

Reviews

Biologics: a new weapon in the war against autoimmune joint disease

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Abstract

Autoimmune joint diseases occur due to uncontrolled abnormal immune responses (autoimmunity). The commonest autoimmune diseases seen in clinical practice are rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and un-differentiated arthritis. These are a source of significant morbidity and some mortality within the population. Non-biologic disease modifying anti-rheumatic drugs (Non-biologic DMARD's) commonly used in the treatment of these disorders include: methotrexate, sulphasalazine, leflunomide, hydroxychloroquine and gold. However, a significant proportion of patients do not show adequate responses to these agents. The last few years has seen the introduction of a class of drugs directed at specific patho-physiological abnormalities identified in these diseases. These drugs have not only brought the promise of better response rates but also the possibility of a cure for some patients. These agents are called biologic disease modifying anti-rheumatic drugs (biologic-DMARDs). Biologic-DMARDs show better response rates and appear to be well tolerated by patients. Currently, the biologic-DMARDs are mainly used in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthropathy. The currently approved biologics for autoimmune diseases are: TNF alpha antagonists (Infliximab, Etanercept, Adalimumab, and Golimumab), IL-1 antagonists (Anakinra), anti CD-20 antibodies (Rituximab), IL-6 antagonists (Tocilizumab) and the T-cell inhibitor (Abatacept). Recently, increased rates of infection have been reported and the long-term safety profiles of the biologic-DMARDs are still unknown. Due to these problems coupled with

the prohibitive costs, the exact place of these agents within treatment algorithms is still been defined. In many developed countries these agents are now included in the management with provision of specific guidance on when and how to use them. Our review outlines important pharmacological and clinical aspects of these agents in the treatment of autoimmune joint diseases.

Introduction

Autoimmune joint diseases with the exception of rheumatoid arthritis (RA) are rare but collectively affect around 5% of the population in western countries¹. These diseases are conventionally managed using non-biologic disease modifying anti-rheumatic drugs (non-biologic DMARDs), which include methotrexate, sulphasalazine, hydroxychloroquine and leflunomide in conjunction with corticosteroids and NSAID's. Other immunosuppressants such as azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil are used occasionally. These agents have the dual disadvantage of acting non-specifically on the immune cascade as well as affecting other cells (some of which play important roles within the protective immune system). This results in their main side effects, which include infections, liver dysfunction, cytopenias and damage to various other organs. Additionally, treatment with corticosteroids and NSAID's leads to increased morbidity and mortality. Trial data shows that around 50% of patients fail to achieve disease remission². Because of these factors, there was a pressing need for more effective drugs for effective control of these diseases. Addressing this need, the first biologics appeared in the 1990's. Many randomized controlled trials in RA and other diseases show significantly greater response rates with the biologics when compared to conventional therapies³⁻⁵.

Compared to traditional drugs these drugs are created by biological processes such as recombinant DNA technologies. They generally exhibit high molecular complexity and are usually monoclonal antibodies or fusion proteins (receptors bound to immunoglobulins). They can be made specifically to counteract or block any given substance in the body or to target any specific cell type. Biologic-DMARD's specifically target selected harmful cells and molecules in the cascade of events involved in autoimmunity.

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Biologics used in autoimmune diseases

Biologics have had a profound impact on several areas of medicine. In rheumatology, biologics are mainly used in RA, ankylosing spondylitis (AS), and psoriatic arthropathy (PsA). Of the autoimmune diseases, biologics have mainly been used in RA and most of the trial data are from use in RA. Table 1 illustrates the commonly used biologics in autoimmune joint diseases⁴.

Rheumatoid arthritis: the prototypical autoimmune disease

In autoimmune disorders, B and/or T cell over-activity continues in the absence of ongoing infections or other discernible causes. This leads to activation of different elements within the immune system, leading to the release a 'slew of immune mediators' that could result in target organ damage. The immune response seen in RA and the sites of action of different biologic-DMARDs are shown in Figure 1.

