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NEW DRUG

Tocilizumab: A new anti-rheumatic drug

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1. Introduction

Tocilizumab, A new anti-rheumatic drug developed by Hoffmann–La Roche and Chugai under the trade name Actemra. It was recently approved by the U.S. Food and Drug Administration (US FDA) on January 2010 for the treatment of moderate to severe rheumatoid arthritis. It is a humanized monoclonal antibody targeted against the interleukin-6 receptor (IL-6R) causing immunosuppression and mainly used for the treatment of rheumatoid arthritis (Haghighi and Safari, 2008). Interleukin 6 is a cytokine that has a main role in immune response and is implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma and prostate cancer (Gabay, 2006).

Tocilizumab is the first Interleukin-6 Receptor Inhibitor. The molecular formula of the drug is [$C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$], CAS number: [375823-41-9] and has a molecular mass of [145.0 kDa]. The drug is a whole antibody designed specifically to target IL-6 receptor (Fig. 1). Tocilizumab is administered by intravenous infusions at 8 mg/kg monthly. It is available in preparations with strength of 20 mg/ml (Stubenrauch et al., 2009).

On June 2005, Tocilizumab was approved in Japan for Castleman's disease (a rare benign tumor of B cells). Intravenous Tocilizumab was proved to be effective and generally well tolerated when administered either as monotherapy or in combination with conventional drugs used for rheumatoid arthritis (Wang and He, 2009). On January 2009, it was approved by the European Medicines Agency (EMEA) for the treatment of rheumatoid arthritis in combination with methotrexate. It can be used as a single medication for patients who are unable to tolerate methotrexate. On January 2010, it was approved by the U.S. Food and Drug Administration (US FDA) for the treatment of moderate to severe rheumatoid arthritis (RA). The compound is still under review and trials by Australia's Therapeutic Goods Administration before licensing (Smolen and Maini, 2006).

2. Pharmacokinetics

A non-compartmental Pharmacokinetic analysis model from single and multiple dose studies showed similar Pharmacokinetic characteristics in rheumatoid arthritis patients compared with other healthy volunteers (Yokota et al., 2008). The Pharmacokinetics of Tocilizumab was characterized by nonlinear pharmacokinetic profile over the dose range tested. Clearance (CL) was concentration-dependent. Rheumatoid arthritis patients showed mean values of 0.26 ml/h/kg for CL, 160 h for half-life ($t_{1/2}$) and 60 ml/kg for volume of distribution at the steady state (V_{ss}) after a 10 mg/kg dose. These values were comparable to healthy volunteers in this dose range (Yokota et al., 2008). It is still unknown up till now whether Tocilizumab is excreted in human breast milk or not. Due to the lack of specific hepatic metabolism, it is not expected that the pharmacokinetics of Tocilizumab are altered in patients with hepatic impairment.

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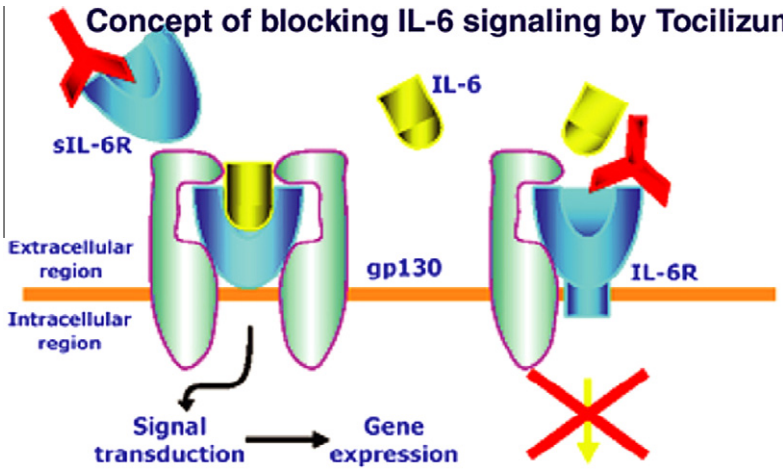

Figure 1 Blockade of IL-6 signals by anti-IL-6 receptor antibody (MRA, Tocilizumab). h, human; IL, interleukin; sIL-6R, soluble interleukin-6 receptor. (Cited with permission from Kishimoto (2006)).

