

Tocilizumab for the Treatment of Juvenile Idiopathic Arthritis

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Based on the International League of Associations for Rheumatology classification, juvenile idiopathic arthritis (JIA) is defined as arthritis with no known etiology, with symptoms beginning before the age of 16 years, lasting at least 6 weeks, and absent of any other known cause.¹ JIA is further subclassified into systemic (sJIA), oligoarthritis (oJIA), and polyarthritis (pJIA) based on the number of involved joints and accompanying systemic effects, such as lymph node enlargement and hepatomegaly. Patients diagnosed with JIA are at risk for a number of long-term functional complications, including growth failure, osteoporosis, and secondary amyloidosis, as well as severe, life-threatening complications such as macrophage activation syndrome (MAS).² Patients diagnosed with MAS have an 8-22% risk of mortality.³

Obtaining an accurate prevalence estimate for JIA is difficult because of wide-ranging and ever-changing classification criteria. Published reports indicate a range of 1.6-86.1 per 100,000 affected by what is loosely defined as juvenile rheumatoid arthritis.⁴

Tocilizumab (Actemra, Chugai Pharmaceutical Co., Ltd. and F. Hoffman-La Roche Ltd, Basel, Switzerland) is a humanized interleukin-6 (IL-6) monoclonal antibody that competes for both membrane-bound (mIL-6R) and soluble (sIL-6R) forms of human IL-6 receptor.⁵ On April

OBJECTIVE: To evaluate the pharmacology, clinical efficacy, safety, and role of tocilizumab for the treatment of juvenile idiopathic arthritis.

DATA SOURCES: A literature search via MEDLINE through PubMed (1970-December 2011) and *International Pharmaceutical Abstracts* (1970-December 2011) was performed to identify clinical trials and review articles. The key search terms tocilizumab, anti-interleukin 6, and juvenile idiopathic arthritis were used, with several combinations of terms. Bibliographies of selected articles were examined to identify additional references, and ongoing trials were identified through a review of www.clinicaltrials.gov.

STUDY SELECTION AND DATA EXTRACTION: Articles were limited to those published in English and studies in humans. Studies included in the review examined pediatric data in systemic and polyarticular juvenile idiopathic arthritis. Background information was obtained through reviews of literature on a wide variety of autoimmune disease states in both adult and pediatric populations.

DATA SYNTHESIS: Tocilizumab is Food and Drug Administration–approved for use in patients aged 2 years and older with systemic juvenile idiopathic arthritis. Tocilizumab was superior to placebo in triggering a symptomatic response during Phase 2 and 3 clinical trials. Tocilizumab was determined to be safe, with only a small number of serious adverse drug events occurring within studies.

CONCLUSIONS: Tocilizumab provides expansion of the available options for the treatment of systemic juvenile idiopathic arthritis, specifically in patients who have not responded to conventional therapies. Tocilizumab is relatively well tolerated and has proven efficacy for up to 52 weeks. Further studies are warranted to determine its utility as a first-line option for systemic juvenile idiopathic arthritis as well as its role within the treatment of polyarticular juvenile idiopathic arthritis.

KEY WORDS: anti-interleukin-6, juvenile idiopathic arthritis, tocilizumab.

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15, 2011, tocilizumab became the first approved medication for the treatment of active sJIA.⁶ Tocilizumab is also approved for the treatment of moderate-to-severe rheumatoid arthritis in adults and is undergoing Phase 3 clinical trials for its use in pJIA.^{7,8}

Interleukin-6, a multifunctional cytokine, has been linked to several pathologic conditions including rheumatoid arthritis, psoriasis, Castleman disease, and JIA.⁹ Ele-

variations of IL-6 have been observed in patients with numerous types of rheumatologic disease, including JIA.¹⁰ There is growing evidence suggesting that IL-6 plays a more prominent role in JIA compared with interleukin-1 (IL-1) or tumor necrosis factor alpha (TNF- α).¹¹ Prominent measures of success for patients receiving treatment for JIA include the American College of Rheumatology (ACR) Pediatric 30%, 50%, or 70% response (ACR30, ACR50, and ACR70, respectively), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

The purpose of this review is to provide an overview of the pharmacology, clinical efficacy, and safety of tocilizumab and to discuss its role in the treatment of JIA.

