Efficacy of Tocilizumab vs. NSAIDs in the Treatment of Juvenile Rheumatoid Arthritis

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ABSTRACT
Tocilizumab is a humanized monoclonal antibody that binds to IL-6 receptors, both the soluble receptor (sIL-6R) and the one located in the cell membrane. In this way it blocks the molecular complex of the receptor and prevents cytokine signaling. It is a drug which has recently been approved by the FDA, several studies recently carried out at international level (USA, Japan, Europe) have demonstrated the great efficacy of tocilizumab in the treatment of juvenile rheumatoid arthritis.

INTRODUCTION
Juvenile rheumatoid arthritis is a heterogeneous group of chronic inflammatory arthritis that begins before the age of 16 years, represents the most common rheumatic disease of childhood and is one of the main causes of acquired disability in this age group. It has been described in all races and geographic areas, with a greater predisposition in populations of European descent. IL-1 and IL-6 are increased in these patients and correlate with the extent of joint involvement, severity of anemia and growth disorders.

The treatment commonly used in these patients are NSAIDs, which do not modify the course of the disease and pediatric patients have gastrointestinal problems due to their prolonged use, there are other types of drugs such as biological agents which are drugs selectively directed against molecules that produce inflammation, among them is Tocilizumab (TCZ) which is a humanized monoclonal antibody directed against the IL-6 receptor, approved by the FDA and NICE for use as a first line biologic agent in patients with IL-1 and IL-6. First-line biologic agent in patients with RA in the USA, Japan and Europe.

Extensive clinical development has demonstrated the efficacy of TCZ in most possible RA situations. TCZ has shown great efficacy in correcting the analytical abnormalities of RA, both in acute phase reactants and in inflammatory disorder anemia. The aim of this study is to prove that the efficacy of tocilizumab is superior to that of NSAIDs in the treatment of rheumatoid arthritis, for which purpose a bibliographic review was carried out with a large number of clinical studies showing the benefits of the use of tocilizumab.

Disease background
Rheumatoid arthritis is a chronic autoimmune disease of unknown cause, whose natural history leads to progressive functional disability, systemic complications, premature death and high socioeconomic costs. Juvenile arthritis is defined by the International League of Associations of Rheumatology (ILAR) as arthritis that begins before the age of 16 years and persists for at least 6 weeks thereafter, excluding other known conditions. It is characterized by joint inflammation that can cause joint damage, delay normal growth, and lead to long-term disability and decreased quality of life. (3). It is also mentioned that it is classified based on age of onset, number and type of joints affected, presence of serological findings and systemic signs and symptoms; including categories such as: systemic, oligoarticular, polyarticular, undifferentiated, among others. (8).

As indicated in the literature, one of the predisposing factors for the development of rheumatoid arthritis is genetics, as well as other factors such as environmental factors, through the activation of T lymphocytes in the synovial membrane. From a histological point of view, the process is characterized by pronounced angiogenic activity, synovial hyperplasia and infiltration of T and B lymphocytes and macrophages, which access the synovium with prior interaction with adhesion molecules expressed on the activated endothelium.(5)
TCD4 lymphocytes are activated by antigen-presenting cell (APC) intervention, grace to interactions between the T lymphocyte receptor and the major histocompatibility complex class II (MHC II) peptide antigen, with a stimulus through the CD28-CD80/86 pathway as well as other signaling pathways (6). It is believed that ligands that bind to Toll-like receptors (TLRs) may increase stimulation of APCs within the joint. Likewise, LTCD4 activate B lymphocytes, some of which differentiate into antibody-producing plasma cells, immune complexes, possibly composed of rheumatoid factors (RF) and antibodies, against cyclic citrullinated peptides (CCP) that may form within the joint, thus activating the complement pathway, amplifying inflammation. Citrullination is an enzymatic deamination process that converts arginine residues to citrulline. This causes modifications in the folding of the affected proteins and the exposure of neoepitopes, recognized as non-self, against which antibodies are generated (5). On the other hand, effector T lymphocytes stimulate synovial macrophages and fibroblasts to secrete proinflammatory mediators, such as tumor necrosis factor α (TNF-α), which increases the number of adhesion molecules in endothelial cells, inducing the penetration of leukocytes into the joint. Likewise, proinflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are produced. TNF-α plays a major role in regulating the balance between osteolysis and osteogenesis (6); it increases dikkopf-1 (Dkk-1) expression and then internalizes Wnt receptors on osteoblast precursors. Wnt is a soluble mediator that induces osteoblast formation, and thus bone synthesis. In rheumatoid arthritis the Wnt pathway is inhibited, thus blocking bone synthesis, probably due to the action of the increased concentrations of DKK-1. TNF-α in addition to its activity as an inhibitor of bone synthesis, acts as a stimulant of osteoclastogenesis, however it cannot do this on its own, it requires macrophage colony-stimulating factor and receptor activator of nuclear factor κB (RANK) for osteoclast differentiation. The activator of nuclear factor κB receptor ligand within the joint comes from stromal cells, synovial fibroblasts, and T cells.

