



**North East Treatment
Advisory Group**

Tocilizumab for Juvenile Idiopathic Arthritis

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Summary

- Tocilizumab (RoActemra®) is a monoclonal antibody licensed for the treatment of rheumatoid arthritis in adults. It is proposed for the off-license treatment of juvenile idiopathic arthritis, as an alternative to off-license use of anakinra in patients with systemic onset disease and as a subsequent treatment option for patients with polyarticular disease. In both cases the only alternative treatment option is considered to be a stem cell transplant.
- The evidence base for use of tocilizumab in these indications is developing. A significant volume of evidence for use in patients with systemic onset juvenile arthritis has demonstrated efficacy compared with placebo. The evidence base in polyarticular disease is less well developed but nonetheless demonstrates a high level of efficacy. All studies have been against placebo or in the absence of a comparator, patient numbers have been small and patient selection was enriched favouring known responders. Long-term follow-up results are available in abstract only and indicate that efficacy is maintained for the majority of patients.
- Tocilizumab presents a predictable and manageable range of adverse effects in paediatric patients, similar to that seen in adult patients. The most common effects are an increased incidence in respiratory infections and gastroenteritis. The long term effects of tocilizumab in paediatric patients, with therapy extending into adolescence or adulthood, are not known.
- The cost of therapy is dependent on patient mass, in turn largely dependent on patient age. Annual cost per patient is estimated to range from £13,000 to £18,500 based on a four-weekly administration schedule. The majority of this cost is due to the tariff price for a paediatric rheumatology day-case admission (£11,000 per patient per annum).
- Substantial off-set costs exist if tocilizumab is used in place of anakinra (about £11,000 per patient per annum) or if a stem-cell transplant is avoided (about £46,000 per patient).
- Patients would preferentially be offered entry into a relevant on-going clinical study, although this might involve treatment outside of the region. It is estimated that about one or two patients per annum from NHS North East may still require treatment.

Introduction and background

Tocilizumab (RoActemra®, Roche) is a monoclonal antibody antagonist acting against the interleukin-6 (IL-6) receptor. It is licensed for the treatment of rheumatoid arthritis in adult patients.¹ A member decision-making group has referred an application for off-license use of tocilizumab to the North East Treatment Advisory Group. The application proposes to use tocilizumab for the treatment of polyarticular juvenile idiopathic arthritis and as an alternative to anakinra for the treatment of systemic-onset juvenile idiopathic arthritis.

Juvenile idiopathic arthritis (JIA) is a chronic autoimmune inflammatory joint disease and is the most common rheumatic disease in children and adolescents. JIA is defined as persistent arthritis of unknown aetiology that begins before the age of 16 years and persists for at least six weeks. In children (age ≤ 15 years) the incidence of JIA in the UK is estimated to be around 1 in 10,000 with a prevalence of 1 in 1,000.²⁻⁴ This equates to about 430 patients with JIA within NHS North East.

Polyarticular JIA (also known as polyarthritic JIA) accounts for around 25% of all cases of JIA and is diagnosed if there is arthritis affecting five or more joints during the first six months of disease. A high proportion of patients (30 to 40%) with polyarticular disease develop destructive joint disease.

Systemic-onset juvenile idiopathic arthritis (SoJIA) is a chronic arthritis in one or more joints associated with systemic features including spiking fever, transient rash, lymphadenopathy and hepatosplenomegaly. Although it accounts for approximately 10% of all patients with JIA it represents a greater burden of disease with increased morbidity and mortality compared with other forms of JIA.^{2,4,5}

The course of JIA can be highly variable with some patients achieving spontaneous resolution whilst others experience significant growth retardation, joint contractures, eye problems, and permanent disability. In patients who develop destructive joint disease multiple surgical interventions, including joint replacements, may be required.

The prognosis generally depends on the subtype of JIA, its severity, how early therapy begins and the adequacy of treatment. Patients with polyarticular or SoJIA tend to have a worse prognosis and more severe disability than other JIA patients. Even with treatment sustained remission occurs in only a small minority of patients with up to 50% of children entering adulthood with ongoing active disease.^{2,4-6}

Management of JIA is complex and requires a combination of drug treatments, physical and occupational therapy, and psychosocial support. Despite recent advances in therapy for JIA, no treatment has been shown to be curative. The goals of drug therapy are to suppress inflammation, reduce

chronic joint pain, prevent or control joint damage, maximise physical function and improve quality of life. In the UK, the majority of children will be managed by a consultant rheumatologist, usually in a tertiary specialist centre.^{2,4}

Non-steroidal anti-inflammatory drugs (NSAIDs) are still a useful treatment option however they do not influence disease progression or prevent joint damage.