Autoimmunity is triggered by antigens which can be endogenous or exogenous⁶. Antigens bind to toll like receptors (TLR) on dendritic cells and macrophages. These cells then act as antigen presenting cells (APC) to activate T-cells. For a T cell to be activated by an APC, two distinct signals are needed⁷. Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) is a negative regulator in this process and its action is mimicked by abatacept (an immunoglobulin to CTLA4), one of the biologic-DMARD's. T-cells secrete cytokines,

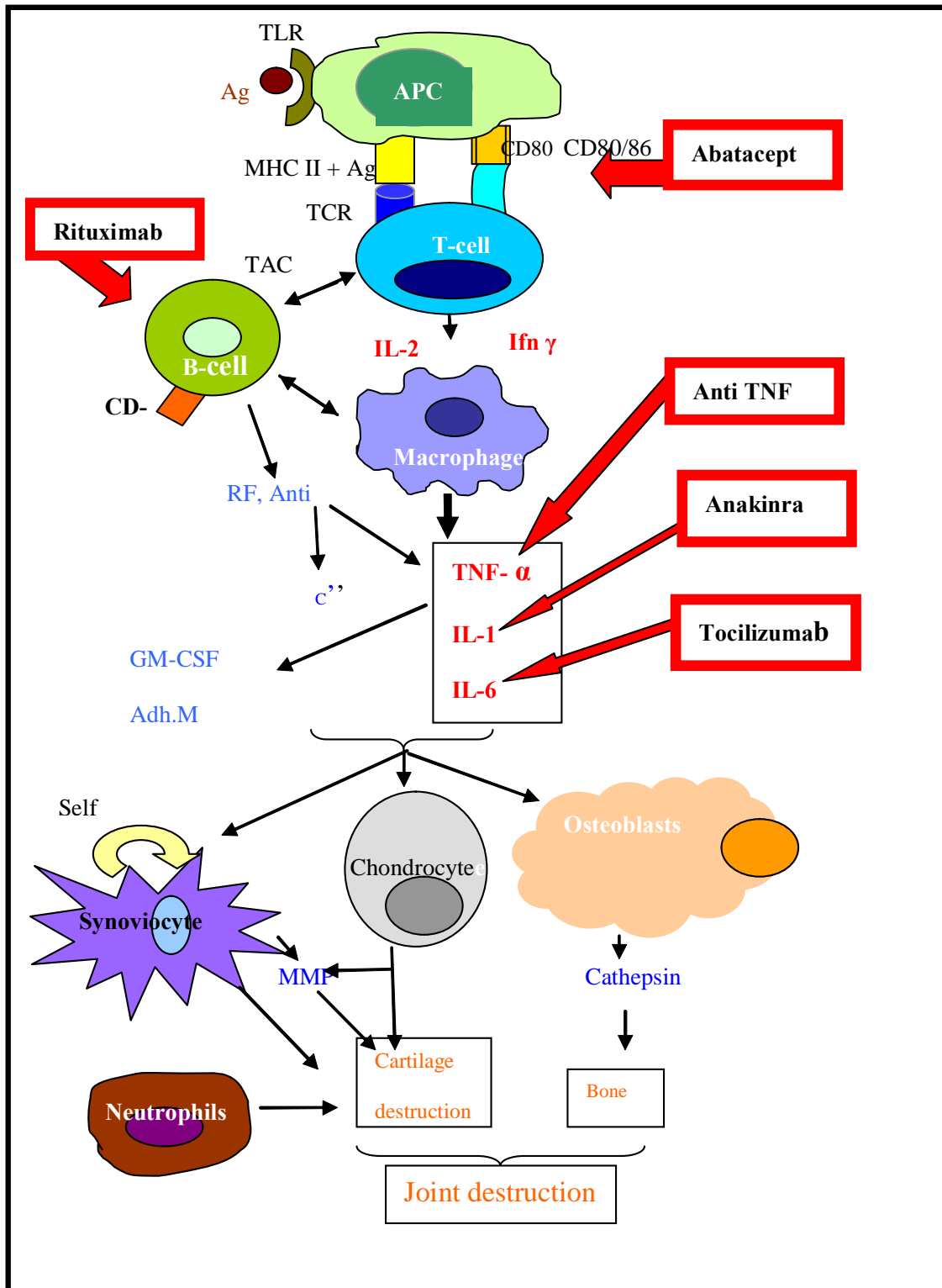
the most important of which are tumor necrosis factor- α (TNF- α), interleukin-1 and interleukin-6. These three cytokines are also the most important cytokines in RA and have been targeted using monoclonal antibodies (Anti-TNF agents, Anakinra and Tocilizumab) as therapy for RA. B-cells are involved in three important roles: antibody production, antigen presentation and cytokine secretion⁸. B-cell depletion using rituximab has proven to be a very effective therapy⁹. B-cell activity also depends on certain cytokines such as BAFF (B-cell activation factor) and APRIL (a proliferation-inducing ligand). Osteoclast activation causes erosions and damage to bones. Osteoclasts need RANKL (Receptor Activator for Nuclear Factor κ B Ligand) interaction with RANK on its surface for its function and survival. Osteoprotegerin (OPG) is the natural inhibitor of this reaction and therapy with OPG may be a future therapeutic direction and is been currently being investigated in the treatment of osteoporosis.

