Overview of biologic therapies in autoimmune rheumatic diseases

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Abstract

First-line treatment of autoimmune rheumatic diseases (ARD) ranging from systemic lupus erythematosus (SLE), through small and large vessel vasculitides to Behçet's syndrome, is still based upon the use of traditional immunosuppressive drugs. Increasingly, the newly developed biologic agents are used as second-line treatments of these diseases. This summary article highlights the biologic agents that are used in clinical practice as well as their indications, contraindications and adverse effect profiles. Efficacy of these biologic agents is tabulated in accordance with current evidence of open-label studies and trials, and new advances in the biologic treatment of several ARDs are also discussed. Overall, this paper highlights the contribution that the biologic therapies have made to progressive advancements in the treatment of ARD.

Keywords Anti-TNF; autoimmune rheumatic diseases; biologic agents; efficacy

Background information

Advances in molecular biology have led to a number of new treatment approaches for autoimmune rheumatic diseases. These agents, termed biologic therapies, are engineered recombinant proteins. Most commonly, they are either monoclonal antibodies or engineered receptor-blocking proteins. Some of the monoclonal antibodies in clinical use contain sequences of mouse protein (termed chimeric), whereas others are fully human antibodies. The theoretical advantage of these agents is that they target specific cytokines, receptors or cell types thought to be involved in the pathogenesis of the diseases in question. The major biologic approaches in clinical use include blocking cytokines (e.g. infliximab) and cytokine receptors (e.g. etanercept), interfering with T cell co-stimulation (e.g. abetacept), or depleting cell types (e.g. rituximab) (Table 1).

The place of biologic agents in the management of autoimmune rheumatic diseases, such as systemic lupus erythematosus (SLE) has not yet been fully defined. In this era of cost constraints there is a need to demonstrate improved efficacy and/or a favourable adverse event profile compared with the use of traditional immunosuppressive agents such as corticosteroids, cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate and others. In many cases, biologic agents are used alongside traditional immunosuppression, or in cases where conventional therapy has failed. However, there is no doubt that these agents provide additional treatment options for our patients. Table 2 lists the current evidence base for the use of common biologic agents in autoimmune rheumatic diseases.

The management strategies for individual diseases are discussed in more detail in the individual disease chapters. Here we discuss the general advantages and disadvantages of biologic agents, and we discuss some of the major pathways targeted.

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Advantages and disadvantages of biologic agents

Advantages of biologic therapy include effectiveness both in terms of disease control and financial cost in the long term. They also do not have to be withdrawn in the pre-pregnancy phase, unlike methotrexate, or require a washout period, as does leflunomide. This said, there is inconclusive evidence regarding the safety of these drugs in pregnancy.

Despite the advantages of anti-tumour necrosis factor (TNF) therapy, there are some disadvantages including allergic/transfusion reaction, infection, particularly with *Mycobacterium tuberculosis* (which will occur within first 6 months), lymphoma, drug-induced SLE, new-onset or exacerbation of heart failure, and demyelination. It is also important to screen patients for hepatitis B and C infections as reactivation of disease may occur when the patient is immunosuppressed. This screening is particularly important as a prelude to anti-TNF therapy because TNF is important for viral clearance.[3] Rituximab has a very similar adverse effect profile to anti-TNF therapy but the risk of infections is lower; it may also be used in patients who have had previous malignancy, whereas anti-TNF therapy is not recommended unless the patient has been cancer free for 10 years. A rare but significant risk of rituximab is the development of JC virus infection, which causes progressive multifocal leucoencephalopathy.[4] An ongoing problem in both drug classes is the formation of antibodies to the drugs, such as human anti-chimeric antibodies (HACA; incidence 10%)[5] or human antimouse antibodies (HAMA; seen with etanercept/adalimumab; incidence 5%).[6] Concomitant treatment with methotrexate decreases the appearance of antibodies.[7]

Targets of biologic agents

Examples of anti-cytokine approaches

TNFα: TNFα is a cytokine that is released by macrophages, mast cells and T-helper 1 cells. TNFα stimulates macrophages to further release cytokines and increase phagocytosis. Anti-TNF agents therefore bind to TNF, neutralizing the pro-inflammatory cytokine effect.

Interleukin (IL)-1 blockade: The IL-1 family is a group of 11 cytokines that induces a complex network of pro-inflammatory cytokines and, by means of an expression of integrins on leukocytes and endothelial cells, regulates and initiates inflammatory responses, notably during the early phases of an immune response. Blocking IL-1 has clear potential in autoimmune rheumatic diseases, but in reality hopes that such blockade would provide a major breakthrough in the treatment of RA have not been sustained. This approach has been more successful in the inherited 'fever syndromes', also known as auto-inflammatory conditions.

An overview of the biologic therapies approved for clinical use, in autoimmune rheumatic diseases[1,2]

Biologic	Target	Clinical indication	NICE approved	Contraindications	Adverse effects
Etanercept	Anti-TNFα human receptor fusion protein	RA, AS, PSA	PSA AS	Congestive cardiac failure Demyelinating disease (rare) Septic arthritis Pregnancy Breast feeding Infection — TB, hepatitis Malignancy Live vaccines	Blood dyscrasia Injection site reaction Allergic reaction Infection
Adalimumab	Anti-TNFα recombinant human IgG1 monoclonal antibody.	RA, AS, PSA	PSA RA Crohn's	As above	As above
Infliximab	Anti-TNFα Chimeric monoclonal antibody.	RA, PSA, AS, IBD	PSA AS RA UC/Crohn's	As above	As above
Golimumab	Anti-TNFα Human monoclonal receptor	RA, PSA, AS, chronic sarcoid, UC	RA	As above	Infection Hypertension Hypersensitivity reaction Skin exfoliation Malignancies Dizziness
Certolizumab	Pegylated TNFα	RA Crohn's	RA	As above	URTI Nausea Lupus-like syndromes Malignancy Hypersensitivity Skin reactions Severe infections
Rituximab	Anti-CD20 cells	RA SLE NHL ANCA vasculitis	RA Vasculitis	Pregnancy Breast feeding Live vaccines	Infusion reaction Infection
Belimumab	Inhibits B-lymphocyte stimulator (BLyS)	SLE		Severe depression Pregnancy Infections	Infusion reaction Hypersensitivity reaction Pyrexia Diarrhoea Infection Depression Nausea Headaches
Abatacept	Chimeric protein that inhibits T lymphocyte activation	RA	RA	Active infections Live vaccines Anti-TNFα ?Severe COPD	Infection Hypertension URTI Dyspepsia Lymphoma Back pain
Anakinra	IL-1 receptor antagonist	RA CAPS Autoimmune inflammatory conditions Gout	RA	Thalidomide/lenalidomide Hypersensitivity to anakinra, *E. coli*-derived proteins Active infection Concomitant live vaccines Concomitant TNFα blockers	Infusion reaction Injection site reaction Nausea Diarrhoea Pyrexia

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