Data Sources and Selection

A literature search via MEDLINE through PubMed (1970-December 2011) and *International Pharmaceutical Abstracts* (1970-December 2011) was performed to identify clinical trials and review articles. The key search terms tocilizumab, anti-interleukin 6, and juvenile idiopathic arthritis were used, with several combination of terms. Bibliographies of selected articles were examined to identify additional references, and ongoing trials were identified through a review of the Web site trial registry www.clinicaltrials.gov.¹²

Pharmacology

Tocilizumab exhibits efficacy in the treatment of JIA through competitive binding of both mIL-6R and sIL-6R, resulting in inhibition of the action of circulating IL-6.¹³ IL-6 is responsible for antibody production through the activation of B-cells; mediation of chronic inflammation through T-cell, neutrophil, and macrophage activation; and joint destruction through osteoclast formation/activation and increases in vascular endothelial growth factor, which increases angiogenesis and vascular permeability of synovial tissues.¹⁴

Through different mechanisms, mIL-6R and sIL-6R mediate IL-6 signals into cells via coupling and expression of glycoprotein 130. Although serum IL-6 subsequently increases following tocilizumab administration, its effects cannot be exerted as long as tocilizumab is bound to IL-6 receptors. Through mIL-6R and sIL-6R blockade, tocilizumab decreases acute phase reactants (eg, CRP) and cytokines.¹⁵

PHARMACOKINETICS

The pharmacokinetic profile of tocilizumab for use in sJIA was initially determined through a population analysis involving 75 patients treated with either 8 mg/kg (patients <30 kg [n = 37]) or 12 mg/kg (patients $\geq$ 30 kg [n = 38]) every 2 weeks in an ongoing Phase 3 (TENDER) tri-

al.¹⁶ Patients were evaluated post hoc to determine the predicted area under the curve at 2 weeks ($AUC_{2\text{ weeks}}$), maximum concentration (C_{max}), and minimum concentration (C_{min}). Predicted means (SD) for all patients receiving tocilizumab were 32,200 (9960) $\mu\text{g}\cdot\text{h/mL}$, 245 (57.2) $\mu\text{g/mL}$, and 57.5 (23.3) $\mu\text{g/mL}$, respectively. Steady-state concentrations were achieved at approximately week 12, and mean serum concentrations between the 2 dosing groups were comparable at weeks 12 and 52 (Table 1).

Tocilizumab undergoes biphasic elimination following intravenous administration, and in patients with sJIA, volume of distribution at steady-state ($V_{d_{ss}}$) is 2.54 L. Tocilizumab undergoes both linear clearance (7.1 mL/h in sJIA) and dose-dependent nonlinear clearance. At low serum concentrations, nonlinear, target-mediated elimination is most prominent. Following target antigen binding by tocilizumab, the drug is internalized by the cell and degraded via lysosomal destruction. This elimination pathway may be saturated at higher serum concentrations due to the limited number of target antigen cells. At higher serum concentrations, linear elimination, which is mediated by the reticuloendothelial system, is most prominent. Following the uptake of tocilizumab by endothelial cells via endocytosis, a portion of the drug is bound by the neonatal Fc receptor and eventually transported back out of the cell. The remaining unbound tocilizumab is transported to lysosomes where it is degraded. This elimination pathway is unlikely to be saturated as therapeutically dosed tocilizumab will produce only a small fraction of the total endogenous IgG.^{17,18}

The half-life ($t_{1/2}$) of tocilizumab is concentration-dependent with prolonged exposure at higher mg/kg weight-based dosing. In sJIA, patients in both the 8- and 12-mg/kg cohorts had a measured $t_{1/2}$ of 23 days at week 12 of therapy. No formal studies of dosing in renal or hepatic impairment have been conducted and no dose adjustment for either is recommended.¹⁹

The pharmacokinetic parameters of tocilizumab in adults were evaluated, based on 7415 serum samples from 1793 patients with rheumatoid arthritis in 4 Phase 3 studies. Most of these patients were white, with a median age of 52 years. Using simulations, $V_{d_{ss}}$ was reported as 6.4 L, clearance as 14 mL/h and $t_{1/2}$ as 23 days. Simulated means for AUC , C_{max} , and C_{min} for tocilizumab 8 mg were 35,000 $\mu\text{g}\cdot\text{h/mL}$, 183 $\mu\text{g/mL}$, and 9.7 $\mu\text{g/mL}$, respectively. Pharmacokinetic parameters in adults, with the exception of $V_{d_{ss}}$ (2.54 L vs 6.4 L), are similar to those in pediatric patients; however, the difference in $V_{d_{ss}}$ likely accounts for the decrease in C_{max} and C_{min} in adults.¹⁷

PHARMACODYNAMICS

Changes in pharmacodynamics occur rapidly following administration of tocilizumab. Zhang et al. found decreases

in both CRP and ESR, as well as an increase in hemoglobin, shortly following the first administration of both 8 and 12 mg/kg of tocilizumab, with sustained effects lasting through 52 weeks of observed treatment.¹⁶ To date, the relationship between CRP and ESR and clinical efficacy is not completely understood, but because these parameters are unspecific markers of inflammation, clinical trials have investigated their response to therapy. If a decrease in CRP and/or ESR indicates a decrease in inflammation, then it is reasonable to assume that these laboratory values may help to determine some level of clinical efficacy. Further study is needed to ascertain their exact role in evaluating the efficacy of tocilizumab therapy.