The cells and mediators initially present may change over time; this has important clinical implications in that treatments used initially may not be useful later and vice versa. Although the pathogenic mechanisms between diseases may be broadly similar, important differences could be exploited and prove important in selecting appropriate and targeted treatment options. For example TNF agents will not work in SLE. Even in RA, some persons respond differently to various drugs, and this may be due to the varying immune response that occurs in different individuals.

Table 1. Summary of commonly used biologics mode of action and indications

<i>Biologic</i>	<i>Action</i>	<i>Diseases drug used</i>
Infliximab	TNF depletion	Rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohns
Etanercept	TNF depletion	RA, PsA, AS, juvenile idiopathic arthritis (JIA)
Adalimumab	TNF depletion	RA, PsA, AS, JIA, Crohns
Golimumab	TNF depletion	RA, PsA, AS
Rituximab	B-cell depletion	RA, SLE, Wegeners, dermatomyositis, polymyositis, immune thrombocytopenic purpura (ITP)
Abatacept	T-cell deactivation	RA
Anakinra	IL-1 antagonist	Adult onset stills disease, periodic fever, JIA
Tocilizumab	IL-6 antagonist	RA, JIA, Castleman's and Crohns

Figure 1. Immune reaction in RA along with biologic action



APC=Antigen presenting cells, TLR=toll like receptors, TcR=T-cell receptor, Ag=antigen, Ifn=interferon, MMP=matrix metalloproteinases, GM-CSF=granulocyte-monocyte colony-stimulating factor, Adhesion molecules -AM, Chemokines=Chm, BCR=B-cell receptor TACI=transmembrane activator and calcium-modulator and cytophilinligand interactor BlyS= B-lymphocyte stimulator, c'=complement, RANKL=RANK- ligand, C'=Complement.

Biologic use in autoimmune joint diseases

Biologics are mainly used in Rheumatoid arthritis, ankylosing spondylitis and psoriatic arthropathy. As described in Figure 1 they act at various places in the immune system. Contraindications for using all classes of biologics are active infections, congestive heart failure, pregnancy and breast feeding¹⁰⁻¹². Malignancies appear to be increased in RA, however there appears to be no additional increased risk in RA patients treated with biologics^{13,14}. Infusion and injection site reactions are the commonest side effects. There is an increased risk of infections with all biologics. Table 2 gives the various biologics along with their dosing regimens and side effects and contraindications which are not common to all biologics.

Tumor necrosing factor alpha (TNF-α) inhibition

The cytokine TNF-α plays a key role in the immune reaction in RA, AS and psoriasis. Four TNF-α inhibitors are available for clinical use and these are infliximab, adalimumab, etanercept¹⁵ and golimumab¹⁶. infliximab is available in Sri Lanka. Other contraindications are latent (untreated) tuberculosis. Screening for TB must be done according to local recom-

mendations. Any patient with features suggestive of TB will need specialist advice regarding anti-TNF treatment. Development of human anti-chimeric antibodies (HACA) to infliximab may decrease its efficacy while increasing the side effect profile¹⁰. Development of anti-nuclear antibodies (ANA)¹⁷ and anti-cardiolipin antibodies have been reported and so has the development of systemic lupus erythematosus (SLE), lupus like syndromes, vasculitis and interstitial lung diseases¹⁸. Patients have also developed demyelinating diseases like optic neuritis, transverse myelitis and multiple sclerosis¹⁹. These patients have reportedly improved after stopping anti-TNF agents and commencing steroids¹⁹.