3. Pharmacokinetic interaction studies

The influence by other drugs on the pharmacokinetics of Tocilizumab has been addressed in many studies mainly for methotrexate (MTX). It is known that MTX can decrease the CL of antibodies. The pharmacokinetic data obtained from more than one study indicated that MTX appears to have no or little influence on the pharmacokinetics of Tocilizumab. However, it cannot be excluded that a small interference is the cause of the slight but not marked increase in all four trough level (C_{min}) values during the four dose intervals in the 8 mg/kg groups with co-medication of MTX (EMEA, 2009).

The bioavailability of omeprazol (10 mg oral dose) was about 20–30% decreased after intravenous dose administration of 8 mg/kg Tocilizumab. Since omeprazole is a substrate (and inhibitor) of CYP2C19. this can be manifested by an inhibition of the down-regulating effect of IL-6 by Tocilizumab (EMEA, 2009).

The CL of dextromethorphan (a CYP3A4 and CYP2D6 substrate) was slightly declined while the CL of its metabolite dextrorphan (CYP3A4 substrate) was elevated (total CL unchanged) and is not consistent with the suggestion of a general inhibition of Tocilizumab on the down-regulating effect of IL-6 which appeared to affect almost all CYP enzyme-isoforms in vitro. However, this IL-6 effect occurred only at very high concentrations in vitro (EMEA, 2009).

Since it cannot be excluded that Tocilizumab can potentially influence the CL of all co-administered drugs which are metabolized by CYP450 enzymes in the liver, the CL of several non-steroidal anti-inflammatory drugs (NSAIDs) and steroids might be affected (Kato et al., 2008). The possible interaction is most important for CYP450 substrates with a narrow therapeutic index drugs such as; warfarin and cyclosporin.

4. Pharmacodynamics

Tocilizumab showed a mechanism of action that it specifically bind to the (interleukin-6) IL-6 binding site of both sIL-6R and mIL-6R receptors with similar affinity at the nanomolar range (Kishimoto, 2006). It was shown that IL-6 functions as a B-cell-stimulatory factor which has a major role in the induction of antibody production and as a hepatocyte-stimulatory factor to trigger acute phase reactions. In addition, IL-6 has many other biological activities. IL-6 is a pleiotropic cytokine that influences antigen-specific immune responses and inflammatory reactions (Kishimoto, 2006). It is known that IL-6 production is regulated by a feedback regulation mechanism in IL-6 signaling triggered by suppressors of cytokine signaling (Fig. 2). It was suggested that the binding region of Tocilizumab was within the cytokine-binding region (CBR) to which IL-6 binds. Therefore, Tocilizumab is able to block IL-6 from binding to both receptors and thereby blocking the IL-6 activity (Bongartz, 2008; Mihara et al., 2005).

Tocilizumab inhibits both the IL-6 classical and trans-signaling pathways by binding to mIL-6R and sIL-6R (Smolen et al., 2008). Tocilizumab binding to the receptor prevents the receptor from binding to IL-6. The Tocilizumab-receptor

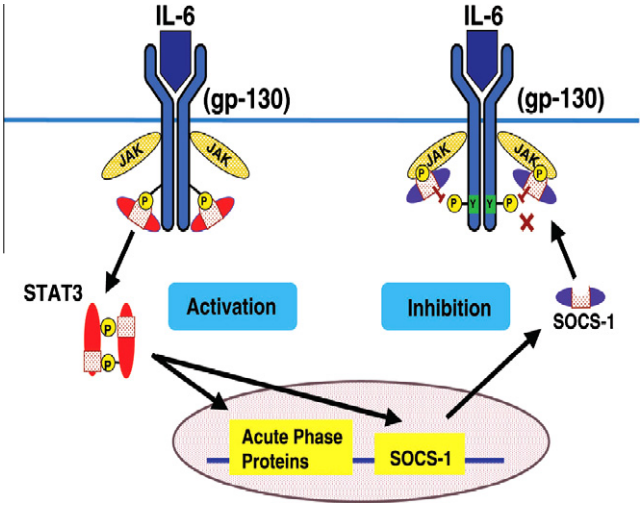

Figure 2 Feedback regulation in IL-6 signaling by SOCS. IL, interleukin; IL-6R, interleukin-6 receptor; JAK, Janus activated kinase; SOCS, suppressors of cytokine signaling; STAT, signal transducer and activator of transcription. (Cited with permission from Kishimoto (2006).)

complex formed cannot be bioactive since it is unable to affect the dimerization of the gp130 molecule. The IL-6 signal is completely blocked when the dimerization step is absent (Lipsky, 2006).

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