



Use of tocilizumab in

## Juvenile Idiopathic Arthritis

Evidence Based Medicine

Official recommendations

Expert opinion

The data generated by clinical trials of tocilizumab in adults with rheumatoid arthritis or Still's disease cannot be directly extended to paediatric patients.

Some subgroups of juvenile idiopathic arthritis (JIA) have no equivalent in adults (oligoarticular JIA with chronic anterior uveitis) and others exist in adults but may present with different initial clinical manifestations (psoriatic arthritis, enthesitis-related arthritis). Furthermore, the distribution of clinical patterns differs between JIA and chronic inflammatory joint disease in adults (for example, juvenile RA <5% of JIA cases).

IL-6 directly and indirectly inhibits the growing bone, from birth to puberty, an effect not relevant to adults.

The same drug may have different safety profiles in paediatric patients and adults, as both the immune system and the drug clearance pathways are at different stages of maturation; and the environment, most notably in terms of exposure to infectious agents, also differs.

The low prevalence of JIA has limited the number of high-quality randomised controlled trials, as well as the number of patients included in each trial. Furthermore, no sufficiently powered long-term trial in paediatric patients is available. Consequently, although effects in adults with RA cannot be extended to paediatric patients, thorough familiarity with the clinical trials in adults is crucial to a sound evaluation of the risks and benefits of a biological agent in JIA <sup>(87)</sup>.

### In what indications has tocilizumab been used in paediatric patients with joint disease?

Depending on the country of travel, specific immunisations are required. Planning ahead is crucial in this situation.

- **Systemic juvenile idiopathic arthritis (systemic JIA or childhood-onset Still's disease)**

Systemic JIA is characterised by an unexplained spiking fever for at least 2 weeks, arthritis, and extra-articular manifestations (rash, hepatosplenomegaly, lymphadenopathy, and serositis) in a patient younger than 16 years of age <sup>(88, 89)</sup>.

This clinical pattern contributes 10% of all cases of JIA. Systemic JIA is a serious disease with a 10-year remission rate of only 37% <sup>(90)</sup>.

Furthermore, among JIA patterns, systemic JIA has the highest mortality rate. The main causes of death are macrophage activation syndrome, infections, and AA amyloidosis.

To achieve disease control, in most cases, high doses of glucocorticoids must be used. These high doses jeopardise the long-term outcome by inducing adverse effects (arrest in statural growth, osteoporosis with fractures) <sup>(91)</sup>.

The results of therapeutic trials indicate that tocilizumab is among the most promising treatments for systemic JIA<sup>(92-95)</sup>, a disease that is often steroid-dependent (50%) and refractory to multiple conventional maintenance drugs (methotrexate, cyclosporine A, intravenous immunoglobulins...) <sup>(96, 97)</sup> and sometimes also to biological agents against TNF and IL-1 <sup>(98, 99)</sup>. Furthermore, tocilizumab may prevent the development of long-term complications of systemic JIA (amyloidosis, statural growth delay, and osteoporosis) <sup>(100-102)</sup>.

### ● Polyarticular-course juvenile idiopathic arthritis

Two open-label studies conducted in Japan and presented at the October 2006 ACR meeting and June 2009 EULAR meeting indicate a high level of effectiveness of tocilizumab in children with polyarticular-course JIA, with a suggestion of structural lesion improvement during treatment <sup>(88, 89, 103, 104)</sup>.

### ● Amyloidosis in a patient with extended oligoarticular JIA

Systemic amyloidosis complicating extended oligoarthritis in a 14-year-old girl was successfully treated with tocilizumab. This case-report deserves careful attention, as no effective treatment for AA amyloidosis is currently available <sup>(105)</sup>.

## Why use tocilizumab in systemic JIA?

### ● Systemic JIA and IL-6

#### – Systemic effects

Patients with systemic JIA have very high serum IL-6 levels that fluctuate in lockstep with the daily fever spikes that characterize the disease. The high serum IL-6 levels contribute also to the profound asthenia and anorexia seen in patients with systemic JIA. IL-6 promotes the development of amyloidosis in systemic JIA by inducing the production of Serum Amyloid A (SAA), the precursor of amyloid protein. IL-6 also promotes the development of macrophage activation syndrome by exacerbating the responses to infectious stimuli. Biologically, IL-6 is the main positive regulator of liver synthesis of acute-phase proteins (CRP, SAA, fibrinogen), whose levels are consistently elevated during flares of systemic JIA. Finally, IL-6 induces thrombocytosis and severe microcytic anaemia (via increased release of hepcidin, an iron metabolism regulator), which is a common finding in refractory systemic JIA <sup>(106-108)</sup>.