In RA, TNF-α inhibitors have been used since the 1998. The National Institute of Clinical Excellence (NICE) guidelines in the UK and American College of Rheumatology guidelines⁴ recommend the use of a TNF-α inhibitor in patients with active RA not responding to at least 2 standard DMARD's including methotrexate. Use of anti TNF agents is also recommended in early RA with severe disease and poor prognostic features⁴. In treatment failures switching to another TNF-α inhibitor or another biologic is recommended²⁰⁻²².

Table 2. Summary of modes of administration, side effects and contraindications of commonly used biologics

	<i>Mode</i>	<i>Frequency and duration</i>	<i>Other side effects</i>	<i>Other contraindications</i>
Infliximab	I.V	0, 2 weeks then 4-6 weekly	Opportunistic infections, SLE, lupus like syndromes, vasculitis and interstitial lung diseases Demyelinating diseases	Latent TB, demyelinating disease
Etanercept	s.c	Twice weekly or weekly		
Adalimumab	s.c	Every 2 weeks		
Golimumab	s.c	Every 4 weeks		
Rituximab	I.V	0, 2 weeks then every 6 months	Progressive multifocal leukoencephalopathy	
Abatacept	I.V	0, 2 weeks then 4 weekly infusions		latent TB
Tocilizumab	I.V	Every 4 weeks	Increased LDL and liver enzyme levels and decreased cell counts	latent TB
Anakinra	s.c	Daily		

I.V= Intravenous, s.c=subcutaneous

The doses and frequency may vary depending on disease treated and response to treatment.

Duration of treatment is still not agreed upon and will depend on response and costs.

TNF- α inhibitors are used in psoriatic arthropathy, psoriasis²³, Juvenile idiopathic arthritis and arthropathy associated with Crohn's disease. In ankylosing spondylitis (AS) they are now recommended as second line therapy after NSAIDs²⁴.

Interleukin - 1 (IL- 1) antagonism with anakinra

Anakinra must be given daily in high doses¹⁰ and data suggests that it was less efficacious than other biologics²⁵. Because of this, it is not commonly used in RA. Anakinra appears to be effective in adult onset stills disease, juvenile idiopathic arthritis as well as in periodic fever syndromes. It is being investigated as a treatment for osteoarthritis¹⁰.

Interleukin - 6 (IL-6) inhibition with tocilizumab

Tocilizumab is a humanized monoclonal antibody directed against the IL-6 receptor complex. It has proven efficacy in RA²⁶. Skin eruptions, neutropenia, altered liver functions and transient elevation of cholesterol are reported²⁶. It is also reported to be effective in JIA, Castleman's disease and Crohn's disease²⁷.

B cell therapies

There are several methods for interfering with B-cell function. Rituximab is an anti-CD20 monoclonal antibody that depletes B-cells in their intermediate-stages. Rituximab was first licensed for use in non-Hodgkin's lymphoma (NHL) and has been used in more than 700,000 patients²⁸. The other main area of use for rituximab is in RA. Several randomized controlled clinical trials (RCT) have proven its efficacy in patients not responding to standard DMARD's as well as TNF blockers²⁰⁻²². Currently rituximab is licensed to be used in combination with methotrexate in patients with moderate to severe RA who have not responded to one or more TNF agents⁴. Rituximab is available in Sri Lanka. After 24 weeks the effect reduces in some patients and repeat infusions may be needed.

There is no mention of increased TB risk in Rituximab treated patients in oncology literature²⁹. Rare

cases of progressive multifocal leukoencephalopathy (PML) were reported in SLE patients treated with rituximab¹⁰. Rituximab has also been used in SLE³⁰, dermatomyositis, polymyositis, immune thrombocytopenic purpura (ITP)³¹, Wegener's granulomatosis³² and type II mixed cryoglobulinemia³³.

