

Novel immunotherapies for rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory condition affecting 1% of adults in the developed world.¹ In addition to joint inflammation and damage, the systemic effects of RA include an enhanced risk of cardiovascular disease, similar to that seen in diabetes.² A greater understanding of RA pathogenesis has enabled the development of targeted biological therapies that modulate inflammation and the immune system.

Joint damage in RA is caused by inflammation of the synovium (synovitis), which becomes hyperplastic and irreversibly destroys the articular cartilage and underlying subchondral bone. Synovitis is ultimately driven by a number of pro-inflammatory cytokines, such as tumour necrosis factor (TNF), interleukin 6 (IL-6) and interleukin 1 (IL-1). Environmental factors, such as smoking, can cause immune tolerance to fail in genetically predisposed individuals, which leads to an autoimmune attack on the joint.¹ Examination of rheumatoid synovitis reveals the presence of a chronic inflammatory infiltrate comprising T-cells, B-cells and macrophages, as well as fibroblasts. Each of these cell types may play a role in maintenance of synovitis. Current immunotherapies target B-cells and T-cells as well as TNF and IL-6 (Fig 1).

Immunotherapies

Unlike small molecule drugs, biological immunotherapies are produced from living

cells.⁴ This increases the cost of their development and production. Furthermore, they are potent drugs, with potentially serious side effects. Consequently, their use is subject to National Institute for Health and Care Excellence (NICE) guidance (Box 1).^{5–8} In brief, biologic therapy may be initiated in patients who have failed to respond to two or more disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (if not contraindicated), and who continue to have high disease activity. Either anti-TNF, anti-IL-6 or costimulation blockade can be prescribed as the first biologic therapy, with NICE guidelines dictating the subsequent treatment algorithm (Box 1). Patients receiving biologic therapy require regular monitoring, both for efficacy and for adverse effects. Treatment must be overseen by a consultant rheumatologist and should only be continued while efficacy can be clearly demonstrated.

Despite their quite different modes of action, the overall efficacy of the different immunotherapies is very similar. On average around one-third of patients respond very well to a particular therapy, but a similar proportion do not respond at all. The reasons for this are poorly understood.

Anti-TNF

A treatment to block TNF was the first biologic therapy to be introduced for RA. Five distinct options are now available.⁴ Three are monoclonal antibodies, one a modified

monoclonal antibody fragment and one a soluble receptor (Table 1). As well as reducing disease activity, TNF blockade dramatically reduces joint damage. These drugs also reduce fatigue and preserve functional capacity leading to improved quality of life, job retention and, ultimately, reduction in joint surgery. Trial data and evidence from biologics registers indicate that these agents are more effective when prescribed in combination with methotrexate, possibly because methotrexate reduces their immunogenicity. This is reflected in NICE guidelines (Box 1).

Compared to patients receiving DMARDs, those receiving anti-TNF therapy have an approximately 20% increased risk of serious infections (requiring intravenous antibiotics or hospitalisation), including septic arthritis, pneumonia and infections of skin and soft tissues.^{9–11} The risk is highest during the first 6 months of treatment, in older patients and in those on steroids. To date there is no evidence to suggest that anti-TNF agents increase the risk of malignancy including lymphoma¹² or non-melanoma skin cancer.¹³

Because TNF blockade disrupts granuloma, anti-TNF treatment is associated with reactivation and dissemination of latent tuberculosis (TB), as well as other intracellular bacteria such as listeria and salmonella.¹⁴ Therefore, all patients must be screened for latent TB prior to starting treatment.

Unpredicted, but rare, complications include demyelination, congestive heart

Key points

Immunotherapies are biological therapies that target specific aspects of rheumatoid arthritis (RA) pathogenesis

Immunotherapies provide an alternative treatment for patients who fail to respond adequately to traditional disease-modifying agents such as methotrexate

Four different classes of targeted immunotherapies are currently licensed. These target cytokines (eg tumour necrosis factor [TNF] and interleukin 6 [IL-6]), B-cells and T-cells

The overall response rate to the different immunotherapies is similar, but individual patients differ in their response to each treatment. Current research is attempting to define biomarkers that will help to identify the optimal treatment for each patient

Immunotherapies are expensive medications. Biosimilars should lead to a reduction in the cost of treatment

KEY WORDS: Rheumatoid arthritis, immunotherapies, personalised medicine, biosimilars, antidrug antibodies

Table 1. The four classes of immunotherapies licensed to treat rheumatoid arthritis.