Clinical Studies of Efficacy

An open-label, Phase 2 trial evaluated the safety and efficacy of single ascending doses of tocilizumab in children with sJIA.²⁰ Eighteen patients, aged 2-18 years, with a diagnosis of sJIA, were enrolled from the United Kingdom and France. Patients had to have active disease for at least 3 months while receiving an equivalent dose of greater than 0.2 mg/kg/day of prednisolone or a maximum dose of 20 mg/m²/wk of methotrexate. Other disease-modifying anti-rheumatic drugs (DMARDs) required a washout period of at least 5 half-lives. Patients with a history of MAS were not included.

Patients were divided into 2 groups depending on age (2-5 and 6-18 years). Patients then received tocilizumab 2, 4, or 8 mg/kg. Clinical assessment was performed through the parent global visual analogue scale (VAS), physician's global VAS, number of active joints, number of joints with limited range, the Childhood Health Assessment Questionnaire (CHAQ), and ESR. Assessments were performed prior to initiation of therapy, 48 hours after initial infusion, and at weekly intervals for 4, 6, and 8 weeks for the 2-, 4-, and 8-mg/kg treatment groups, respectively. No sample size calculation or statistics were performed because of the preliminary nature of this study.

Efficacy of tocilizumab was evaluated in 15 patients who completed the protocol (2 mg/kg, n = 4; 4 mg/kg, n = 6; and 8 mg/kg, n = 5). Clinical improvement, defined as

an ACR30, was achieved in 11 patients across all doses at 1 week. In the 4-mg/kg group, 4 patients achieved ACR50 and 2 patients achieved ACR70 at 1 week. This improvement continued through week 6 in both the 4- and 8-mg/kg groups. CRP and ESR levels decreased during the first 2 weeks for all groups, and serum IL-6 increased for 2-4 weeks following tocilizumab administration. This was followed by a decrease in levels for the 4- and 8-mg/kg groups.

No patients withdrew from the study because of adverse reactions. Fifteen of the 18 patients reported at least 1 adverse effect; however, the majority were considered mild. Adverse effects were described as gastrointestinal disorders, elevated hepatic enzymes, respiratory disorders, and infections. Four patients reported drug-related adverse effects including urticaria in 1 patient receiving 2 mg/kg. Severe adverse effects occurred in 4 patients, including varicella infection, herpes simplex mouth ulcer, and pancytopenia. One patient receiving 4 mg/kg and 1 patient receiving 8 mg/kg experienced a disease flare.

Yokota et al. conducted an escalating-dose trial on 11 children aged 2-19 years with sJIA.²¹ Patients who fulfilled the International League of Associations for Rheumatology classification criteria with a CRP level greater than 1.5 mg/dL and an ESR greater than 30 mm/h were considered to have active sJIA. Patients already taking medications for sJIA were maintained on these medications and observed for 4 weeks. No new medications, such as DMARDs or TNF- α inhibitors, were added. Patients with evidence of having had thrombocytopenia, cardiac disease, or MAS within the previous month were excluded.

The primary end point was evaluation of patient response every 2 weeks, based on 6 core variables of sJIA: febrile episodes, patient overall well-being, functional ability (CHAQ score), number of joints with arthritis, number of joints with limited range of motion, and ESR. Patients were initially given tocilizumab 2 mg/kg infusions every 2 weeks for 3 doses. Patients considered to have a disease flare (CRP >1.5 mg/dL) had subsequent doses increased to 4 mg/kg every 2 weeks for 3 doses. If CRP levels continued to increase, the dose was increased to 8 mg/kg every 2 weeks for 3 doses.

Table 1. Estimation of Tocilizumab Pharmacokinetic Parameters During the TENDER Trial¹⁶

Tocilizumab Dose	C _{max} (μg/mL) at Week 12	C _{min} (μg/mL) at Week 12	C _{min} (μg/mL) at Week 52	AUC _{2weeks} (μg·day/mL) at Week 12
8 mg/kg, mean (SD)	226 (54.5)	69 (25)	65 (31)	1337 (409)
12 mg/kg, mean (SD)	263 (54.1)	71 (31)	77 (29)	1346 (426)
All, mean (SD)	245 (57.2)	70 (28)	71 (30)	1341 (415)

AUC_{2weeks} = area under the curve at 2 weeks; C_{max} = maximum concentration; C_{min} = minimum concentration.