T cell costimulation inhibition with abatacept

Abatacept (CTLA4-Ig) is a recombinant fusion protein that inhibits T-cell stimulation by APC³⁴. RA patients not responding to methotrexate and anti-TNF agents have shown clinically significant responses to abatacept^{35,36}. Abatacept is recommended in patients with moderate to severe RA having inadequate responses to one or more DMARD's or to anti-TNF therapies¹⁰.

Biologics used for other indications

Some biologic agents already registered for use in oncology and other diseases may in future be used for treating autoimmune diseases. The details of these agents are shown in Table 3.

There are many other biological agents under investigation in laboratories worldwide. Some new agents inhibit B-cell activation (e.g Belimumab³⁷ and atacicept (immunoglobulin against TACI)³⁸). Recently, The Arthritis Advisory Committee of the US Food and Drug Administration recommended an approval for Benlysta (belimumab) for treatment of autoantibody-positive patients with active systemic lupus erythematosus. They thought the medication was effective in relieving lupus disease flares and that it was safe (despite a slight rise in deaths and suicides among those on the drug compared to placebo). The primary end-points were met in the two BLISS (-52 and -76) trials³⁹. Furthermore, several new Anti-TNF agents including certolizumab (CDP-870)⁴⁰ are in the pipeline. Other agents undergoing trials are denosumab⁴¹, Anti IL-17, Iatruculin A⁴² and drugs targeting the toll like receptors (MD-2, CD-36). Details of these agents are shown in Table 4.

Table 3. Summary of biologics mode used in other diseases

<i>Drug</i>	<i>Target</i>	<i>Action</i>	<i>Current use</i>
Epratuzumab	anti-CD22	B-cell depletion	Lymphoma
Alefacept	CD2	Memory effector T cells	Psoriasis
Efalizumab	CD11A	Inhibiting T-cell activation	Psoriasis
Trastuzumab	HER2 receptor	HER2 antagonist	Breast cancer
Denileukin diftitox	Interleukin-2 receptor	Inhibition Il-2 activity	Cutaneous T-cell lymphoma (CTCL)

Table 4. Summary of biologics currently being investigated

<i>Drug</i>	<i>Action</i>	<i>Current status</i>	<i>Future use</i>
Atacicept	B-cell	Phase II	SLE, MS
Certolizumab	Anti-TNF	Phase III (Precise, RAPID)	Same as other TNF agents
Denosumab	Osteoclasts RANKL-RANK interaction	-	RA, osteoporosis
Anti-IL-17 mAb	IL-17	Early-phase trials	RA, Crohns
Latrunculin A	Synoviocytes	-	RA
Ustekinumab	IL 12/23 inhibition	Phase II	Psoriatic arthritis
JAK3 Inhibitor	Signaling molecules	Phase 2	RA

Mab=monoclonal antibody, RA=Rheumatoid arthritis, MS=Multiple sclerosis

Conclusion

The first line of treatment for RA are the non-biologic DMARD's. In treatment failures, biologic-DMARDS (TNF inhibitors, rituximab, abatacept) come into consideration. In the case of biologic-DMARD treatment failures, one could switch to another class of biologics. Although head to head trials comparing biologics are still not available, available data points to all agents been equally efficacious. The role of biologics in early RA (less than 3 months) is not well established.

In the near future, patients with autoimmune disease may receive customized treatment (Biologics and DMARD's) depending on their genetic and immune makeup, thus improving patient outcomes and reducing long term costs. We may also see the development of the ideal biologic which would be cheap, safe, efficacious and administered orally. However, at the present juncture biologics continue to be costly and there are worries regarding infections and several unknowns about their long term safety profile especially in relation to its risk of malignancies. We are practicing medicine in an age of new discoveries and treatments, but each of these come with its own downsides such as increased cost and new adverse events. We should thus strive towards optimizing our clinical management with the first line treatment regimens and reserve these new marvels for the select few who really need them and would show the most benefit.

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