Certolizumab pegol: a PEGylated anti-tumour necrosis factor alpha biological agent

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Abstract

Tumour necrosis factor (TNF)α is a proinflammatory cytokine involved in systemic inflammation that mediates chronic inflammatory diseases such as rheumatoid arthritis (RA), Crohn’s disease (CD) and psoriasis. Recognition of TNFα as a primary mediator of inflammatory disease has driven the development of monoclonal antibodies (mAbs) against TNFα as potential novel therapies for these disorders. Certolizumab pegol is a novel, polyethylene glycol (PEG)-conjugated, humanised, antigen-binding fragment (Fab’) of an anti-TNFα mAb that does not mediate apoptosis or neutrophil degranulation. Preclinical studies have shown excellent bioavailability, with preferential distribution and retention in inflamed tissue, which could be due to the low diffusion rate of PEGylated molecules and/or the lack of an Fc, which prevents FcRn-mediated transport. Pharmacokinetics are linear and predictable. Certolizumab pegol is a potentially valuable new treatment option for several inflammatory diseases. It has shown promising efficacy and tolerability results in Phase II and III trials for RA, CD and psoriasis.

History of anti-tumour necrosis factor agents in autoimmune inflammatory disease states

Tumour necrosis factor α, its structure and function and biological roles

Tumour necrosis factor (TNF)α is a proinflammatory cytokine involved in systemic inflammation that is known to be a mediator of chronic inflammatory diseases such as Crohn’s disease (CD), rheumatoid arthritis (RA) and psoriasis [1]. The existence of lymphotoxin (LT), a cytotoxic factor produced by lymphocytes, was first described at the University of California in 1968 [2]. TNF itself was subsequently isolated by researchers at the Memorial Sloan-Kettering Cancer Center in New York from macrophages in 1975 [3].

Recognition of the sequential and functional homology of TNF and LT led to the renaming of these two compounds as TNFα and TNFβ, respectively. TNFα was then recognised as having a key role in cachexia and as a principal mediator of septic shock in patients with infection [4, 5]. This molecule was ultimately found to be the prototype for the large family of TNF cytokines whose members are involved in the control of cell differentiation, proliferation...
and apoptosis, most notably in the immune and haematopoietic systems. Human TNFα is a nonglycosylated protein consisting of 157 amino acids that exists in both soluble and membrane-bound forms and is secreted by a variety of cell types, including macrophages, monocytes, neutrophils and T cells [6].

TNFα binds to two receptors, the 55 kDa TNFR1 (CD120a or p55, widely expressed on virtually all nucleated cell types) and the 75 kDa TNFR2 (CD120b or p75, expressed mainly by activated white blood cells and endothelial cells) [7]. The extracellular domains of TNFR1 and TNFR2 bind to the cleft between the subunits of the TNFα molecule, which initiates signalling [8]. The presence of two receptors allows for a wide diversity of signalling functions. Activation of TNFR1 can have a number of outcomes, depending on the availability of accessory proteins in differing cell types: the cytoplasmic domain of TNFR1 includes a death domain motif that initiates apoptosis after activation of caspases 3 and 8 (Fig. 1). Alternatively, TNF receptor–associated factor 2 (TRAF2) can recruit cellular inhibitors of apoptosis and activate pathways leading to nuclear translocation of antiapoptotic transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) (Fig. 1).

Figure 1. Simplified signaling pathways of TNFα. Dashed lines represent multiple steps. AP-1, activator protein-1; ASK1, apoptosis signal-regulating kinase 1; FADD, Fas-associated death domain; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; MEK, mitogen-activated protein kinase kinase; MEKK1, MEK kinase 1; MKK, mitogen-activated protein kinase kinase 7; NF, nuclear factor-κB; RIP, receptor-interacting protein; TNFR, TNF receptor; TRADD, TNF receptor-associated death domain; TRAF2, TNF receptor-associated factor 2. Bid is a pro-apoptotic member of the Bcl-2 family.