Drug category	Mode of action	Examples	Route of administration	Administration interval
TNF inhibitors	Neutralisation of TNF- α	Adalimumab (fully human antibody)	SC	Fortnightly
		Golimumab (fully human antibody)	SC	Monthly
		Certolizumab (PEGylated Fab fragment)	SC	Fortnightly
		Etanercept (p75 TNF receptor – Fc fusion protein)	SC	Weekly
		Infliximab (chimeric mouse-human antibody)	IV	Every 8 weeks after loading at 0, 2 and 6 weeks
B-cell depletion	Lysis of B-cells	Rituximab (chimeric mouse-human antibody)	IV	Two infusions 2 weeks apart. This can be repeated every 6 months if symptoms return. Infusions are preceded by IV methylprednisolone to reduce the incidence of infusion reactions
T-cell inhibition	Costimulation blockade	Abatacept (CTLA4-Fc fusion protein)	IV	Every 4 weeks following three loading infusions at 0, 2 and 4 weeks
			IV followed by SC	Weekly SC injection following IV loading dose
IL-6 inhibition	Blockade of IL-6 receptor	Tocilizumab (humanised antibody)	IV	Every 4 weeks

CTLA-4 = cytotoxic T-lymphocyte associated-antigen 4; IL-6 = interleukin 6; IV = intravenous injection; PEG = polyethylene glycol; SC = subcutaneous; TNF = tumour necrosis factor.

failure, vasculitis, drug-induced systemic lupus erythematosus (SLE) and haematological complications such as aplastic anaemia, neutropenia and pancytopenia. Anti-TNF therapy may worsen interstitial lung disease, although this remains unproven.¹⁵

B-cell depletion

B-cells produce auto-antibodies and pro-inflammatory cytokines, and also present antigen to T-cells. Rituximab is a chimeric monoclonal antibody against CD20, a B-lymphocyte antigen that potently depletes mature B-cells but spares B-cell precursors and plasma cells. Rituximab is prescribed for RA patients who fail to respond to anti-TNF therapy.¹⁶

Like anti-TNF, rituximab has potent effects on the symptoms and signs of RA, as well as slowing joint damage, with consequent benefit on the quality of life of patients. Rituximab is administered by intravenous (IV) infusion – two doses 14 days apart, in combination with methotrexate. Treatment can be repeated after a minimum of 6 months if symptoms have returned. It is not currently clear how depletion of B-cells leads to improvement of RA symptoms and there are no useful

biomarkers to trigger the need for retreatment. Some evidence suggests that rituximab is more effective in patients who are positive for rheumatoid factor (RF) or anti-citrullinated protein antibodies.¹⁷

Infusion reactions, such as fever and urticaria, affect up to one-third of patients receiving rituximab. These reactions are most frequent with the first infusion and reflect B-cell lysis. Reactions are reduced by pre-medication with IV methylprednisolone before every infusion. Severe infections may also complicate rituximab treatment, with a similar incidence to anti-TNF therapy. Opportunistic infections are rare, although progressive multifocal leucoencephalopathy has been very occasionally reported in association with rituximab, usually in combination with other immunosuppressive medication.¹⁸

Co-stimulation blockade

T-cells are activated by a combination of two signals. The first is recognition of antigens by the T-cell receptor and the second is a co-stimulatory signal, triggered by the interaction of CD28 with CD80 and CD86. After activation, T-cells upregulate cytotoxic T-lymphocyte antigen 4 (CTLA4), which de-activates the T-cell. It has a higher

affinity for CD80 and CD86 than CD28, which it displaces. Abatacept is a soluble form of CTLA4 which also prevents the interaction of CD28 with CD80 and CD86, thereby blocking co-stimulation and preventing T-cell activation.¹⁶

Much like TNF blockade and B-cell depletion, abatacept reduces the symptoms and signs of RA, as well as slowing joint damage. The major adverse effect is, again, serious infection, at a rate of between three and four serious infections per 100 patient-years – the same as with the other classes of biologic therapy. Abatacept is administered by 4-weekly IV infusions, or weekly subcutaneous (SC) injections following an IV loading dose, and in combination with methotrexate.