#### – Osteoarticular effects

Serum IL-6 levels correlate with the extent and severity of joint involvement in patients with systemic JIA <sup>(108)</sup>. IL-6 may play a direct role in joint destruction and osteoporosis, as it promotes osteoclast differentiation.

Serum IL-6 elevation in children with systemic JIA correlates with decreases in growth velocity. This effect is related to at least two mechanisms: IL-6 decreases the growth-promoting effects of serum IGF1 and locally inhibits the early stages of chondrogenesis <sup>(109, 110)</sup>.

### ● Systemic JIA and tocilizumab

How can the effectiveness of treatment be evaluated in systemic JIA?

The effectiveness of treatment in patients with JIA is evaluated using the ACRPedi scale based on six variables (1/ global VAS assessment by the physician, 2/ global VAS assessment by the patient or parent, 3/ C-HAQ, 4/ number of joints with active arthritis, 5/ number of joints with limited range of motion, and, 6/ ESR). ACRPedi30 is an at least 30% improvement in at least three of the six variables, without a 30% or greater worsening of more than one of the six variables<sup>(111)</sup>.

In studies of systemic JIA, the ACRPedi scale was modified to take the systemic manifestations into account. In some studies, the CRP level had to remain below a threshold, which varied across studies. In other studies, a more comprehensive tool was used, such as the systemic score developed by Woo et al. and based on the presence of a fever, peripheral lymphadenopathy, hepatosplenomegaly, serositis (pericarditis, pleuritis, or peritonitis), and a rash<sup>(92)</sup>. To date, no systemic score has been validated.

It has been suggested that the steroid-sparing effect of the study treatment may deserve to be evaluated.

Results of therapeutic trials of tocilizumab in systemic JIA

➤ Tocilizumab has been proven effective in improving both the systemic and the articular manifestations of systemic JIA refractory to conventional DMARDs or to biologics against TNF or IL-1<sup>(92-94)</sup> (Table 11).

➤ Two phase II studies have been published, one from the UK and the other from Japan<sup>(92, 93)</sup>.

- The study from the UK included 18 patients with systemic JIA, who were allocated at random to tocilizumab in a fixed dose of 2, 4, or 8 mg/kg [in systemics, the doses are given every 2 weeks, and the trial attributed in a random manner 3 fixed doses], with follow-up for 4, 6, and 8 weeks, respectively<sup>(92)</sup> (Table 11). In addition to steroid therapy, 12 patients also received fixed-dose methotrexate (< 20 mg/m<sup>2</sup>/week). Three patients were excluded because of protocol violations (rescue by increasing the steroid dosage). The proportions of patients with an ACRPedi30 response at week 1 were 75% with 2 mg/kg (n=4), 83% with 4 mg/kg (n=6), and 60% with 8 mg/kg (n=5); corresponding proportions at week 6 were 0%, 67%, and 40%, respectively; and at week 8 0%, 0%, and 20%, respectively. The systemic score (cervical, axillary, and inguinal lymphadenopathy; hepatomegaly and splenomegaly; fever; rash; and clinical serositis [pericarditis, pleuritis, or peritonitis]) and the laboratory markers for inflammation showed marked improvements as early as 1 week after the infusion. This study showed that the efficacy of the 4 and 8 mg/kg dosages was greater and longer lasting in patients with systemic JIA

- The Japanese study was done in 11 patients with systemic JIA who received escalating tocilizumab dosages (2, 4, and 8 mg/kg/2 weeks) depending on the serum CRP level measured 15 days after the infusion<sup>(93)</sup> (Table 11). Two weeks after the third fixed-dose tocilizumab infusion, the proportions of patients with an ACRPedi30 response were 64% with 2 mg/kg (n=11), 87% with 4 mg/kg (n=8), and 100% with 8 mg/kg (n=3); in these three groups, an ACRPedi70 response was obtained in 9%, 50%, and 100% of patients, respectively. As early as the first treatment week, 6 of the 11 patients were afebrile. Abrupt CRP elevations were noted between the second and fourth treatment weeks until an adequate serum tocilizumab level was achieved; these elevations coincided with systemic symptom recurrences. The authors concluded that tocilizumab produced a highly significant decrease in the activity of systemic JIA, with a marked dose-effect.

