International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 09 Issue: 05 | May - 2025 SJIF Rating: 8.586 ISSN: 2582-3930

Tocilizumab In Treatment of Giant Cell Arteritis (GCA)

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Abstract:
Large and medium-sized arteries are the main target of giant cell arteritis (GCA), a chronic vasculitis that frequently manifests as headache, blurred vision, and jaw claudication. An important treatment option for GCA is tocilizumab, an antagonist of the interleukin-6 (IL-6) receptor. A key player in the pathophysiology of GCA, IL-6 promotes vascular injury and systemic inflammation. When used with a glucocorticoid taper, tocilizumab dramatically increases sustained remission rates. It decreases cumulative glucocorticoid exposure when compared to glucocorticoid therapy alone, according to clinical trials, including the seminal GiACTA experiment. Though hazards including infection and hepatotoxicity need to be watched, tocilizumab has been linked to a good safety profile. Its application signals a change in GCA toward targeted immunotherapy, offering hope for improved disease Control and reduce steroid related complications.

Tocilizumab is a medication used in the treatment of giant cell arteritis (GCA). It's a monoclonal antibody that blocks the IL-6 receptor, helping to reduce inflammation.
Studies have shown that tocilizumab can effectively induce and maintain remission in patients with GCA, and it can also help reduce the need for corticosteroids.

Introduction Head discomfort and tenderness, which are frequently severe and typically involve both temples, are the most typical signs of giant cell arteritis. Head pain may get worse over time, come and go, or go away for a while. In general, giant cell arteritis manifests as the following symptoms

Severe, ongoing headache discomfort, typically in the temple region Tenderness in the scalp Jaw ache when opening your mouth wide or chewing A fever Weariness Unintentional weight loss Double vision or visual loss, especially in those who also experience jaw pain abrupt and irreversible blindness in one eye Polymyalgia rheumatica is a similar illness that frequently manifests as neck, shoulder, or hip pain and stiffness. Polymyalgia rheumatica affects around half of patients with giant cell arteritis.

Tocilizumab :

A monoclonal antibody called tocilizumab targets the interleukin-6 (IL-6) receptor, which is a major inflammatory mediator. Rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis are among the inflammatory and autoimmune diseases that it is used to treat. Moreover, tocilizumab has been authorized to treat COVID-19 in hospitalized individuals on mechanical ventilation or supplementary oxygen in addition to systemic corticosteroids. Method of Action: Tocilizumab inhibits the IL-6 receptor, which stops IL-6 from attaching and triggering inflammation. One cytokine that is important in inflammation and is raised in a variety of inflammatory diseases is IL.

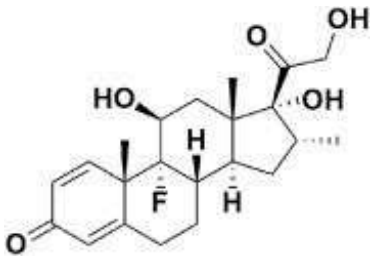
Keywords: Tenderness, polymyalgia rheumatica, interleukin.

Symptoms :

1. Head discomfort and tenderness, which are frequently severe and typically involve both temples, are the most typical signs of giant cell arteritis.
2. Head pain may get worse over time, come and go, or go away for a while. In general, giant cell arteritis manifests as the following symptoms:
3. Severe, ongoing headache discomfort, typically in the temple region Tenderness in the scalp Jaw ache when opening your mouth wide or chewing A fever Weariness
4. Unintentional weight loss Double vision or visual loss, especially in those who also experience jaw pain abrupt and irreversible blindness in one eye.

5. Polymyalgia rheumatica is a similar illness that frequently manifests as neck, shoulder, or hip pain and stiffness.
6. Polymyalgia rheumatica affects around half of patients with giant cell arteritis.