Other treatment options include disease-modifying and immunosuppressant drugs such as corticosteroids (including intravenous and intra-articular) and methotrexate. Subcutaneous methotrexate is used as the first-line disease-modifying agent in polyarticular JIA and SoJIA.

Some of the newer, biological agents are licensed for JIA. Etanercept (Enbrel®) and adalimumab (Humira®) are the only anti-tumour necrosis factor (aTNF) drugs licensed for paediatric patients. NICE has recommended the use of etanercept in children aged 4 to 17 years with active polyarticular JIA. Adalimumab is also now licensed for the treatment of polyarticular JIA in adolescent patients aged 13 to 17 years although NICE has not issued guidance relating to this indication.^{2,4-7} Abatacept (Orencia®) is the only other biological therapy licensed for JIA, specifically polyarticular disease.

Patients who fail to respond to subcutaneous methotrexate are treated with etanercept in addition to or instead of methotrexate. Older patients or those considered at risk of uveitis are offered adalimumab instead.

The off-license use of anakinra (Kineret®) for treatment of refractory SoJIA has been reported.^{5,6,8} Evidence from uncontrolled studies suggests that anakinra is effective for systemic non-arthritic and arthritic symptoms in patients with SoJIA. However the data also indicates that only around 50% of patients with SoJIA respond to treatment.^{9,10} There is limited evidence for the efficacy of anakinra in patients with polyarticular JIA.¹¹

The final treatment option for JIA is considered to be an autologous stem-cell transplant (also known as a 'bone marrow transplant'). This is an intensive and costly procedure with a relatively high mortality rate (~10%) although complete remission of disease in the absence of further drug therapy can be achieved in about half of patients.¹²

Clinical evidence

The majority of the evidence for the use of tocilizumab in JIA is in patients with SoJIA. Only one source of evidence relating to use in polyarticular JIA was identified. In common with other studies of biological therapies in JIA, the main outcome measure was the proportion of patients achieving a specific ACR Pedi threshold (see appendix 1).

Polyarticular juvenile arthritis

Unpublished evidence presented to the American College of Rheumatology conference in 2006 evaluated the efficacy of tocilizumab in a 12-week open label trial in patients with polyarticular or oligoarticular JIA.¹³ The study enrolled 19 patients with a mean age of 12 years. Seventeen patients had polyarticular disease. Patients were treated with tocilizumab 8 mg/kg every four weeks. After 12 weeks of treatment ACR Pedi 30, 50, and 70 responses were achieved by 18 (95%), 18 (95%), and 11 (58%) children, respectively.

All 19 patients were enrolled in a 48-week extension study with continued treatment with tocilizumab 8 mg/kg every four weeks.¹⁴ Concomitant treatment with other anti-rheumatic therapies was not permitted. After 48-weeks 17 of 19 patients were still receiving tocilizumab with 11 completing the 48-week efficacy assessment. All of these 11 patients achieved ACR Pedi 30 and 50 responses levels and ten achieved the ACR Pedi 70 response level. One patient was withdrawn from the study due to development of antibodies against tocilizumab.

Systemic onset juvenile arthritis

The key tocilizumab study in SoJIA is a small phase III study.¹⁵ Eligible patients had received a mean of two prior therapies although it is not clear the proportion that had received prior aTNF therapy specifically. The study consisted of three phases with an open label six-week lead in phase followed by a 12-week double-blind placebo-controlled phase for responders, followed by ≥ 48-week open label follow-up phase. Fifty-six patients aged 2 to 19 years (mean 8 years) were recruited to the study.

In the first phase patients received three doses of tocilizumab 8 mg/kg every two weeks, with six patients withdrawing due to presence of antibodies against tocilizumab (n = 3), adverse effects (n = 2) and lack of efficacy (n = 1). At the end of the open-label lead-in phase ACR Pedi 30 responses were achieved by 51 (91%) patients and ACR Pedi 50 and 70 responses by 48 (86%) and 36 (68%) patients, respectively.¹⁵

Of the responding patients (n = 50), six were recruited directly to the third open-label phase for compassionate reasons. The remaining patients (n = 44) were then randomly assigned to placebo (n = 23) or continuation with tocilizumab treatment 8mg/kg every two weeks for 12 weeks (n = 20). One patient was disqualified (reason not specified). Other than stable doses of oral corticosteroids, disease modifying and immunosuppressant drugs were not permitted throughout this second phase of the study. The primary endpoint of this phase was the proportion of patients in each treatment group who

completed the 12-week study period and maintained an ACR Pedi 30 response and C-reactive protein concentration of < 15 mg/l. Of the 43 patients who continued to treatment in the double-blind phase, four (17%) placebo patients and 16 (80%) tocilizumab patients met the primary endpoint ($p < 0.0001$).¹⁵

