

# Monoclonal antibody therapy for non-malignant disease

Sanjay Swaminathan and Sean Riminton, Department of Clinical Immunology, Concord Hospital, Sydney

## Summary

Advances in technology have enabled monoclonal antibodies to be produced which bind to specific antigens associated with disease processes. By targeting these antigens the antibodies can destroy or alter the function of cells which express the target. They may also bind and thereby inhibit pro-inflammatory cytokines such as tumour necrosis factor. In addition to cancer treatment, monoclonal antibodies may be useful in diseases with an immune component such as rheumatoid arthritis and psoriasis. Monoclonal antibodies can have serious adverse reactions such as severe allergy and infection.

Key words: allergy, arthritis, inflammation, tumour necrosis factor.

(Aust Prescr 2006;29:130–3)

## Introduction

The use of monoclonal antibodies in clinical medicine stems from their ability to modulate the natural course of disease by targeting critical pathogenic molecules. As cancer cells have particular surface antigens, they are suitable targets for therapy.<sup>1</sup> Monoclonal antibodies are now finding roles in many non-malignant diseases such as inflammatory joint, skin and bowel diseases, organ transplantation, allergy and asthma. They are also used as antithrombotic drugs. The role of monoclonal antibodies is, however, limited by expense, the requirement for parenteral administration and concerns about new adverse effects.

## Nomenclature

Monoclonal antibodies are created by a single clone of antibody-producing cells so they share the same unique antigen target. Although initially produced using hybridoma technology, recombinant techniques are now used.

The names of monoclonal antibodies use a suffix to characterise the structure and method of production (Table 1). The most recent products are wholly human molecules generated by recombinant techniques and carry the suffix '-umab'.

## Mechanisms of action

The effectiveness of monoclonal antibodies is dependent on:

- the function and characteristics of the target antigen
- the cell surface density or tissue distribution of the antigen
- factors associated with the monoclonal antibody itself (specificity, avidity and isotype).

Monoclonal antibodies work by a number of mechanisms such as blocking the function of the target molecule, inducing the death of cells that express the target, or by modulating signalling pathways.<sup>2</sup>

These actions have been exploited in a range of proven and experimental indications (Table 2). Immune-mediated inflammatory diseases are particularly suitable candidates for this form of therapy. This is because key immune control molecules are secreted or expressed transiently on the surface of cells during the pathogenic process. Blocking these molecules with monoclonal antibodies may have specific effects on the disease.

## Inhibition of tumour necrosis factor

Tumour necrosis factor (TNF) is a major pro-inflammatory cytokine with a wide range of roles in immunity. Anti-TNF monoclonal antibodies (infliximab and adalimumab) have been an advance in the treatment of rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease and psoriasis/psoriatic arthritis. Although etanercept is also widely used to inhibit TNF in rheumatoid arthritis, it is not a monoclonal antibody. It is a soluble TNF-receptor-IgG Fc fusion molecule.

In rheumatoid arthritis, the benefits of infliximab and adalimumab have included reduced pain, improvements in all disease measures, inhibition of structural damage, and reduction in surgery and hospitalisation.<sup>3</sup> Synergistic effects with methotrexate have been observed. However, partial responses are more common than complete responses and treatment is not curative.

In Crohn's disease, infliximab is useful for inducing and maintaining clinical remission, closing fistulae (enterocutaneous, perianal, rectovaginal) and for reducing steroid dependence. Infliximab is also effective at inducing a clinical response in patients with moderate to severe ulcerative colitis.

## Inhibition of lymphocyte traffic

Multiple sclerosis is likely to be an immune-mediated demyelination in the central nervous system. The migration of activated T cells into the brain and spinal cord is thought

Table 1

**Nomenclature of monoclonal antibodies**





Type of monoclonal antibody	Structure	Suffix	Example
Murine 	Wholly mouse derived antibody	-omab	edrecolomab
Chimeric 	Murine antigen binding site; human Fc portion	-ximab	infliximab
Humanised 	Murine complementarity determining regions only	-zumab	daclizumab
Human 	Wholly human derived antibody	-umab	adalimumab