Eight of 11 (72.7%) patients evaluated experienced a disease flare with the initial dose of 2 mg/kg. Following dose escalation, 5 patients received all 3 doses of 4 mg/kg without a disease flare. The remaining 3 patients received 3 doses of 8 mg/kg without further increases of CRP.

Seven of 11 patients receiving tocilizumab 2 mg/kg achieved ACR30 and ACR50, while 1 patient achieved ACR70. Of the 8 patients who were administered 4 mg/kg, 7 achieved both ACR30 and ACR50. Four of these patients reached ACR70 by last observation. All 3 patients receiving 8 mg/kg achieved ACR30, ACR50, and ACR70.

No patient withdrew from the study because of safety or adverse effect concerns. Adverse events included upper respiratory tract infections ($n = 2$), pustules on extremities ($n = 3$), and eczema ($n = 1$).

Yokota et al. conducted a 3-phase trial consisting of a 6-week open-label phase; a 12-week, double-blind, randomized, placebo-controlled phase; and a 48-week open-label extension phase.²² Enrolled patients were aged 2-19 years, with a diagnosis of active sJIA defined as CRP greater than or equal to 15 mg/L, with an inadequate response to 3 months of corticosteroids. Patients were excluded on the basis of a number of medical disorders (leukopenia, thrombocytopenia, cardiac disease, MAS) or were concurrently using immunosuppressive medications, including corticosteroids, DMARDs, or TNF- α inhibitors 12 weeks prior to starting tocilizumab.

The primary end point for the initial open-label phase was proportion of patients achieving ACR30 response and CRP concentrations less than 15 mg/L at the end of the 6-week treatment protocol. The primary end point for the double-blind, placebo-controlled portion was proportion of patients in each treatment group who completed the 12-week period and maintained an ACR30 response and CRP less than 15 mg/L. Finally, the primary end point of the final open-label phase was proportion of patients achieving ACR30 response at the final visit.

Of the 56 patients enrolled in the initial open-label phase, 44 (79%) achieved ACR30 and maintained CRP levels below 5 mg/L at week 6. ACR30, ACR50, and ACR70 responses were recorded in 51, 48, and 38 patients, respectively. Forty patients showed improvements in their CRP concentrations (<5 mg/L) within 2 weeks. Additionally, similar decreases in ESR were evident at week 2, and joint counts and childhood assessment scores improved by week 4. Improvements in ESR and CRP from baseline to 6 weeks were recorded, on average, as an 82% decline (44.5 mm/h to 4 mm/h) and a 90% decline (43.5 mg/L to 0.5 mg/L), respectively.

Upon completion of the open-label phase, 43 patients were randomized for the 12-week, double-blind phase (tocilizumab $n = 20$; placebo $n = 23$). Four (17%) patients in the placebo group and 16 (80%) in the treatment arm completed the 12-week study and maintained an ACR30

response and CRP level less than 15 mg/L. This same proportion of patients also achieved ACR50. Although slightly fewer patients achieved ACR70, the results favored tocilizumab over placebo (15/20 [75%] vs 3/23 [13%]). Efficacy, determined by median time of clinical relapse, was sustained longer in the tocilizumab group compared with patients receiving placebo (>12 weeks vs 4.9 weeks; $p < 0.0001$).

Following completion of the double-blind phase, 50 patients were enrolled in a 48-week, open-label extension phase. At the 48-week analysis, 48 of 50 patients were continuing to receive tocilizumab. For these patients, ACR30, ACR50, and ACR70 responses were 47 (98%), 45 (94%), and 43 (90%), respectively. Median absolute changes from baseline in ESR and CRP were -34 (-121 to -7) and -43.5 (-190 to -16), respectively. These changes resulted in a median percentage decline of 93.2% in ESR and 99.7% in CRP.

Additional 48-week analysis showed improvements in both hemoglobin concentrations (median increase from 111 g/L to 124 g/L) and platelet counts (median decrease from 41.8×10^{10} to 30.2×10^{10}). All patients ($n = 48$) included in the 48-week efficacy analysis received oral corticosteroids throughout all arms of the study. Throughout the duration of the study, 33 (69%) patients were able to decrease their corticosteroid dose by 30%, while 22 (46%) were able to decrease by 50%. Due to patients receiving concomitant high-dose corticosteroids, manifestations of joint and systemic features could not be completely assessed, as it would have been unethical to force patients to lower their steroid dose.