Structure :



Tocilizumab

Physiochemical properties of the drug :

The following are some of the physiochemical characteristics of tocilizumab, a

Monoclonal antibody primarily used to treat autoimmune diseases such as cytokine release syndrome and rheumatoid arthritis:

1. The Molecular Formula:-H9976N1712O2018S42 C6428
2. The weight of molecules: 148 kDa, or kilodaltons, roughly
3. Organization: Type: IgG1 subclass humanized monoclonal antibody Interleukin-6 receptor (IL-6R) is the target.
4. Solubility Aqueous solution soluble made in water with a pH of about 6.0 for injection
5. Stability Stable between 2°C and 8°C in a refrigerator Heat and light sensitivity Don't freeze
6. Point of Isoelectricity (pI): Its charge at physiological.

According to the Biopharmaceutics Classification System (BCS), tocilizumab is categorized as follows:

- BCS Class IV: Low permeability and low solubility Justification: Low Solubility:
- Since tocilizumab is a monoclonal antibody, it often dissolves poorly in aqueous solutions, as do big protein-based medications.
- Low Permeability: It is difficult to pass through cell membranes and be absorbed through the gastrointestinal tract because of its enormous molecular size and shape. Tocilizumab is therefore given by injection (IV or subcutaneous) as opposed to oral.

Mechanism of action :

Action Mechanism Tocilizumab is a monoclonal antibody used to treat autoimmune and inflammatory diseases. It preferentially binds to the interleukin-6 receptor and stops IL-6 from attaching to its receptor (IL-6R) on the liver, lung, and synovial fibroblasts, for example.[1]

- One significant modulator of chronic inflammation is IL-6. IL-6 can Decrease albumin synthesis in the liver while increasing the production of C-reactive protein (CRP), serum amyloid A, fibrinogen, and hepcidin.

- Amyloidosis, cardiovascular events, edema, and anemia can all be brought on by these liver mediator effects. The way that tocilizumab treats COVID-19 pneumonia is by blocking IL-6R in the lungs.

- In order to promote angiogenesis, vascular permeability, and the synthesis of vascular endothelial growth factor (VEGF), IL-6 can stimulate synovial fibroblasts in the joints.

Pharmacokinetics:

Absorption:

Intake The mean observed steady-state predose tocilizumab concentrations in week 24 of clinical trials were 18 µg/mL for intravenous dosing and 40 µg/mL for subcutaneous weekly and bi-weekly doses, respectively. According to these investigations, body weight had a significant impact on both clearance and distribution volume. These studies validated the label's recommendations for tocilizumab subcutaneous dosage in individuals with rheumatoid arthritis. [2]

Distribution :

In adult patients, tocilizumab has a steady-state volume of distribution of

6.4 L, with a central volume of distribution of roughly 3.5 L to 4.09 L. The steady-state volume of distribution in pediatric patients is approximately 4.0 L, while the central volume of distribution is approximately 2.0 L.

Metabolism:

The metabolism Tocilizumab, like other monoclonal antibodies, undergoes limited hepatic metabolism through the CYP450 enzymatic system and is broken down by proteolytic enzymes into smaller proteins and amino acids. Removal The half-life of tocilizumab is 5–13 days. It seems that clearance is dose-dependent, linear at larger dosages, and non-linear at lower ones.

Synthesis:

Synthesis of Tocilizumab:

1. Cloning genes: Expression vectors contain the genes that code for the heavy and light chains of tocilizumab, a humanized monoclonal antibody.
2. Culture of Cells: Chinese Hamster Ovary (CHO) cells are exposed to these vectors. The antibody is expressed by the CHO cells while they are cultivated in bioreactors.
3. Gathering and Cleaning: The antibody is extracted from the culturing medium. To guarantee safety and effectiveness, it is purified utilizing
methods such as protein A affinity chromatography, filtering, and further procedures.
4. Creation: An injectable solution is created using the purified antibody.