Interleukin 6 receptor blockade

Interleukin 6 (IL-6) is an important pro-inflammatory cytokine whose pathological effects include synovitis, fatigue, the anaemia of chronic disease and joint destruction. Tocilizumab is a humanised monoclonal antibody that binds and blocks the IL-6 receptor (IL6R). Its beneficial effects are similar to the preceding agents, with a particularly pronounced normalisation of the acute phase response and improvement in

anaemia of chronic disease. Apart from serious infections, adverse effects include neutropenia, abnormal liver function tests and an increase in lipid levels.¹⁹ Unlike other biologic therapies, tocilizumab may be equally effective when used as monotherapy as when combined with methotrexate – although current NICE guidance stipulates it be combined with methotrexate.

Immunogenicity

Immunogenicity describes the development of anti-drug antibodies which can bind to therapeutic antibodies and inactivate them, or accelerate their clearance, reducing response by as much as 80%.²⁰ Testing patients for these 'antiglobulins' is currently not mandated, in part due to a lack of assay standardisation. Studies suggest that the chimeric infliximab is more immunogenic than other anti-TNF antibodies, potentially accounting for infusion reactions as well as tachyphylaxis. Nonetheless, even fully human antibodies can provoke surprising immunogenicity that impacts on their effectiveness. Concomitant use of methotrexate appears to reduce the incidence of antiglobulins, perhaps accounting for the synergy seen with combination therapy.²¹

Biosimilars

The patents for the earliest anti-rheumatic biologic therapies are approaching expiration and there has been much interest in the production of so-called biosimilars. Unlike chemically produced small molecule drugs, it is not possible to faithfully replicate the precise manufacturing conditions for a biologic drug. Subtle alterations in culture conditions, and even stabilising agents and packaging, can result in a slightly different product. For example, a biosimilar may have a slightly different glycosylation profile to the original biologic of which it is a 'copy'. The consequences of these relatively minor changes are currently unclear, but they could alter efficacy and side effect profiles.²² Consequently, biosimilars are required to pass through a relatively stringent licensing programme, including intensive laboratory comparisons as well as formal clinical trials. As a result, the price

reductions seen with generics may not be so evident for biologics, although some cost savings are to be expected. Until these drugs are widely used the precise implications will not be known but post-marketing surveillance and registries will be essential to determine whether the theoretical differences become clinically relevant.

The future

A major area of interest with RA is personalised or stratified medicine. Approximately one-third of patients will not respond to any particular biologic therapy.²³ At present, no response predictors have been identified and the order in which therapies are prescribed is algorithmic and dictated by NICE guidance. RA is a highly heterogeneous condition and this is likely to explain differing response profiles at the patient level. Currently, much investment is being made

in attempts to discriminate distinct RA 'pathotypes' that underpin responsiveness. In the future, it is hoped that a more personalised approach will be possible, whereby a composite scoring system based on a number of biomarkers, demographics and clinical findings may be used to match each patient to their most effective treatment. This will improve outcomes, limit adverse effects and reduce cost.

We are also starting to see 'head-to-head' studies of different biologic therapies, which may also inform treatment choices. For example, the ADACTA study suggests that tocilizumab may be the more appropriate choice of first biologic therapy for patients who cannot tolerate methotrexate.²⁴ Nonetheless, such studies must be interpreted within the context of the precise clinical trial population and will be superseded if biomarkers of treatment response can be identified as above.

