinical trial design in order to advance the field of stratified medicine, which is currently in its infancy.
- Potent immune modulators may trigger compensatory immune mechanisms, leading to previously rare adverse effects such as secondary autoimmunity following alemtuzumab therapy in multiple sclerosis.

with IFN- β 1a alone, and the other in a clinical trial of natalizumab in Crohn's disease. The patient with Crohn's disease was also lymphopenic and had received prior immunosuppressants, including anti-TNF agents.^{90–92} PML is caused by reactivation of JC virus, usually in patients who receive intense immunosuppressive therapy or who are immunosuppressed for other reasons, such as HIV infection. This leads to infection of glial cells and expanding demyelinating white-matter CNS lesions. Presenting symptoms include cognitive dysfunction, sensorimotor abnormalities, incoordination and visual defects, with rapid progression over a number of weeks. MRI changes are characteristic, but diagnosis rests upon molecular identification of JC virus in brain biopsy tissue or cerebrospinal fluid (CSF). Natalizumab was withdrawn from the US market in response to these initial reports, but after reappraisal of efficacy and safety data it was reintroduced, with restrictions, notwithstanding a PML incidence of 1 per 1,000 patients treated. Requirements included surveillance for PML, including annual MRI, its use as monotherapy only, and a reassessment of the risk-to-benefit ratio after 2 years of therapy.⁹³

Asymptomatic infection with JC virus is thought to occur in childhood, and it subsequently remains latent in the kidneys, bone marrow and lymphoid tissues. Reactivation occurs with immunosuppression; factors essential for viral replication are present in tonsillar stromal cells, some CD20⁺ B cells and CD34⁺ hematopoietic progenitor cells.⁹⁴ Natalizumab enhances the egress of both hematopoietic progenitor cells and pre-B cells from bone marrow into the circulation. It also upregulates transcription factors important for B-cell differentiation and activation, potentially predisposing to JC viremia, from where the virus may enter the CNS.⁹⁵ As a result of the reduced immune surveillance in the brain (lower numbers of lymphocytes have been noted in the CSF following natalizumab treatment), the JC virus can then infect oligodendrocytes and cause clinical PML. There are no effective therapies for PML in association

with biologic therapy, although plasmapheresis can be used to accelerate drug clearance.⁹⁶ However, rapid immune recovery predisposes to immune reconstitution inflammatory syndrome (IRIS), with temporary worsening of symptoms.⁹⁷

PML has also been reported in patients receiving rituximab for RA and other conditions.⁹⁸ In most RA cases, the patients had previously or concurrently received additional immunosuppression, although in one case no other drugs were implicated. To date there have been six reported cases of PML in RA patients receiving rituximab—an incidence of approximately 1 in 25,000 patients treated.⁹⁹ The link between PML and rituximab therapy remains uncertain. However, cytotoxic lymphocytes are essential for viral elimination, and B-cell depletion might reduce antigen presentation in the CNS.^{95,97} The occurrence of PML during treatment with biologic agents highlights the need for close monitoring of patients receiving these therapies for rare adverse effects during and after the completion of clinical trials. There is currently no validated test that anticipates productive JC virus infection, although monitoring of blood and urine during immunosuppressive therapy may help to detect asymptomatic reactivation.¹⁰⁰

Lymphocyte depletion

B-cell depletion with rituximab is currently being investigated in MS. In a phase II trial, a single course of rituximab reduced clinical relapses and gadolinium-enhancing MRI brain lesions over a 48 week period compared with placebo. Corticosteroid prophylaxis was not given, and first-dose infusion reactions were the main adverse event associated with rituximab therapy.¹⁰¹

Lymphocyte depletion with alemtuzumab is currently undergoing phase III trials in MS. This anti-CD52 monoclonal antibody demonstrated superior efficacy to IFN- β in a head-to-head trial, but its use has sometimes been associated with the development of secondary autoimmunity.^{102,103} This has most commonly manifested as thyroid autoimmunity, but more serious developments have included idiopathic thrombocytopenic purpura and Goodpasture's syndrome. A possible explanation for this phenomenon is dysregulated immune homeostasis, which describes the attempt by residual lymphocytes to

expand into the depleted lymphocyte compartment left by therapy. Such proliferation occurs on self MHC molecules, which may enhance the risk of autoimmunity.¹⁰⁴ Elegant *ex vivo* work has suggested that the strength of the stimulus to immune homeostasis may predict the likelihood of secondary autoimmunity and, furthermore, that serum IL-21 levels before alemtuzumab therapy might prove a useful predictive biomarker.¹⁰⁵ This work demonstrates the potency of biologic therapies and how they might trigger compensatory immune mechanisms to provoke adverse events that are rarely seen with conventional drugs.

Conclusions

The use of biologic therapies in non-rheumatic disorders offers potential insights to their use in rheumatological disease (Box 1). For example, the lack of a class effect for TNF blockade in IBD and its lack of efficacy in MS and CCF demonstrates the paradoxical complexity of these therapies and their targets. As we understand more about the mechanisms of action of biologic agents, this will, in parallel, provide greater insights into disease pathogenesis, which in turn will facilitate trial design, particularly in terms of patient stratification and personalized medicines. In the medium term, the induction of therapeutic tolerance may avoid the constraints of non-specific immunosuppression, but this will not reduce the importance of close post-marketing surveillance and registries to monitor the potential, and sometimes unexpected, adverse effects of newer therapies.

Review criteria

Ovid and MEDLINE databases were searched for papers published from 1996 to the present day. Search terms included “biologics”, “rheumatoid arthritis”, “monoclonal antibodies”, “anti-TNF”, “inflammatory bowel disease”, “Crohn's disease”, “ulcerative colitis”, “psoriasis”, “cardiac failure”, “multiple sclerosis”, “asthma”, “type 1 diabetes”, “type 2 diabetes”, “uveitis”, “anti-CD3”, “IL-1Ra”, “alemtuzumab”, “progressive multifocal leukoencephalopathy”, “rituximab”, “IL-17” and “IL-23”. Selected papers were published in English, and included full-text articles and abstracts.

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Author contributions

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