Medicinal uses:

1. **Reduces Inflammation**: One of the main causes of inflammation in GCA, the interleukin-6 receptor (IL-6R), is blocked by tocilizumab. In big and
medium arteries, this lessens vascular inflammation.
2. **Avoids Illness Flare-ups**: Consistent use helps avoid GCA symptom flare-ups or relapses.
3. **Steroid-Sparing Effect:** It minimizes negative effects like osteoporosis, diabetes, and hypertension while drastically lowering the requirement for long-term corticosteroid therapy (such as prednisone).
4. **Reduces Symptoms:** Assists in easing symptoms like headaches

Claudication of the jaw Tenderness in the scalp issues with vision (such as hazy vision or vision loss) Fever and exhaustion

5. **Prevents Vision Loss**: One major consequence of GCA is irreversible vision loss, which can be avoided by managing inflammation early.
6. **Enhances Quality of Life**: Enhances everyday functioning by lowering systemic symptoms such as weariness and pain.

Adverse effects :

- Common (>10%)
- elevated plasma cholesterol levels (19–20%).
- Teenagers and children (<2%)

- Elevated ALT (<36%) and AST (<22%) in plasma [3]
- Reaction at the SQ injection site (7% to 10%)
- Teenagers and children (15–44%) Reaction associated with infusion (4% to 20%)

Less common(1%–10%)

- 6 percent hypertension
- Edema in the periphery (<2%)
- Rash <2%
- hypothyroidism
- Having diarrhea
- Teenagers and children (>5%) ulcer of the stomach (<2%)
- Gastritis (1%). Ulcers of the oral mucosa (2%)
- Stomatitis (less than 2%)
- Pain in the upper abdomen (2%)
- Gain in weight (less than 2%
- Leukopenia (less than 2%)
- Neutropenia
- Development of neutralizing antibodies (<1%)
- Infection with herpes simplex (<2%) Lightheadedness (3%)
- 7 percent of people have headaches. <2% conjunctivitis (<2%) Nephrolithiasis
- (3) Bronchitis Cough (less than 2%). Dyspnea (less than 2%)
- (7%) Nasopharyngitis
- Infection of the upper respiratory tract (7%)

Contraindications:

1. A hypersensitive reaction to the tocilizumab dosage form is a contraindication to tocilizumab therapy. Polysorbate 80 may be present in some tocilizumab dose formulations.
2. Patients with allergies may experience a delayed hypersensitivity reaction as a result of polysorbate 80. [4] [5] [6]
3. Hypersensitivity reactions in premature newborns can result in thrombocytopenia, ascites, and damage to the kidneys, liver, and lungs. [7] [8]

Patents :

Publication number	Priority date	Publication date	Assignee	Title
CA1341152C	1988-01-22	2000-12-12	Tadamitsu Kishimoto	Receptor protein for human b cell stimulatory factor-2
EP0399429A1	1989-05-22	1990-11-28	Toray Industries, Inc.	Anti-human interleukin- 6 Monoclonal antibody
CA2021594C	1989-07-20	2002-01-08	Tadamitsu Kishimoto	Antibody to human interleukin- 6 receptor
AU648777B2	1989-12-04	1994-05-05	Schering Corporation	Method of treating septic shock

Conclusion:

Giant Cell Arteritis (GCA) can now be effectively treated with tocilizumab, an interleukin-6 (IL-6) receptor antagonist, especially when it comes to lowering disease activity and minimizing long-term corticosteroid reliance. In comparison to glucocorticoids alone, weekly or biweekly subcutaneous tocilizumab in conjunction with a glucocorticoid taper dramatically improved maintained remission rates, according to the seminal GiACTA trial. Pro-inflammatory cytokines like IL-6, which are essential for vascular wall inflammation, are part of the pathophysiology of GCA. Tocilizumab provides a mechanism-based approach to
disease control by specifically targeting this route. Clinical results show that tocilizumab patients had better quality of life, fewer relapses, and lower cumulative steroid dosages.

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