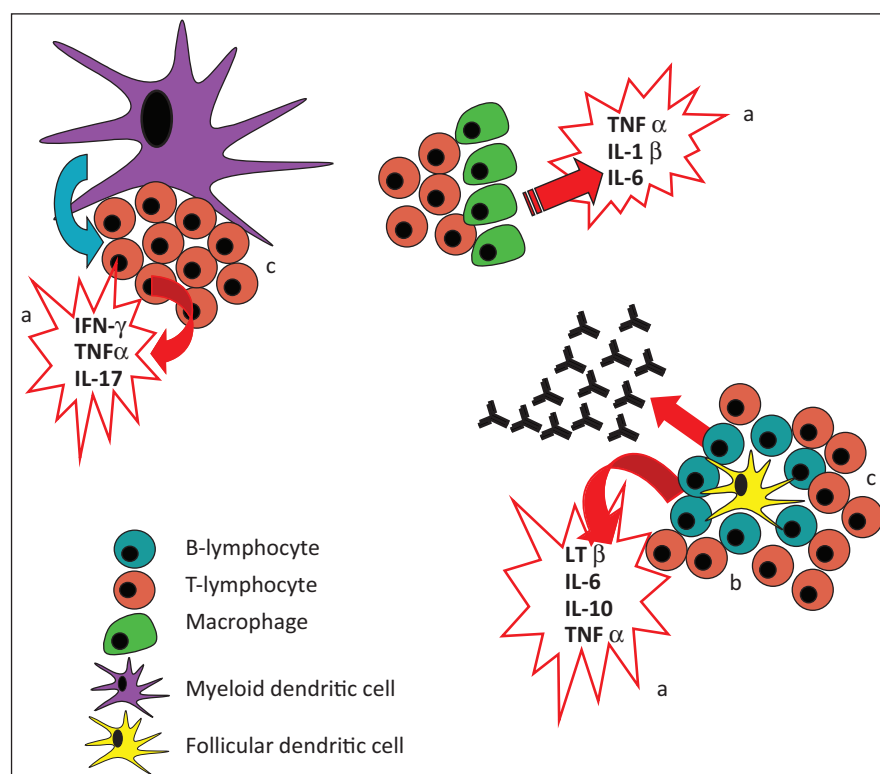


Fig 1. Targets of biologic therapies in RA. (a) TNF and IL-6 are produced primarily by activated synovial macrophages, but also by B-cells and T-cells. Blockade of either cytokine has proved effective in the management of RA. (b) As well as producing cytokines, B-cells produce autoantibodies and activate T-cells. B-cell depletion using rituximab is a further successful therapeutic modality. (c) T-cells play an important role, both by activating other cells such as macrophages, but also by producing potentially important cytokines such as IL-17 (a possible future therapeutic target). T-cells are activated by dendritic cells and B-cells, a process inhibited by costimulation blockade with abatacept. IL = interleukin; RA = rheumatoid arthritis; TNF = tumour necrosis factor.

Box 1. NICE guidance for the use of biologics.

- Anti-TNF therapy can be prescribed for patients who have failed to respond to two or more DMARDs including methotrexate (if not contraindicated) and have a DAS28 score greater than 5.1 on two occasions at least 1 month apart.
- A second anti-TNF agent can be started if a patient has side effects within the first 3 months of the first agent.
- Methotrexate should be prescribed alongside all anti-TNF agents unless contraindicated.
- Following failure of an anti-TNF agent, rituximab should be used as a second line treatment with methotrexate.
- If rituximab is contraindicated, a second TNF agent, abatacept or tocilizumab* may be trialled.
- Biologics should only be prescribed by a consultant rheumatologist.
- Biological agents should only be continued if DAS28 falls by greater than 1.2 units after 6 months of treatment

DAS28 = disease activity score (out of a possible 28 joints); NICE = National Institute for Health and Care Excellence; TNF = tumour necrosis factor.

*NICE also permits the use of tocilizumab or abatacept as first-line biologic therapy, as an alternative to TNF blockade, where the manufacturers provide the drugs with the discounts agreed in the patient access schemes. Tocilizumab is licensed as monotherapy in methotrexate-intolerant patients although this mode of administration is not currently supported by current NICE guidelines.

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