IL-6 promotes the occurrence of synovitis because it induces neovascularization through vascular endothelial growth factor (VEGF)-stimulated pannus proliferation, which results in inflammatory and synovial cell infiltration causing hyperplasia. In terms of joint erosion, IL-6 causes bone resorption by inducing osteoclast formation through the induction of RANKL in synovial cells and cartilage degeneration by producing matrix metalloproteinases (MMP) in synovial cells and chondrocytes (9). It is also responsible for the systemic manifestations that occur in RA.

The current assessment of the disease and the efficacy of the different treatments is carried out by means of combined indexes that give an overall idea of the clinical activity of the disease. Currently the DAS28 (Disease Activity Score 28) is used, which assesses a total of 28 joints and counts how many of these are painful, swollen and also the erythrocyte sedimentation rate and the patient's overall assessment of disease activity on a scale of 0 to 100. Current treatment focuses on controlling pain and inflammation, decreasing morning stiffness and halting the course of joint destruction, with the goal of achieving clinical remission.

### Main pharmacotherapy regimen for rheumatoid arthritis

The pharmacological treatment of peripheral inflammatory arthropathies contemplates the use of drugs belonging to the following groups:

**NSAIDs -** It is mainly symptomatic treatment. They relieve pain and morning stiffness but do not alter the development of the disease or prevent structural injury. Their use is recommended at the onset of the disease, when a DMARD is introduced or when isolated uncontrolled symptoms persist despite a good objective response to a DMARD - Recommended: Indomethacin, diclofenac, naproxen, etoricoxib, among others.

**Disease-modifying antirheumatic drugs (DMARDs) -** These are drugs obtained by chemical synthesis and produced in cell or bacterial cultures. They are used earlier and more aggressively both in monotherapy and in combination. Classical drugs such as methotrexate, leflunomide, sulfasalazine and hydroxychloroquine are found. Monoclonal antibodies that are directed to block certain molecules are also in second line. Their efficacy is unquestionable but their high cost and probability of causing adverse effects keep them in second line in the treatment of RA. Among these is tocilizumab.

**Glucocorticoids:** They are basically used to control synovitis and slow bone erosion, in the context of treatment with DMARDs. They effectively control synovial inflammation in patients with active rheumatoid arthritis, after local injection into the inflamed joints.

### Mechanism of action NSAIDs and treatment

They are mainly used to reduce inflammatory manifestations in joints such as synovitis and as analgesics to reduce pain in joint stiffness. They intervene in the arachidonic acid cascade by directly inhibiting COX-1/COX-2. By inhibiting these molecules, the symptomatology presented by patients with RA is avoided. Its main adverse effects are usually on the gastrointestinal tract. Pediatric patients tolerate these drugs well and usually present minimal toxicity to them.

Naproxen: directly inhibits COX-1/COX-2, 10mg/kg/day, mainly in children.

Etoricoxib: inhibits COX-2, 90 mg/day in one dose.

Indomethacin: potent inhibitor of PG synthesis, 25 - 50 mg/2 - 4 times a day; if well tolerated, change at weekly intervals until a satisfactory response is obtained without exceeding 200 mg/day.

Diclofenac: Inhibitor of PG synthesis and decreases the concentration of arachidonic acid in leukocytes; 100-200
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mg/day in 2-4 doses orally and after satisfactory response, 75-100 mg/day, in 2-3 doses. Despite their efficacy, none of these agents leads to response in all patients, and even among responders, improvement is often limited. Half of the patients who received nonsteroidal anti-inflammatory drugs or corticosteroids continue to show progressive involvement of an increased number of joints and severe functional disability with marked growth impairment.