Currently, Roche Pharmaceuticals is conducting a Phase 3, 12-week, randomized, placebo-controlled study (TENDER trial) to evaluate the efficacy of tocilizumab in sJIA.⁷ The primary end point was number of patients achieving at least ACR30 with absence of fever. Secondary end points examined all ACR responses, ESR, hemoglobin, CHAQ, VAS, systemic features of sJIA with concurrent use of corticosteroids, and white blood cell (WBC) count at the end of the 12 weeks. Patients aged 2-17 years, with at least a 6-month history of sJIA and nonresponsiveness to non-steroidal antiinflammatory drug or corticosteroid treatment, were randomized to tocilizumab 8 mg/kg (>30 kg), tocilizumab 12 mg/kg (<30 kg), or placebo.

Additionally, a 92-week, open-label extension phase of the TENDER trial will examine the long-term efficacy of tocilizumab. Secondary end points include exploration of pharmacokinetic and pharmacodynamic parameters. This trial is no longer enrolling patients and preliminary results have been released.

Baseline characteristics were similar in both the tocilizumab and placebo groups. Sixty-four of 75 (85.3%) patients in the tocilizumab arm achieved an ACR30 response with an absence of fever compared with 9 of 37

(24.3%) patients in the placebo group ($p < 0.0001$). All ACR responses (30, 50, 70, and 90) at week 12 were statistically significant with tocilizumab compared with placebo. ACR core components and systemic features of tocilizumab were statistically significant compared with those of placebo at week 12. Finally, normalization of hemoglobin, CRP, WBC, and platelets in the tocilizumab group was statistically significant compared with effects in the placebo group. Pharmacokinetic and pharmacodynamic properties of tocilizumab from this trial are summarized in earlier sections of the article and demonstrate that there was no significant difference in serum concentrations for tocilizumab 8 mg/kg versus 12 mg/kg. Overall, tocilizumab was well tolerated in both the 8- and 12-mg/kg groups, with no statistically significant differences in adverse events. Two patients withdrew from the study: 1 in the tocilizumab 12-mg/kg group (angioedema) and 1 in the placebo group (histiocytosis hematophagic).

Imagawa et al. conducted an open-label, multicenter study at 5 institutions that evaluated the safety and efficacy of tocilizumab 8 mg/kg every 4 weeks in patients with pJIA and oJIA.²³ Patients were 2–19 years of age and had the following: an active diagnosis of pJIA or oJIA, at least 3 tender joints with limited range of motion, an ESR at or above 300 mm/h, a CRP at or above 1 mg/dL, and no treatment with biologics in the previous 3 months. Patients were excluded due to the following criteria: classification as ACR functional class IV, abnormal laboratory results (alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, WBC count, neutrophils), severe infection, allergy to protein formulations, or had not received DMARDs, corticosteroids, cytotoxic agents, or immunoglobulin in the past.

The primary end point of this study was ACR30 at week 12 and at the final visit of the 48-week extension phase. Nineteen patients participated in the initial study, while 17 continued in the extension phase. At weeks 4, 8, and 12, ACR30 was observed in 63.2%, 89.5%, and 94.7% of patients, respectively. ACR50 response rates were 78.9% at week 8 and 94.7% at week 12. ACR70 was achieved in 52.6% of patients at week 8 and 57.9% at week 12. Throughout the 48-week extension phase, ACR70 response rate remained high. ACR90 was unremarkable at week 12 (10.9%) but continued to increase to 64.7% by week 48. Seventy-five adverse events were reported throughout the study. The most common adverse events included nasopharyngitis (9), upper respiratory tract infection (9), gastroenteritis (4), pharyngitis (3), abdominal pain (3), diarrhea (3), and stomatitis (3).

Place in Therapy

The ACR released guidelines for the treatment of JIA in April 2011.²⁴ Recommendations include glucocorticoid

joint injections or methotrexate for the initial treatment of sJIA, followed by TNF- α inhibitors (adalimumab, etanercept, or infliximab) or abatacept (T-cell stimulation inhibitor). Choice of therapy is dependent on disease severity. Tocilizumab is not included in the ACR guidelines, as its Food and Drug Administration (FDA) approval for sJIA came after their publication. The guidelines state that future updates should focus on the expanding role of tocilizumab for patients with sJIA who have not achieved an adequate response with methotrexate and TNF- α inhibitors. As such, tocilizumab may be considered as an alternative treatment in steroid- and/or methotrexate-refractory sJIA; however, head-to-head studies against TNF- α inhibitors and abatacept have not been performed. Further such studies are warranted to solidify the place of tocilizumab in therapy.

