SOCIETÀ ITALIANA DI FARMACOLOGIA

Riconosciuta con D.M. del MURST del 02/01/1996
Iscritta Registro Persone Giuridiche Prefettura di Milano n. 467 pag 722 vol. 2°
C.F.: 97053420150 – P.I.: 11453180157

UNI EN ISO 9001:2015 CERTIQUALITY SISTEMA DI GESTIONE QUALITÀ CERTIFICATO

ANAKINRA

Edited by Annalisa Capuano, Società Italiana di Farmacologia, SIF Crisis Unit on SARS-CoV-2, Carmen Ferrajolo, Gabriella di Mauro, University of Campania "Luigi Vanvitelli"

8 April 2020

Description of the drug

Anakinra is an interleukin 1 (IL-1) receptor antagonist, authorized in European Union countries for treatment of rheumatoid arthritis (RA), of Cryopyrin-Associated Periodic Syndromes (CAPS) and Still's Disease. It can be used alone or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs) [1].

Pharmacokinetic characteristics

The pharmacokinetics of anakinra was evaluated in patients with normal and impaired renal function. Clinical trials have shown that the absolute bioavailability of the drug after 70 mg subcutaneous bolus injection is 95%. The maximum plasma concentration of anakinra occurs 3-7 hours after subcutaneous administration, with a half-life of 4-6 hours. The elimination of anakinra is proportional to kidney function with first-order kinetics. Finally, it has been shown that anakinra clearance increased with increasing in creatinine clearance in patients with RA [2].

Mechanism of action and pharmacodynamic characteristics

Anakinra is an interleukin-1 type I receptor (IL-1RI) antagonist. In particular, the drug inhibits the biological activity of important pro-inflammatory cytokines, IL-1α and IL-1β [3]. The use of this drug in patients with SARS-CoV-2 infection could have important effects on the "cytokine storm" induced by the virus; therefore, anakinra could reduce the risk of developing acute respiratory distress syndrome (ARDS), respiratory failure, organ failure and potentially death [4].

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

The rationale for the use of anakinra in the treatment of SARS-CoV-2 infection is based on the excessive response of the immune system to the virus infection that cause the so-called "cytokine storm" with consequent hyper-inflammation. Two clinical trials are currently ongoing to evaluate the efficacy and safety of anakinra in patients with SARS-CoV-2 infection (NCT04324021 and NCT04330638). Specifically, the study NCT04324021 [Sobi.IMMUNO-101],

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

authorized by the Italian Medicine Agency (AIFA), will evaluate the efficacy and safety of **anakinra** and emapalumab in the prevention of lung complications caused by SARS-CoV-2 infection compared to standard therapy [5]. The clinical study NCT04330638, promoted by the University Hospital of Ghent (Belgium), is a phase 4, randomized, open-label, controlled trial that will evaluate the safety and efficacy of several treatments, including **anakinra**, on the recovery of pulmonary homeostasis in patients with SARS-CoV-2 infection [6].

Treatment scheme in COVID-19 patients

The protocol of the ongoing clinical trial Sobi.IMMUNO-101 approved by the AIFA [5] reported the following dosage regimens on the first day of treatment:

- emapalumab i.v. infusion every 3 day for a total 5 infusions. The drug will be administered at a dosage of 6 mg/kg on day 1 and 3 mg/ g on days 4, 7, 10 and 13;
- **anakinra** i.v. infusion four times daily for 15 days. Specifically, patients will receive 400 mg/day divided into 4 daily doses administered every 6 hours;
- standard therapy according to the local practice.

All patients will receive methylprednisolone (mPDN) as standard therapy. The administration of IL-6 inhibitor drugs (e.g. tocilizumab), other IL-1 inhibitors (e.g. canakinumab), TNF inhibitors, Janus kinase (JAK) inhibitors and hydroxychloroquine is not allowed. The full version of the protocol is available on the link: https: //www.aifa.gov.it/documents/20142/1131319/Sobi. IMMUNO101_documenti.zip.

Instead, the Belgian study NCT04330638 provides six treatment arms. Anakinra is administered subcutaneously in three arms at a lower dosage (100 mg) for a longer duration (28 days) (two of these treatments involve the co-administration with siltuximab or tocilizumab).

Inclusion Criteria:

- age > 30 to < 80 years at the time of screening;
- SARS-CoV-2 infection confirmed by blood parameters of PCR:
- Presence of respiratory distress, defined as PaO2/FiO2 < 300 mm Hg and >200 mm Hg or Respiratory Rate (RR) ≥30 breaths/min or SpO2 < 93 percent in air at rest;
- presence of hyperinflammation defined as a lymphocyte counts < 1000 cells/µL and two of the following three criteria: i. Ferritin > 500ng/mL ii. LDH > 300 U/L iii. D-Dimers > 1000 ng/mL

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

Exclusion criteria:

- patients with severe respiratory insufficiency or evidence of rapid worsening (respiratory distress requiring mechanical ventilation or shock or concomitant organ failure requiring ICU admission);
- patients in mechanical ventilation or with modified early warning score (MEWS) >4 with evidence of moderate or above ARDS;
- impairment of cardiac function;
- severe renal dysfunction;
- uncontrolled hypertension;
- history of hypersensitivity or allergy to any component of the study drug;

The Belgian trial will include hospitalized adult patients with a SARS-CoV-2 infection and with hypoxia defined as PaO2/FiO2 of less than 350 mmHg with vertical breathing or PaO2 / FiO2 of less than 280 mmHg in patients with oxygen therapy and with signs of cytokine release syndrome.

Toxicity monitoring

The most frequently reported adverse reactions with anakinra are: injection site reaction (erythema, bruising, inflammation and pain), serious infections (including cellulitis, pneumonia, and bone and joint infections), neutropenia, thrombocytopenia, anaphylactic reactions, headache, alteration of liver enzymes and blood cholesterol increased [1].
In the clinical study Sobi.IMMUNO-101 it was specified that the safety will be assessed by monitoring adverse events.

Potential interactions

No particular phenomena of interaction with other drugs (including non-steroidal anti-inflammatory drugs, lucocorticoids and DMARDs) have been observed. However, the concomitant treatment of anakinra with TNF-α antagonists may not be recommended. Moreover, high levels of interleukin-1 (IL-1) can reduce the activity of CYP. Therefore, caution should be used in patients initiating anakinra treatment while CYP3A4 substrate therapy is ongoing.

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

References

1.https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information_it.pdf

2. Waugh J, Perry CM. Anakinra: a review of its use in the management of rheumatoid arthritis. BioDrugs. 2005;19(3):189-202. Review

3. Dinarello CA, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov. 2012 Aug;11(8):633-52.

4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-1034.

5. https://clinicaltrials.gov/ct2/show/NCT04324021?intr=Emapalumab&draw=2&rank=3

6.https://clinicaltrials.gov/ct2/show/study/NCT04330638?cond=Corona+Virus+infection&intr=Anakinra&draw=2&rank=1

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/