



# **FACTSHEET**

## **MABS / CYTOKINE MODULATORS / ANIT- TNF AGENTS AND MORE**

A medication ending with the stem 'mab' indicates that it is a monoclonal antibody. This is the internationally recognised nomenclature for the naming of monoclonal antibodies.

Nomenclature has become somewhat confusing though as the BNF includes 'mabs' under the heading of cytokine modulators and anti-lymphocyte monoclonal antibodies in several chapters.

Monoclonal antibody production for medical use was first discovered by Milstein and Kohler in 1975, but it was confined mainly to diagnostics until Vilcek and Li approached Centacor (now part of Johnson & Johnson) to help them produce 'mabs' against TNF $\alpha$ .

Tumour necrosis factor-alpha (TNF $\alpha$ ) is a cytokine (an immunomodulating agent) produced by monocytes and macrophages, two types of white blood cells. It mediates the immune response by increasing the transport of white blood cells to sites of inflammation, and through additional molecular mechanisms which initiate and amplify inflammation. Inhibition of its action by 'mabs' reduces the inflammatory response which is especially useful for treating autoimmune diseases.

The 'mab' that Vilcek and Li discovered became known as Infliximab (Remicade) and it became an important treatment for severe Crohn's disease, including the fistulating variety. It has subsequently been used to treat other auto-immune system diseases such as psoriasis and rheumatoid arthritis. Infliximab became known as 'Kwik Fiximab' in medical circles due to its clinical success in treating otherwise unresponsive patients.

There are two types of TNF receptors: those found embedded in white blood cells that respond to TNF by releasing other cytokines, and soluble TNF receptors which are used to deactivate TNF and blunt the immune response. In addition, TNF receptors are found on the surface of virtually all nucleated cells. Red blood cells, which are not nucleated, do not contain TNF receptors on their surface.

A 'mab' neutralises the biological activity of TNF $\alpha$  by binding with high affinity to the soluble (free floating in the blood) and transmembrane (located on the

outer membranes of T cells and similar immune cells) forms of TNF $\alpha$  and inhibits or prevents the effective binding of TNF $\alpha$  with its receptors. Infliximab and adalimumab (another TNF antagonist) are in the subclass of "anti-TNF antibodies" (they are in the form of naturally occurring antibodies), and are capable of neutralising all forms (extracellular, transmembrane, and receptor-bound) of TNF $\alpha$ . Etanercept, a third TNF antagonist, is not a 'mab' and it is in a different subclass (receptor-construct fusion protein), and, because of its modified form, cannot neutralize receptor-bound TNF $\alpha$ . Etanercept is sometimes referred to as a 'non-biological' agent to distinguish it further from the 'mabs' Additionally, the anti-TNF antibodies adalimumab and infliximab have the capability of lysing cells involved in the inflammatory process, whereas the receptor fusion protein apparently lacks this capability. Although the clinical significance of these differences have not been absolutely proven, they may account for the differential actions of these drugs in both efficacy and side effects.

Infliximab has high specificity for TNF $\alpha$ , and does not neutralise TNF beta (TNF $\beta$ , also called lymphotoxin  $\alpha$ ), an unrelated cytokine that uses different receptors from TNF $\alpha$ . Biological activities that are attributed to TNF $\alpha$  include: induction of proinflammatory cytokines such as interleukin (IL) 1 and IL 6, enhancement of leukocyte movement or migration from the blood vessels into the tissues by increasing the permeability of endothelial layer of blood vessels; and increasing the release of adhesion molecules.

A range of newer agents which act against these other cytokines have subsequently been developed.

The table below summarises the anti- TNF mabs available in the UK currently. None-mab anti-TNF agents are also included for comparison

MOLECULE	BRAND	CLASS	DERIVATION	INDICATION	NICE APPROVED
Adalimumab	Humira (Abbott)	Anti-TNF $\alpha$	Recombinant human 'mab' From hamster ovary	RA PJIA PA AS CD P	Yes No Yes Yes Yes Yes
Anakinra	Kineret (Swedish Orphan)	Anti-IL-1	Recombinant human 'mab' From E Coli	RA	No
Alemtuzumab	MabCampath (Genzyme)	Anti-lymphocyte	Recombinant human 'mab' from hamster ovary	CLL	Yes
Certolizumab Pegol	Cimzia (UCB Pharma)	Anti-TNF $\alpha$	Recombinant human 'mab' From E Coli	RA	Yes
Golimumab	Simponi (Schering-Plough)	Anti-TNF $\alpha$	Recombinant human 'mab' from murine cell line	RA PA AS	Yes No Yes

Infliximab	Remicade (Schering-Plough)	Anti-TNF $\alpha$	Recombinant human 'mab'	RA CD UC AS PA P	Yes Yes Yes Yes Yes Yes
Ofatumumab	Arzerra (GSK)	Anti-lymphocyte	Recombinant human 'mab' from murine cell line	CLL	No
Rituximab	MabThera (Roche)	Anti-TNF $\alpha$	Recombinant human 'mab' from hamster ovary	RA CLL NHL FL	Yes Yes Yes Yes
Tocilizumab	RoActemra (Roche)	Anti-IL-6	Recombinant human 'mab' from hamster ovary	RA PJIA	Yes Yes
Ustekinumab	Stelara (Janssen-Cilag)	Anti-IL-12/23	Recombinant human 'mab' from murine cell line	P	Yes
Abatacept	Orencia (Bristol-Myers Squibb)	T-cell modulator	Fused protein formed by recombinant DNA technology	RA PJIA	No No
Etanercept	Enbrel (Wyeth)	Anti-TNF $\alpha$ (soluble receptor specific)	Fused protein formed by recombinant DNA technology from hamster ovary	RA PJIA PA AS P	Yes Yes Yes Yes Yes

### KEY

RA = Rheumatoid arthritis

PJIA = Polyarticular juvenile idiopathic arthritis

PA = Psoriatic arthritis

AS = Ankylosing spondylitis

CD = Crohn's disease

P = Psoriasis

CLL = Chronic lymphocytic leukaemia

NHL = Non-Hodgkin's lymphoma

FL= Follicular lymphoma

NICE approval status correct as of Feb 2012. Please refer to NICE website for very latest guidance <http://www.nice.org.uk/>

Sources: NICE, manufacturers Summaries of Product Characteristics, and BNF vol 61



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