Initial treatment for patients with pJIA includes glucocorticoid joint injections, with or without methotrexate, depending on the severity of disease.²⁴ If methotrexate therapy is not initially used, it should be considered if glucocorticoid joint injections prove to provide an inadequate response. Following 3–6 months of methotrexate therapy, a TNF- α inhibitor may be considered. If an adequate response is not achieved, the following treatment options are viable: switching to a second TNF- α inhibitor, initiation of abatacept, or initiation of tocilizumab.

Approved Labeling

Tocilizumab is FDA-approved for use in patients aged 2 years and older with active sJIA. It is recommended that tocilizumab only be initiated following an inadequate response to methotrexate and a TNF- α inhibitor. Biologic DMARDs and TNF- α inhibitors should not be administered with tocilizumab because of increased immunosuppression and risk for infection. Tocilizumab is also approved for treatment of moderate-to-severe rheumatoid arthritis in adults following an inadequate response to DMARDs and TNF- α inhibitors. Off-label uses of tocilizumab include the improvement of symptoms associated with Castleman disease and pJIA, and in patients with rheumatoid arthritis who have not been treated with a DMARD or TNF- α inhibitor.¹⁹

Dosage and Administration

The tocilizumab dosing regimen for sJIA is 8 mg/kg as a single intravenous drip infusion at 2-week intervals. Dosing for sJIA can be reduced to an interval of 1 week depending on the severity of the disease and the condition of the patient. Dosing for tocilizumab in pJIA is also 8 mg/kg as a single intravenous drip infusion, but given at 4-week intervals. Tocilizumab is a concentrate for solution for infusion and should be diluted to 100 mL with 0.9% sodium

chloride for patients who weigh more than 25 kg. For patients weighing less than 25 kg, tocilizumab should be diluted to 50 mL.¹⁹ Tocilizumab should be administered through an in-line filter at a rate of 10 mL/hour for the first 15 minutes. After patient vital signs have been assessed, the rate may be increased to 50 mL/hour for patients weighing less than 25 kg or 100 mL/hour for those weighing more than 25 kg, so that the volume is administered over 1 hour.²⁵

Warnings and Precautions

Tocilizumab should not be prescribed for patients with hypersensitivity to tocilizumab or any component of the medication. Patients with liver dysfunction should be administered tocilizumab cautiously; however, there are no current studies that support dose reduction in this population. With AST or ALT levels greater than 1.5 times the upper limit of normal (ULN), tocilizumab should not be initiated. Additionally, any patient taking tocilizumab whose AST/ALT levels subsequently rise to more than 5 times the ULN should immediately discontinue the medication. Tocilizumab has not been studied in patients with moderate-to-severe renal dysfunction (creatinine clearance <50 mL/min).¹⁹ There is a black box warning associated with tocilizumab, including an increased risk of developing serious infections such as tuberculosis, invasive fungal infections, MAS, and sepsis. Due to IL-6 inhibition, signs and symptoms may be masked during the acute phase reactions of an infection.⁸ The risk of serious infections is a class effect seen with all biologics, including adalimumab, etanercept, and infliximab, which are used in the treatment of sJIA and other autoimmune disorders.

Drug Interactions

Tocilizumab should not be coadministered with other biologic DMARDs, TNF- α inhibitors, IL-1R antagonists such as anakinra, or anti-CD20 monoclonal antibodies such as rituximab. Coadministration of these products can increase immunosuppression and the risk of infection. Live vaccines, such as herpes zoster vaccine, should not be administered to patients taking tocilizumab. Administration of live vaccines and immunosuppressants, such as tocilizumab, must be separated by at least 3 months to avoid an increased risk of infection.^{8,19} Inactivated vaccines, such as certain influenza vaccines, are approved for administration in patients taking tocilizumab. Through suppression of IL-6, tocilizumab indirectly increases the expression of CYP1A2, 2C9, 2C19, and 3A4.¹⁸ Therapeutic monitoring of substrates of these isoenzymes is recommended if coadministration is necessary. Due to the extended $t_{1/2}$ of tocilizumab, drug interactions may occur up to several weeks following discontinuation of therapy.

Therefore, it is recommended that medications with a narrow therapeutic index (eg, cyclosporine, warfarin) be individually dosed and monitored.