Table 2

**Monoclonal antibodies available for clinical use**

Monoclonal antibody	Target antigen	Current use	Potential use
<b>Cell surface molecules</b>			
Rituximab	CD20 (B cells)	Oncology	Cryoglobulinaemia, bullous pemphigoid, Wegener's granulomatosis, other B cell-mediated autoimmune diseases
Basiliximab, daclizumab	CD25	Prevention of organ rejection	
Muromonab	CD3	Treatment of acute organ rejection	Type 1 diabetes mellitus
Abciximab	Platelet IIb/IIIa	Acute coronary syndromes	
Efalizumab	CD11a component of LFA-1		Psoriasis
<b>Affecting cell traffic</b>			
Natalizumab	$\alpha$ 4 integrin		Crohn's disease, multiple sclerosis
<b>Cytokine directed</b>			
Infliximab, adalimumab	TNF	Rheumatoid arthritis, Crohn's disease, ankylosing spondylitis	Psoriasis
<b>Directed against antibodies</b>			
Omalizumab	IgE		Asthma, eczema, peanut allergy
IgE	immunoglobulin E		
LFA-1	lymphocyte function-associated antigen-1		
TNF	tumour necrosis factor		

to be part of the pathogenesis. These activated lymphocytes have antigens called integrins on their surface. Natalizumab, a humanised monoclonal antibody directed against  $\alpha_4$  integrin, has been studied in multiple sclerosis and Crohn's disease. Compared to placebo, natalizumab led to increased remission rates in multiple sclerosis. In Crohn's disease there were higher rates of sustained response when natalizumab was added to standard treatment.<sup>4</sup> Subsequent studies have questioned the safety of natalizumab. Studies were halted because of case reports of progressive multiple leucoencephalopathy, a devastating degenerative opportunistic viral disease of the central nervous system.

### Preventing organ rejection

Allogeneic transplantation can only succeed if immune rejection of the graft by the host can be controlled. Host T cells, and the cytokines/cytokine receptors that activate them, are key targets for control. T cell depletion using muromonab has been a successful strategy in patients suffering acute organ rejection, although it is broadly immunosuppressive. The monoclonal antibodies basiliximab and daclizumab (targeting T cell activation) are as effective as traditional immunosuppressive drugs in preventing organ rejection.<sup>5,6,7</sup>

Drugs successfully used in preventing transplant rejection are often subsequently studied in other immune-mediated conditions. Daclizumab, for example, is effective in some patients with psoriasis. The scope of these drugs in other conditions has yet to be fully explored.

### B cell depletion

Rituximab is a monoclonal antibody that targets a molecule (CD20) on the surface of B lymphocytes. The main use of rituximab is in oncology especially in B cell lymphomas.

B cell depletion using rituximab has also been successfully used in a number of other antibody-mediated conditions including cryoglobulinaemia, Wegener's granulomatosis and bullous pemphigoid. After single cycles of rituximab, circulating mature CD20+ B cells are promptly lost from the circulation, but serum concentrations of pathogenic antibody may not be acutely reduced. Clinical improvement without measurable improvement in antibody concentrations challenges a simplistic model of B cell pathology mediated solely by antibody production. Other roles of relevance might include antigen presentation and cytokine production, and this has been supported by recent studies in animal models of autoimmune disease.

### Use in skin disorders

The pathogenesis of psoriasis involves a number of immune mechanisms including the activation of T lymphocytes and the release of inflammatory cytokines such as TNF.<sup>8</sup> Inhibitors of TNF can induce an improvement in many patients with moderate

to severe plaque psoriasis. For example, a placebo-controlled trial of infliximab infusions showed that after 50 weeks 61% of patients had a 75% improvement in their psoriasis.<sup>9</sup> This response may be sustained following treatment cessation.

Efalizumab is a monoclonal antibody that targets part of the lymphocyte function-associated antigen-1 (LFA-1) on T cells. This antigen has roles in both T cell activation and migration so binding to it can improve moderate to severe psoriasis.

### Use in preventing thrombosis

When a monoclonal antibody binds to the glycoprotein IIb/IIIa receptor on the platelet surface it disrupts the final common pathway of platelet activation and aggregation. Abciximab, a chimeric monoclonal antibody that blocks this receptor, successfully reduces myocardial infarctions in patients with acute coronary syndromes who are having angioplasty. The infusion can be complicated by bleeding, but the risk can be reduced by altering the concomitant heparin therapy.

### Use in allergic diseases

Immunoglobulin E (IgE) is a pivotal antibody in the allergic response. When allergen-specific IgE on the surface of mast cells is cross-linked by allergen exposure it results in degranulation and the release of mediators such as histamine in sensitised individuals.

Allergic eosinophilic inflammation is driven by cytokines such as interleukin-5 (IL-5) so these molecules are suitable targets for monoclonal antibodies. Unfortunately, anti-IgE and anti-IL-5 therapies have failed to deliver on their therapeutic promise. Anti-IgE antibodies such as omalizumab have been used with some success in the treatment of allergic disorders such as asthma, eczema and in raising tolerance to certain food allergens. However, omalizumab is yet to find a routine place in management.

