TOCILIZUMAB

DESCRIPTION

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H2L2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Tocilizumab has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

Mechanism of action

Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. 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.

Routes of administration

Intravenous Infusion Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion

Subcutaneous Injection : 162 mg/0.9 mL in a single-dose prefilled syringe

- **Indications**

Rheumatoid Arthritis (RA) • Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Giant Cell Arteritis (GCA) • Adult patients with giant cell arteritis.

Polyarticular Juvenile Idiopathic Arthritis (PJIA) • Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

Systemic Juvenile Idiopathic Arthritis (SJIA) • Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

Cytokine Release Syndrome (CRS) • Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

- **Recommendations in COVID- 19**

- The Panel recommends using tocilizumab (single intravenous [IV] dose of tocilizumab 8 mg/kg actual body weight up to 800 mg) in combination with dexamethasone (6 mg daily for up to 10 days) in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. These patients are:
    - Recently hospitalized patients (i.e., within first 3 days of admission) who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow nasal cannula (HFNC) oxygen (>0.4 FiO2/30 L/min of oxygen flow) ; or
    - Recently hospitalized patients (i.e., within first 3 days of admission) not admitted to the ICU who have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC oxygen and who have significantly increased markers of inflammation (CRP ≥75 mg/L)

- For hospitalized patients with hypoxemia who require conventional oxygen therapy, there is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L, but who do not yet require

noninvasive ventilation or HFNC oxygen as described above.

- **Additional considerations for using Tocilizumab in COVID-19**

• Tocilizumab should be avoided in patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs, and in patients who have alanine aminotransferase >5 times the upper limit of normal; high risk for gastrointestinal perforation; an uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection; absolute neutrophil count <500 cells/μL; platelet count <50,000 cells/μL; or known hypersensitivity to tocilizumab.

• Tocilizumab should only be given in combination with a course of dexamethasone (or an alternative corticosteroid at a dose equivalency to dexamethasone 6 mg) therapy.

• Cases of severe and disseminated strongyloidiasis have been reported with use of tocilizumab and corticosteroids in patients with COVID-19.Prophylactic treatment with ivermectin should be considered for patients who are from strongyloidiasis endemic areas.

- **Warnings and precautions**

• Serious Infections – do not administer Tocilizumab during an active infection, including localized infections. If a serious infection develops, interrupt Tocilizumab until the infection is controlled.

• Gastrointestinal (GI) perforation—use with caution in patients who may be at increased risk.

• Laboratory monitoring—recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests.

• Hypersensitivity reactions, including anaphylaxis and death have occurred.

• Live vaccines—Avoid use with Tocilizumab.

● Adverse reactions

Most common adverse reactions (incidence of at least 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions.

● Considerations in pregnancy

- Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses in utero in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.
- Decisions about tocilizumab administration during pregnancy must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks.

● Considerations in Children

- There are no systematic observational or randomized controlled trial data available on the effectiveness of tocilizumab for the treatment of COVID-19 or multisystem inflammatory syndrome in children (MIS-C) in children.
- There are insufficient data for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or MIS-C.

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