➤ The only published Phase III study was done in Japan in 56 patients with refractory systemic JIA that was inadequately controlled by steroid therapy<sup>(94)</sup> (Table 11). Conventional DMARDs were not allowed during the trial. After a 6-week open-label lead-in phase during which all patients received tocilizumab (8 mg/kg/2 weeks), patients with an ACRPedi30 response and a CRP level <5 mg/L were allocated at random to double-blind treatment with tocilizumab or a placebo for 12 weeks. A 48-week open-label extension was then conducted. During the double-blind phase, patients in the placebo group who relapsed (i.e., who did not maintain an ACRPedi30 response and/or had CRP levels >15 mg/L) were transferred to the open-label extension phase.

At the end of the open-label lead-in phase, the proportions of patients with ACRPedi30, 50, and 70 responses were 91%, 86%, and 68%, respectively. Among the 43 randomised patients, 17%<sup>(4/23)</sup> of the placebo patients and 80%<sup>(16/20)</sup> of the tocilizumab patients maintained an ACRPedi30 response and CRP levels <15 mg/L ( $p<0.001$ ). At the end of the open-label extension phase (n=48), the proportions of patients with ACRPedi30, 50, and 70 responses were 100%, 95%, and 90%, respectively. These data confirm that IL-6 blockade significantly improves the health status of patients with systemic JIA.

➤ An international Phase III study in patients with systemic JIA is under way to generate further efficacy and safety data in this indication and to identify the optimal tocilizumab dosage, particularly in children weighing less than 30 kg, in whom the Phase II Japanese trial showed decreased efficacy related to pharmacokinetic differences (ClinicalTrials.gov identifier: NCT00642460).

➤ The beneficial effects of tocilizumab 8 mg/kg/2 weeks in patients with systemic JIA were maintained in the long term. A single long-term study is available; it was conducted in patients entered into open-label extension phases of Phase II and III studies and in 61 additional patients with systemic JIA, for a total of 128 patients with a median follow-up of 9 years<sup>(94)</sup> (Table 11). The median steroid dosage was 0.5 mg/kg/d before tocilizumab initiation and the median duration of tocilizumab treatment was 78 weeks. At week 48 (n=78), the proportions of patients with ACRPedi30, 50, and 70 responses were 94%, 88%, and 81%, respectively; corresponding proportions at week 96 (n=58) were 100%, 98%, and 93%; and at week 144 (n=41) 100%, 100%, and 90%.

- Tocilizumab may also be able to slow structural disease progression. The first report of the effects of tocilizumab therapy (8 mg/kg/2 weeks) on radiological lesions in patients with systemic JIA was presented at the June 2009 EULAR meeting<sup>(95)</sup>. The 20 patients underwent radiographs of all large joints before and during tocilizumab therapy. Mean treatment duration was 41 months. Marked improvements were noted not only in the periarticular osteoporosis and swelling, but also in the joint space narrowing and joint erosions. All 20 patients achieved a clinical and biological response. The structural effects of tocilizumab therapy deserve to be investigated in larger cohorts.
- Finally, tocilizumab therapy improves the extra-articular manifestations of systemic JIA. More specifically, a highly significant improvement in statural growth was observed, as well as a decrease in osteoporosis and effective prevention of systemic amyloidosis<sup>(93, 101, 102)</sup>.

### Why use tocilizumab in polyarticular-course JIA?

#### ● Polyarticular-course JIA and IL-6

As with systemic JIA, significant correlations are found in extended oligoarticular and polyarticular JIA between serum IL-6 levels and both CRP and ESR values<sup>(112)</sup>, and 95% of joint fluids from patients with extended oligoarticular or polyarticular JIA contain high IL-6 levels<sup>(112, 113)</sup>. These data, together with the results of studies in adults, indicate that IL-6 blockade is a worthwhile treatment objective in polyarticular-course JIA (see the fact sheets for adults).

#### ● Polyarticular-course JIA and tocilizumab

➤ The effects of tocilizumab in polyarticular-course JIA were reported at the ACR meeting held in October 2006<sup>(103)</sup> (Table 11). In 19 patients aged 3 to 19 years and having extended oligoarticular or polyarticular JIA, open-label tocilizumab monotherapy was given in a dosage of 8 mg/kg every 4 weeks for 12 weeks. At week 12, the proportions of patients with ACRPedi30, 50, and 70 responses were 95%, 95%, and 58%, respectively. These highly promising preliminary findings may warrant the use of tocilizumab in international Phase III therapeutic trials in patients with polyarticular-course JIA.

