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SARILUMAB

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Description of the drug

Sarilumab is an interleukin 6 (IL-6) receptor antagonist, produced by Sanofi-Aventis and authorized in European Union countries for treatment of moderate to severe active rheumatoid arthritis, alone or in combination with methotrexate (MTX), in adult patients who do not respond to disease-modifying antirheumatic drugs (DMARDs) [1].

Pharmacokinetic characteristics

The pharmacokinetics of sarilumab was evaluated in a clinical study of 2,186 patients with rheumatoid arthritis treated with subcutaneous (SC) doses of the 150 mg (n = 751) and 200 mg (n = 891) drugs every 2 weeks. The absolute bioavailability of sarilumab after SC injection was estimated to be 80% and the apparent steady-state volume of distribution was 8.3L. The metabolic pathway of sarilumab has not been characterized. The elimination of the drug occurs mainly via proteolytics, while, at lower concentrations, the elimination is target-mediated. Both elimination pathways determine a half-life of the drug in the steady state of 21 days.

Mechanism of action and pharmacodynamic characteristics

Sarilumab is a human monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 (IL-6Rα) receptors, inhibiting IL-6 mediated signaling. IL-6 is a pleiotropic cytokine that stimulates cellular responses such as proliferation, differentiation, survival and apoptosis and which can activate hepatocytes to release acute phase proteins, such as C-reactive protein (PCR) and serum amyloid protein A. IL6 participates in various physiological processes, such as migration and activation of T lymphocytes, B lymphocytes, monocytes and osteoclasts that lead to systemic inflammation, synovial inflammation and bone erosion of patients with RA. The activity of sarilumab in reducing inflammation is associated with laboratory abnormalities such as decreased PCR, absolute neutrophil count, fibrinogen and amyloid serum A and increased hemoglobin, serum albumin and lipids.

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Rationale for the use of the drug in the treatment of SARS-CoV-2 infection

The latest scientific evidence regarding the SARS-CoV-2 epidemic suggests that the IL-6 pathway plays a key role in guiding the inflammatory immune response, which occurs at the level of the pulmonary alveoli [2,3]. This immune response and the consequent "cytokine storm" produce significant damage to the lung parenchyma, which significantly reduces respiratory function. It was assumed that the specific binding of sarilumab to the IL-6 receptors, both soluble and membrane, may inhibit the IL-6 pathway, counteracting the excessive inflammatory response triggered by the new coronavirus, with consequent improvement potentially life-threatening lung complications. Given the possible role of sarilumab in counteracting the excessive inflammatory response triggered at the lung level by the new coronavirus, the Italian Medicine Agency (AIFA) authorized a clinical trial that will enroll 400 patients [4-5].

Treatment scheme in COVID-19 patients

The protocol of the ongoing clinical trial approved by AIFA [5] reported the following dosage regimens on the first day of treatment:

- Sarilumab (IV) high dosage (400 mg): two pre-filled syringes with a single dose of 200 mg in a 100 ml solution of 0.9% sodium chloride infusion;
- Sarilumab IV low dose (200 mg): a pre-filled syringe with a single dose of 200 mg in a 100 ml solution of 0.9% sodium chloride infusion;
- Placebo (IV): 100 ml solution of 0.9% sodium chloride in infusion.

Inclusion Criteria:

- Age ≥18;
- Inpatients with pneumonia confirmed by chest radiography or CT and auscultation;
- SARS-CoV-2 infection confirmed by blood parameters of PCR or other sample within 72 hours of randomization;
- Fever;
- At least one of the following baseline criteria: serious patients (need for oxygen therapy via nasal cannula, simple face mask or other similar devices; critically ill patients (need for oxygen therapy with masks without "rebreathering" or high flow nasal cannula or invasive or non-invasive assisted ventilation or request for access to intensive care patients with multi-organ dysfunction); use of vasopressors, or ECMO or Renal replacement therapy.

Exclusion criteria:

- Patients with low probability of survival over 48 hours from initial screening;

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- ASL and ALT valued 5 times higher than normal;
- Treatment in the last 30 days with anti-IL-6 or IL-6 antagonists;
- Treatment with immunosuppressive agents;
- Use of chronic oral corticosteroids for a condition unrelated to COVID-19;
- History of systemic or localized autoimmune or inflammatory diseases;
- Active tuberculosis (TB), history of TB not fully treated, suspected or known extrapulmonary TB, suspected or known bacterial or fungal systemic infections.

Patients included in the study will be randomized into 2 experimental groups and 1 placebo group. The end of this study is estimated on March 16, 2021 [5]. Two other trials are currently underway aimed at evaluating the efficacy and safety of this drug in patients with pneumonia associated with COVID-19 (CORIMUNO-SARI and NCT04321993) [6, 7].

Toxicity monitoring

No particular safety concerns have emerged from repeated dose toxicity studies, carcinogenicity risk assessment, reproductive and toxicity studies. Data related to the use of sarilumab in pregnant women are extremely limited. Therefore, this drug should not be used during pregnancy. The most frequently observed adverse reactions in clinical trials were neutropenia, ALT elevation, injection site erythema, and upper respiratory and urinary tract infections.

Potential interactions

In vitro and in vivo studies have shown that cytokines and related cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) and therefore have the potential to alter the pharmacokinetics of concurrently administered medicines which are substrates of these enzymes. High levels of interleukin 6 (IL-6) can reduce the activity of CYP. Therefore, caution should be used in patients initiating sarilumab treatment while CYP3A4 substrate therapy (e.g. oral contraceptives or statins) is ongoing, as sarilumab can reverse the inhibitory effect of IL-6 and restore the CYP3A4 activity, leading to a reduction in the exposure and activity of the CYP3A4 substrate drug (e.g. no contraception or lipid-lowering effect). The interaction of sarilumab with substrates of other CYPs (CYP2C9, CYP 2C19, CYP2D6) has not been studied.

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