CHAPTER 36

TOCILIZUMAB: A NEW ALTERNATIVE THERAPY IN DERMATOLOGY

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INTRODUCTION

Interleukin 6 (IL-6) and IL-6 receptor were discovered by Tadamitsu Kishimoto at Osaka University in Japan in the 1980s. Tocilizumab (TCZ) is a recombinant humanized anti-human interleukin 6 receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass with a H2L2 polypeptide structure. In 1997, 2001 and 2003 clinical studies for rheumatoid arthritis (RA), Castleman's disease and systemic juvenile idiopathic arthritis started respectively. Tocilizumab effectiveness for RA in combination therapy or as a monotherapy firstly reported in 2003.[1,2] In further investigations, the effectivenes, tolerability and safety of TCZ in RA has been proven. In 2005, the first approval for the treatment of Castleman disease is taken in Japan. Tocilizumab has been approved as a treatment for RA and systemic juvenile idiopathic arthritis (SJIA) since 2008. In 2010, it was approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe active RA. In 2011 and 2013 it was approved by FDA for the treatment of SJIA, polyarticular juvenile idiopathic arthritis, respectively. Tocilizumab has been used in limited dermatological diseases, however especially in the diseases that the IL-6 plays an important role in the pathogenesis, successful results have been reported with TCZ. Below TCZ treatment in dermatology has been reviewed with the study reports after the pharmacology, mechanism of action, dosage and administration have been summarized.

PHARMACOLOGY

Pharmacodynamics

In clinical studies with the 4 mg/kg and 8 mg/kg TCZ doses, within 2 weeks levels of C-reactive protein were decreased to normal ranges. Changes in pharmacodynamic parameters like erythrocyte sedimentation rate, serum amyloid A and increases in hemoglobin were observed with both doses, however the greatest improvements were observed with 8 mg/kg. In healthy subjects after administered TCZ in doses from 2 to 8 mg/kg, absolute neutrophil counts reversibly decreased to the 3 to 5 days following.[3]

Pharmacokinetics

A concentration of free TCZ above 1 μg/mL in the serum enables the binding of 95% of the soluble IL-6 receptor inhibiting IL-6 actions and doubling the IL-6 serum levels after 2 weeks with intravenous application.[4] Following subcutane (SC) dosing in rheumatoid arthritis patients, the absorption half-life was around 4 days. The bioavailability for the SC formulation was 0.8. Following intravenous(IV) dosing, tocilizumab undergoes biphasic elimination from the circulation. The half life of tocilizumab is concentration dependent. For IV administration, the concentration-dependent apparent half life is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state. For SC administration, the concentration-dependent apparent half life is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state. Population pharmacokinetic analyses in adult rheumatoid arthritis patients showed that; age, gender and race did not affect the pharmacokinetics of tocilizumab. There was an inverse relationship between tocilizumab exposure and body weight for flat dose SC regimens.[3, 5, 6]

Mechanism of action

Tocilizumab blocks IL-6-mediated signal transduction by inhibiting IL-6 binding to both transmembrane and soluble IL-6 receptors.[7] This complex binds to the 130 gp signal transducer and then the inflammatory cascade enhances, induces angiogenesis, amplifies the activity of adhesion molecules and the activation of osteoclasts.[8] IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.[9]

patients who may be at increased risk for gastrointestinal perforation. TCZ is not recommended in patients with a low neutrophil count before treatment and who develop an absolute neutrophil count less than 500 per mm^3; a platelet count below 100,000 per mm^3 before treatment and who develop a platelet count less than 50,000 per mm^3, elevated transaminases greater than 1.5x upper limit of normal levels before treatment and who develop elevated ALT or AST greater than 5x upper limit of normal levels. Neutrophil, platelet counts, ALT and AST levels, lipid parameters sould be monitored 4 to 8 weeks after the beginning of the therapy and every 3 months.When clinically indicated, other liver function tests such as bilirubin should be considered. Serological tests for hepatitis B and C should be done at the beginning of the therapy. TCZ is not recommended in patients with active hepatic disease or hepatic impairment. Usage of live vaccines concurrently with TCZ should be avoided as clinical safety has not been established. Besides patients should be monitored for signs and symptoms of demyelinating disorders and malignancies.[106] Pregnancy category of TCZ is category C.[125] Because of the TCZ elimination, half-life suggests three months, conception is recommended three months after the last infusion for both gender. TCZ is present in human milk or if it would be absorbed systemically in a breastfed infant after ingestion.

Future direction

During the next decade TCZ will be widely used especially for the refractory various diseases. Therefore, further well-designed studies with wider spectrum of subjects will be required to comprehensively investigate the efficacy and safety that will be able to contribute to the clinical management of the diseases especially refractory to the other treatments.

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