➤ Finally, the first prospective data on the effects of tocilizumab on structural disease progression in polyarticular-course JIA were presented at the June 2009 EULAR meeting<sup>(104)</sup>. Tocilizumab 8 mg/kg/2 weeks was given to 3 patients with JIA (6-19 years) for 24 to 31 months. There was an excellent response in terms of the swollen and tender joint counts and laboratory markers for inflammation. Furthermore, the joint space narrowing decreased in over half the affected joints. Thus, IL-6 blockade in patients with polyarticular-course JIA may decrease or reverse radiographic joint lesion progression.

## What adverse effects have been reported in tocilizumab-treated paediatric patients with systemic or polyarticular-course JIA?

Table 11 reports the adverse events (AEs) and serious adverse events (SAEs) in the Phase II and III studies and long-term study of systemic JIA and in the only open-label study in polyarticular-course JIA <sup>(92-94)</sup>.

### ● Systemic JIA

➤ In brief, in systemic JIA, the most common adverse events were nasopharyngitis (59%), upper airway infections (34%), and gastroenteritis (29%), as well as moderate and transient transaminase elevations (20-30%), particularly in patients receiving concomitant methotrexate therapy.

Mild-to-moderate infusion-related reactions occurred in 18% of patients. Elevations in total cholesterol levels seem moderate and within the normal range in patients with systemic JIA.

Potential effects of tocilizumab on immunity, such as immunogenicity (production of IgE antibodies to tocilizumab) and a decrease in lymphocyte counts should be carefully looked for and monitored in these patients who often have severe immunodeficiency, related to the many years spent with a markedly steroid-dependent disease.

➤ To date, no cases of tuberculosis, opportunistic infections, cancer, or autoimmune disease have been reported in paediatric patients treated with tocilizumab.

➤ The main SAEs in patients with systemic JIA were severe infections (14.5/100 patient-years), which chiefly affected the gastrointestinal tract and lungs. The rate of serious infections may be ascribable in part to the low level of clinical and biological inflammation during infections in tocilizumab-treated patients, which contributes to delay the diagnosis. Other reported SAEs consist of 1 case each of transient pancytopenia, macrophage activation syndrome, gastrointestinal bleeding, anaphylaxis, and cardiac amyloidosis. Finally, 2 children with systemic JIA died during tocilizumab treatment, one from macrophage activation syndrome and the other from cardiac amyloidosis; of these two complications, only macrophage activation syndrome may be related to tocilizumab treatment <sup>(94)</sup>.

### ● Polyarticular-course JIA

The experience acquired with tocilizumab in polyarticular-course JIA (extended oligoarticular and polyarticular forms) is consistent with the results in children with systemic JIA. Thus, the most common adverse events were commonplace upper respiratory tract infections and modest elevations in serum transaminases and lipids <sup>(103)</sup>.

### Selecting patients with systemic or extended oligoarticular/polyarticular JIA for tocilizumab therapy

➤ Tocilizumab was granted a marketing licence (AMM) in 2009 in France for rheumatoid arthritis in adults; to date, this drug is not approved for use in paediatric patients in Europe in any indication.

In Japan, tocilizumab was granted a marketing licence for systemic JIA and polyarticular-course JIA in April 2008. Tocilizumab is delivered only after inclusion of the patient in the Japanese nationwide registry.

➤ The analysis of the data on JIA rests on both valid scientific evidence and expert opinion.

- Tocilizumab is a treatment alternative in patients with systemic JIA refractory to appropriate steroid therapy. An international study in patients with systemic JIA is ongoing to determine the optimal tocilizumab dosage, particularly in children weighing less than 30 kg, and to validate the efficacy and safety data reported by the Japanese groups. This study will also determine whether tocilizumab has a steroid-sparing effect.

The youngest age for using tocilizumab therapy in systemic JIA was 2 to 3 years, depending on the trial (Table 11).

The optimal dosage used in the trials was 8 mg/kg and the interval between intravenous infusions in patients with systemic JIA was 2 weeks. An international randomised double-blind placebo-controlled trial in this indication has already started. The results will show whether the efficacy and safety data presented at rheumatology meetings are confirmed.

According to the therapeutic trials, the lowest age at which tocilizumab can be prescribed in polyarticular-course JIA is 2 years (Table 11).

The optimal dosage used in the trials was 8 mg/kg and the interval between intravenous infusions in patients with polyarticular-course JIA was 4 weeks.

- Tocilizumab is a treatment alternative in patients with polyarticular-course JIA refractory to one or more DMARDs or anti TNF therapy.