Mechanism of action of monoclonal antibodies and treatment with tocilizumab

As mentioned above, the immune system plays an important role in the development of this pathology, by activating signaling and therefore the secretion of proinflammatory cytokines, such as IL-1, IL-6, TNF, among others, contributing to joint inflammation. This is why new drugs have been developed that block these cytokines in order to inhibit or decrease inflammation. Interleukin-6 (IL-6) is produced by various cells of the immune system such as T and B lymphocytes, monocytes, fibroblasts, endothelial cells, among others. IL-6 can activate cells through two signaling pathways: the first is the membrane receptor (mIL-6R) through activation of glycoprotein (gp) 130 and the second is through proteolytic cleavage of the mIL-6R leading to the generation of a soluble receptor for IL-6 (sIL-6R). IL-6 plays a role in adaptive immunity. IL-6 stimulates B cells to differentiate into plasma cells, which produce immunoglobulin. Excess IL-6 production has been found in the synovial fluid and blood of RA patients and correlates with disease activity and joint destruction (9). Serum interleukin-6 concentrations are related to the degree and severity of joint involvement, fever patterns, platelet counts, growth retardation, and osteoporosis. Tocilizumab is a humanized monoclonal antibody that binds to IL-6 receptors, both soluble (sIL-6R) and cell membrane-bound (1). The molecular weight of this drug is approximately 148 kDa (2). This blocks the molecular complex of the receptor and prevents cytokine signaling. Both the UK National Institute for Health and Clinical Excellence (NICE) and the US Food and Drug Administration (FDA) agency expanded the approved indication of tocilizumab for use as a first-line biologic agent in patients with RA who have had an inadequate response to one or more synthetic DMARDs. In clinical practice, our results suggest that tocilizumab can be administered to all patients, but priority should be given to IL-6 blockade in those patients with high IL-6 and low sIL-6R levels (1). It is administered 8 mg/kg i.v. over 1 h, once every 4 weeks(5). Among other indications, an initial treatment of 4 mg/kg i.v. every 4 weeks is recommended to assess the patient's response to treatment, followed by an increase to 8 mg/kg (not to exceed 800 mg per administration) depending on clinical response (7). These data provide evidence that inhibition of interleukin-6-mediated proinflammatory effects significantly and rapidly improves the signs and symptoms of rheumatoid arthritis. Likewise, improvements with tocilizumab were evident at early assessments, i.e., 2 to 4 weeks after treatment initiation, for all efficacy endpoints studied and were maintained or improved throughout the treatment period. Similarly, in recent reports, tocilizumab was effective in achieving rapid and sustained improvements in RA signs and symptoms in patients with inadequate response to TNF-α inhibitors and had a manageable safety profile (4). Tocilizumab was safe, tolerable, and clinically effective for patients with inadequate responses to TNF-α therapy and for those who were inexperienced with biologic therapy, according to the various studies performed. As adverse effects tocilizumab elevates liver enzyme levels, neutropenia, infections, sometimes severe and anaphylactictype allergic phenomena and occur rarely (5). Tocilizumab was approved for the treatment of juvenile rheumatoid arthritis in April 2008 in Japan, in April 2011 in the U.S. and in August 2011 in the EU. (2)

DISCUSSION

The various studies presented in the articles reviewed have shown that the use of tocilizumab improves disease activity according to the American College of Rheumatology criteria. Similarly, other studies have shown that tocilizumab significantly decreases VEGF levels and is more effective than methotrexate. However, when treated with these drugs, an abnormal increase in liver transaminases was noted, which represents a safety risk. Likewise, in the SAMURAI study it was shown that tocilizumab monotherapy is superior when compared to DMARDs when it comes to radiographic progression. Another study showed that baseline sIL-6R levels predicted clinical remission in RA patients treated with tocilizumab (1). Many other studies demonstrated good outcomes and improvement in patients given tocilizumab. These results are mainly due to the fact that therapies with NSAIDs, glucocorticoids and FAMES are mainly used for the treatment of symptoms and not as such to treat the system that is altered in this pathology. That is why tocilizumab, being a treatment that consists of inhibiting IL-6, one of the main mechanisms that triggers the disease, the value of blocking IL-6 lies in its versatility to neutralize several cytokine pathways responsible for immune regulation, hematopoiesis and inflammation. IL-6 is a potent proinflammatory agent that induces fever, fatigue and many other clinical attributes associated with inflammation. Therefore, blockade of the IL-6 pathway has proven to be popular in recent times in the treatment of systemic inflammatory diseases such as RA and systemic Juvenile Rheumatoid Arthritis (9), which is why it not only improves symptoms but also disease progression.

CONCLUSION

The origin and progression of rheumatoid arthritis is an enigma in the medical world since it is a pathology of
autoimmune origin. For this same reason, the most convenient pharmacotherapy scheme to treat the disease is also an enigma. The different drugs used have their advantages and disadvantages, however, after an analysis of the different articles collected for this research, the benefits of tocilizumab over traditional treatments in RA were found. One of the objectives of this research was to study and understand the pathophysiology of juvenile rheumatoid arthritis and to make known the mechanism of action of the different drugs that are administered for its treatment. Once the pathophysiology of RA is known, it is easier to understand the use of the different drugs recommended for RA. In this way it was also possible for us to establish a conclusion and answer to our research question.

After the above mentioned, it is possible to conclude that tocilizumab treatment is more effective than NSAID treatment due to its mechanism of action. As was made known, tocilizumab is an IL-6 receptor antagonist, blocking the molecular complex of the receptor, preventing cytosine signaling and thus avoiding the stimulation of various proinflammatory cells and molecules that cause the clinical picture in the patient. This mechanism is what makes tocilizumab more effective than NSAIDs, since NSAIDs only treat the symptoms of the disease but do not delay its progression. In other words, tocilizumab treats the disease by attacking the source of the disease, while NSAIDs somehow mask the disease and do not prevent further disease progression. NSAIDs treat the disease through the arachidonic acid pathway while tocilizumab treats the disease through the immune system pathway, and taking into account that this pathology is of autoimmune origin, it is possible to conclude that tocilizumab has a better mechanism of action to treat the disease.

REFERENCES