Adverse Events

During clinical Phase 2 and 3 trials, tocilizumab was generally well tolerated and safe, with no major drug-related adverse events identified. The incidence of adverse events is described in Table 2. The most commonly observed treatment-related adverse effects include nasopharyngitis, gastroenteritis, upper respiratory tract infections, increased liver enzymes, bronchitis, and elevated lactate dehydrogenase (LDH).^{7,20-23} Serious adverse effects were limited, and only 1 patient discontinued therapy due to an adverse reaction, which was documented as angioedema.⁷ There was no significant difference in adverse reactions between different doses of tocilizumab.⁷

The incidence of anti-tocilizumab neutralizing antibodies, which is a concern for all patients taking monoclonal antibodies and can lead to potentially life-threatening hypersensitivity reactions, has been low in all pediatric studies. The incidence of anti-tocilizumab antibodies was 8.6% (11/128 patients) in sJIA and 5.3% (1/19 patients) in pJIA, compared with 3% (18/601 patients) in adult rheumatoid arthritis studies.¹⁹ Patients prescribed tocilizumab should be screened periodically for anti-tocilizumab antibodies, and therapy should be discontinued if they are detected.

Although tocilizumab has a black box warning for increased risk of serious infection, none of these events was seen during short-term trials.¹⁹ Long-term safety data are warranted to better assess the significance of these potentially serious adverse events in pediatric patients.

Summary

Tocilizumab is currently the only medication with an FDA-approved indication for active sJIA. Clinical trials have demonstrated that tocilizumab is superior to placebo for sJIA and pJIA in terms of symptomatic response measured by ACR30, ACR50, and ACR70 following an inadequate response to either DMARDs or TNF- α inhibitor therapy. Tocilizumab provides an expansion of the currently available options for sJIA treatment, specifically in patients who have not responded to conventional therapies. Tocilizumab is generally well tolerated and has proven efficacy for up to 52 weeks, although further studies are warranted to determine its safety profile in long-term use. Comparative trials against other traditional therapies for JIA (ie, methotrexate, abatacept, etanercept, infliximab, and adalimumab) have not been conducted and are warranted to further solidify the utility of tocilizumab in the treatment of JIA, specifically as a first-line agent in sJIA, and its role in the treatment of pJIA.

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Table 2. Summary of Clinical Trial Adverse Drug Reactions

Adverse Drug Reaction	Woo ²⁰ (N = 15)	Yokota ²¹ (N = 11)	Imagawa ²³ (N = 19)	Yokota ²² (N = 56)	TENDER Trial ⁷ (N = 75)
Chicken pox, n (%)	1 (6.7)	NR	NR	NR	1 (1.3)
Pancytopenia, n (%)	1 (6.7)	NR	NR	NR	NR
Disease flares, n (%)	4 (26.7)	NR	NR	NR	NR
Herpes simplex mouth sores, n (%)	1 (6.7)	NR	NR	NR	NR
Upper respiratory tract infection, n (%)	NR	2 (18.2)	9 (47.4)	NR	NR
Pustules on extremities, n (%)	NR	3 (27.3)	NR	NR	NR
Eczema, n (%)	NR	1 (9.1)	NR	NR	NR
Increases in total cholesterol, n (%)	NR	4 (36.4)	NR	NR	NR
Mild decreases in gamma globulin, n (%)	NR	4 (36.4)	NR	NR	NR
Mild increases in β -N-acetyl-D-glucosaminidase, n (%)	NR	3 (27.3)	NR	NR	NR
Elevation of aminotransferase, n (%)	NR	2 (18.2)	NR	alanine 16 (28.6) aspartate 12 (21.4)	NR
Glucosuria, n (%)	NR	2(18.2)	NR	NR	NR
Nasopharyngitis, n (%)	NR	NR	9 (47.4)	33 (58.9)	8 (10.7)
Insect bite, n (%)	NR	NR	4 (21.1)	NR	NR
Gastroenteritis, n (%)	NR	NR	4 (21.1)	16 (28.6)	NR
Pharyngitis, n (%)	NR	NR	3 (15.8)	NR	NR
Diarrhea/vomiting/abdominal pain, n (%)	NR	NR	6 (31.6)	NR	14 (18.7)
Stomatitis, n (%)	NR	NR	3 (15.8)	NR	NR
Bronchitis, n (%)	NR	NR	NR	14 (25)	NR
LDH elevation, n (%)	NR	NR	NR	10 (17.9)	NR
Anaphylactoid reaction, n (%)	NR	NR	NR	1 (1.8)	1 (1.3)
Gastrointestinal hemorrhage, n (%)	NR	NR	NR	1 (1.8)	NR
Herpes zoster, n (%)	NR	NR	NR	1 (1.8)	NR
Infectious mononucleosis, n (%)	NR	NR	NR	1 (1.8)	NR
Fever, n (%)	NR	NR	NR	NR	5 (6.7)
Bacterial arthritis infection, n (%)	NR	NR	NR	NR	1 (1.3)
Neutropenia, n (%)	NR	NR	NR	NR	3 (4)

LDH = lactic dehydrogenase; NR = not reported.