### Work-up before initiating tocilizumab therapy in a paediatric patient

This workup is separate from the assessment of disease activity and severity.

➤ Look for contraindications to tocilizumab (hypersensitivity and severe uncontrolled infections such as sepsis and opportunistic infections) and/or conditions requiring special precautions (active liver disease, neutropenia and thrombocytopenia, dyslipidaemia, malignancy within the last 5 years).

➤ Identify and eradicate any active foci of acute, chronic, or recurring infection.

➤ Look for active or latent tuberculosis (symptoms, history, contact, suggestive clinical signs): Tubertest 5IU, read between the 48<sup>th</sup> and 72<sup>nd</sup> hour and considered positive (i) if induration >5 mm in children not immunized with the BCG vaccine or having severe immunosuppression, (ii) if induration >10 mm in children immunized

with the BCG or having mild immunodepression. Even the slightest doubt about the Tubertest result, most notably in BCG-immunized children, should prompt testing with Quantiferon or TB-Spot (which may raise problems with health insurance reimbursement) and a chest radiograph.

- Look for concomitant medications that interact with tocilizumab (see the fact sheet on drug-drug interactions)
- In teenagers, a discussion of birth control is crucial.

The pre-treatment blood tests should include the following:

- Blood cell counts, ESR, CRP
- ASAT and ALAT
- Total cholesterol, LDL and HDL cholesterol, triglycerides
- Urea, serum creatinine, urine dipstick test
- Serological tests for hepatitis B and C and, with the parents' consent, HIV infection.

Immunisations should be up to date. Tocilizumab therapy does not place any restrictions on the administration of inactivated vaccines (hexavalent vaccines to diphtheria, tetanus, polio, pertussis, haemophilus, and pneumococcus; pneumococcal vaccines; influenza vaccines; vaccines against typhoid fever, hepatitis A, hepatitis B, and papilloma virus, etc.), which are best given during periods of lesser disease activity.

At present, tocilizumab therapy contraindicates all live attenuated vaccines (MMR, varicella, BCG, yellow fever, and oral polio) for as long as tocilizumab is given. If allowed by the patient's status and the treatment regimen, a useful measure may consist in administering live attenuated vaccines at least 3 weeks before starting tocilizumab therapy (particularly in children who have a negative history for varicella).

### Evaluating the safety and effectiveness of tocilizumab therapy in paediatric patients: how and how often?

- Before each tocilizumab infusion, a physical examination should be performed to look for evidence suggesting an infection, cancer, autoimmune disease, or demyelination. The parents should be informed of the risk of infection associated with tocilizumab therapy. Any symptoms that suggest an infection in a tocilizumab-treated patient should lead routinely to prompt evaluation by a physician and to appropriate treatment. It should always be borne in mind that tocilizumab therapy blunts or abolishes the acute-phase inflammatory response. The risk of demyelination in paediatric patients treated with tocilizumab is unknown. Neither are any data available on the risk of cancer in this population.
- Before the tocilizumab infusion, the following laboratory tests should be obtained.
  - Blood cell counts, a platelet count, and transaminase levels every 15 days for the first 3 months to look for cytopenia (neutropenia, lymphopenia, and thrombocytopenia) and transaminase elevation,



which may contraindicate further tocilizumab therapy (transaminase elevation may be more common in patients on concomitant methotrexate therapy, and the risk of neutropenia may be increased in patients with a history of TNF antagonist therapy). Subsequently, the laboratory tests may be performed monthly for 6 months then every 3 months as long as the results remain normal. In patients with cytopenia or transaminase elevation, given the absence of paediatric data, the tocilizumab dosage should be adjusted based on current practice in adults with RA and on normal ranges for paediatric individuals, which vary across age groups.

- Serum lipid assays should be obtained 4 to 8 weeks after tocilizumab initiation. The patients should be monitored in compliance with clinical practice guidelines for the management of dyslipidaemia. No cardiovascular abnormalities related to tocilizumab-induced dyslipidaemia have been reported in paediatric patients.
  - CRP monitoring should prove helpful for tocilizumab dosage adjustment, as CRP is a marker for complete inhibition of IL-6 effects.
- During the tocilizumab infusion and for 2 hours after the end of the infusion, the patient should be monitored in the hospital for evidence of intolerance and for skin reactions.

**Evaluation of the effectiveness of tocilizumab in JIA relies chiefly on the ACRPedi criteria <sup>(108)</sup> and on resolution of the clinical and laboratory evidence of systemic inflammation, which should be checked at least once every 3 months as long as the treatment proceeds uneventfully.**