### Limitations of monoclonal antibody therapy

Monoclonal antibody therapies are not used more widely because of:

- expense
- requirement for parenteral administration
- adverse effects
- host anti-drug responses limiting ongoing therapy
- limitations in current concepts of molecular pathogenesis of disease.

The first monoclonal antibodies were mouse derived and anti-mouse antibodies were common although they only occasionally caused adverse effects. Nevertheless, this limited repeat exposures to the drugs. As monoclonal antibodies now resemble human antibodies this problem has been reduced, but not entirely eliminated. On re-exposure to the initial monoclonal antibody an allergic and/or anaphylactic reaction may occur.

## Adverse effects

Monoclonal antibodies have to be administered parenterally. The costs of cannulation and injection site reactions may be considerable.

New and unexpected serious adverse effects are emerging. Anti-TNF therapies are limited by serious infections including, but not restricted to, reactivation of latent tuberculosis. In addition, there are concerns that TNF inhibition might precipitate episodes of central nervous system demyelination, worsen heart failure, increase the risk of lymphoma, or trigger lupus-like syndromes. Natalizumab has been associated with progressive multiple leucoencephalopathy. Therapy aimed at depleting either B cells (rituximab) or T cells may lead to infections with opportunistic pathogens. There is therefore a need for patients to be informed of these problems when they are considering treatment.

## Conclusion

Monoclonal antibodies collectively represent a significant advance in clinical medicine. Due to their expense and mode of administration they tend to be reserved for when conventional drugs have failed to elicit a response. Although these drugs are highly targeted, adverse effects do occur and clinicians should be aware of the risk of hypersensitivity reactions and infection. The future may see combinations of monoclonal antibodies being used to better target complex disease processes.

## References

1. Ward R. Experimental and clinical pharmacology. Antineoplastic antibodies – clinical applications. *Aust Prescr* 2003;26:141-3.
2. Breedveld FC. Therapeutic monoclonal antibodies. *Lancet* 2000;355:735-40.
3. McColl G. Experimental and clinical pharmacology. Tumour necrosis factor alpha inhibitors for the treatment of adult rheumatoid arthritis. *Aust Prescr* 2004;27:43-6.
4. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005;353:1912-25.
5. Halloran PF. Immunosuppressive drugs for kidney transplantation [published erratum appears in *N Engl J Med* 2005;352:1056]. *N Engl J Med* 2004;351:2715-29.
6. Pillans P. Experimental and clinical pharmacology. Immunosuppressants – mechanisms of action and monitoring. *Aust Prescr* 2006;29:99-101.
7. Trevillian P. Experimental and clinical pharmacology. Immunosuppressants – clinical applications. *Aust Prescr* 2006;29:102-8.
8. Schon MP. Advances in psoriasis treatment. *Lancet* 2005;366:1333-5.
9. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al, for the EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005;366:1367-74.

*Conflict of interest: none declared*

## Self-test questions

*The following statements are either true or false (answers on page 143)*

1. Patients should have a chest X-ray before starting treatment with a tumour necrosis factor inhibitor.
2. By binding to the surface of platelets, abciximab reduces the risk of bleeding during angioplasty.

## Letters (continued from page 121)

(OACIS)), paper-based hospital discharge summaries are being replaced by a standardised web-based application. Summaries can be automatically faxed via computer to the relevant general practitioner or specialist, or emailed to desktop patient management systems.

Approximately 60% of all hospital discharge summaries in the eight major Adelaide hospitals are now completed this way. Over 125 000 completed summaries are stored within the system and are accessible to treating clinicians at Adelaide public hospitals. New summaries are being generated at a rate of approximately 220 per day.

Legibility problems are now avoided. Changes in discharge medication as well as reasons for these changes must be declared. The duration of treatments must also be stated. The summary may be accompanied by an interim

medication list which can be reviewed by the hospital pharmacist before discharge. If a patient is re-admitted the previous discharge medications can be imported into the new summary, reducing errors.

South Australia has improved practice in this area, nevertheless thoroughness and timeliness in clinical practice remain paramount.

Peter Herriot  
Consultant Psychiatrist and OACIS Clinical Sponsor  
Noarlunga Health Services  
Noarlunga Centre, SA

David Taverner  
Head, General Medicine  
Royal Adelaide Hospital  
Adelaide