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EXTRACTO

Tocilizumab para el Tratamiento de la Artritis Idiopática Juvenil

K Decelle y ER Horton

Ann Pharmacother 2012;46:822-9.

OBJETIVO: Evaluar la farmacología, eficacia clínica, seguridad, y rol de tocilizumab para el tratamiento de la artritis idiopática juvenil.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda bibliográfica a través de MEDLINE mediante la base de datos PubMed (1970-diciembre de 2011) y de *Abstractos Farmacéuticos Internacionales* (1970-diciembre de 2011) para identificar los ensayos clínicos y revisar los artículos. Se utilizaron los siguientes términos de búsqueda clave en inglés en distintas combinaciones de términos: tocilizumab, anti-interleukin 6 (anti-interleuquina 6), y juvenile idiopathic arthritis (artritis idiopática juvenil). Se examinaron las bibliografías de artículos seleccionados para identificar las referencias adicionales y los ensayos en curso se obtuvieron mediante una revisión de la página web www.clinicaltrials.gov.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Los artículos se limitaron a aquellos escritos en lengua inglesa y realizados en humanos. Los estudios incluidos en la revisión examinaron los datos pediátricos sobre la artritis idiopática juvenil sistémica y poliarticular. Se obtuvo información general al respecto mediante la revisión de la literatura en adultos y niños en una amplia variedad de enfermedades autoinmunes.

SÍNTESIS: Tocilizumab está aprobado actualmente por la FDA para su uso en niños mayores de 2 años con artritis idiopática juvenil sistémica. Tocilizumab ha mostrado su superioridad con respecto al placebo a la hora de producir una respuesta sintomática durante los ensayos clínicos de fase II y III. Se determinó que tocilizumab era seguro con solo un pequeño número de eventos farmacológicos adversos graves acontecidos durante la realización de los estudios.

CONCLUSIONES: Tocilizumab aumenta las opciones disponibles para el tratamiento de la artritis idiopática juvenil sistémica, específicamente en pacientes que no han respondido a las terapias convencionales. Tocilizumab se tolera relativamente bien y se ha probado su eficacia durante hasta 52 semanas. Es necesario la realización de estudios posteriores que determinen su utilidad como opción de tratamiento de primera línea para la artritis idiopática juvenil sistémica, así como su papel dentro del tratamiento de la artritis idiopática juvenil poliarticular.

Traducido por Enrique Muñoz Soler

RÉSUMÉ

Le Tocilizumab Pour le Traitement de l'Arthrite Juvénile Idiopathique

K Decelle et ER Horton

Ann Pharmacother 2012;46:822-9.

OBJECTIF: Évaluer la pharmacologie, les données d'efficacité et d'innocuité ainsi que le rôle du tocilizumab pour le traitement de l'arthrite juvénile idiopathique (AJI).

SOURCES D'INFORMATION: Une recherche de littérature a été effectuée dans les banques de données MEDLINE et *International Pharmaceutique Résumé* (période de publication entre 1970 et le mois de décembre 2011) en utilisant les mots-clés suivants: tocilizumab, antagoniste de l'interleukine 6 et arthrite juvénile idiopathique. Les bibliographies des articles identifiés ont aussi été revues afin d'obtenir des références additionnelles.

SÉLECTION DE L'INFORMATION ET EXTRACTION DES DONNÉES: Tous les articles publiés en anglais ainsi que les essais cliniques ayant évalué le tocilizumab chez les enfants atteints d'AJI systémique et poly-articulaire ont été évalués. Des informations générales sur ce nouvel anticorps monoclonal ont aussi été recueillies d'articles de revue décrivant l'utilisation du tocilizumab chez les patients adultes et pédiatriques souffrant de différentes maladies auto-immunes.

RÉSULTATS: Le tocilizumab est officiellement indiqué par l'agence réglementaire américaine pour traiter les enfants de plus de 2 ans atteints d'AJI. Le tocilizumab a démontré une efficacité supérieure au placebo dans les essais cliniques de phase II et III. Il semble bien toléré et n'a été associé qu'avec un nombre limité d'effets indésirables graves.

CONCLUSIONS: Le tocilizumab offre une nouvelle option thérapeutique pour les enfants atteints d'AJI, particulièrement chez les enfants n'ayant pas répondu aux thérapies conventionnelles. Les données disponibles démontrent une bonne efficacité et une innocuité acceptable jusqu'à une période de 52 semaines d'utilisation. Des essais additionnels sont toutefois requis afin de déterminer la place du tocilizumab dans l'arsenal thérapeutique de l'AJI ainsi que son rôle possible comme agent de première intention.

Traduit par Sylvie Robert