Fifty patients entered the open-label extension phase with 48 patients still receiving tocilizumab at week 48. Week-48 efficacy results demonstrated that ACR Pedi 30, 50, and 70 responses were achieved by 47 (98%), 45 (94%), and 43 (90%) of the 48 patients, respectively.¹⁵

Another placebo-controlled phase III trial of tocilizumab in SoJIA refractory to NSAIDs and corticosteroids was initiated in May 2008 and is known as the TENDER study. Patients ($n = 112$) were randomised to receive tocilizumab 8 mg/kg (body mass ≥ 30 kg) or 12 mg/kg (body mass < 30kg) or placebo every two weeks for 12 weeks. NSAIDs and methotrexate were continued throughout the study. After 12 weeks of double-blind treatment patients could enrol for long-term follow up and receive open-label treatment with tocilizumab for a further 92 weeks. In November 2009 the manufacturer reported that the trial had met its primary endpoint with patients receiving tocilizumab benefiting from a significant reduction in the signs and symptoms (ACR Pedi 30 and absence of fever) after 12 weeks of therapy, compared to those receiving placebo. Further results were published in June 2010 and reveal that, after three months of treatment, 85% of patients achieved $\geq 30\%$ improvement in the signs and symptoms of SoJIA and absence of fever, compared with 24% of placebo patients. In addition, 70% of patients achieved an ACR Pedi 70 response and 37% achieved an ACR Pedi 90 response, and two-thirds of patients were free of rash, a common symptom associated with SoJIA, after three months. The trial is expected to be complete in June 2011.¹⁶⁻¹⁹

Two fully-published open-label Phase II studies provide supporting evidence to the body of clinical data for tocilizumab in patients with SoJIA.^{20,21}

Yokota et al evaluated the efficacy of tocilizumab in a dose-escalating study in 11 children (aged 3 to 18 years) with active SoJIA refractory to corticosteroids and/or disease modifying drugs. The children initially received three doses of tocilizumab 2 mg/kg every two weeks, with the dose increased stepwise to 4 mg/kg and again to 8 mg/kg if lower doses failed to maintain C-reactive protein levels below 1.5 mg/dl. Efficacy was evaluated every two weeks according to ACR Pedi responses and results of laboratory tests. Ten children met the criteria for improvement two weeks after the first dose of tocilizumab. In total ten children achieved an ACR Pedi 30 and 50 response, and seven children an ACR Pedi 70 response. Three children had a sustained response at the 2 mg/kg dose, five required 4 mg/kg and three were stabilised at the highest dose. No children required rescue therapy.²⁰

Woo et al evaluated tocilizumab in 18 children aged 2 to 17 years with severe SoJIA refractory to corticosteroids who received a single dose of tocilizumab 2, 4, or 8 mg/kg. Twelve patients also received methotrexate ($\leq 20 \text{ mg/m}^2/\text{week}$). The efficacy analysis was only based on 15 children, as there were three unspecified protocol violations. All three groups showed a marked improvement at one-week follow up. Eleven children achieved an ACR Pedi 30 response, eight an ACR Pedi 50 response, and three an ACR Pedi 70 response. However, a prolonged clinical response was only observed in the 4 and 8 mg/kg groups with four and three children achieving ACR Pedi 50 and 70 responses, respectively, at week six. Three children required rescue corticosteroid therapy, one at each of the three doses.²¹

Long-term efficacy in SoJIA

Yokota et al reported data on the long-term safety and efficacy of tocilizumab in 128 patients with SoJIA, including 67 who had completed phase II and phase III studies. All patients received tocilizumab 8 mg/kg every two weeks. Efficacy was assessed every 12 weeks using ACR Pedi criteria. The median age was nine years and the median disease duration was four years. At the time of analysis the median duration of tocilizumab treatment was 78 weeks and 14 patients had been withdrawn from study, eight due to adverse events five due to development of anti-tocilizumab antibodies and one due to lack of efficacy. ACR Pedi 30, 50, and 70 response were achieved in 94%, 88% and 81% of patients at week 48 (n = 78), 100%, 98% and 93% at week 96 (n = 58), and 100%, 100% and 90% at week 144 (n = 41), respectively. Four patients were in remission without tocilizumab or any other medication.²²

Even longer-term results have also been reported in abstract which appear to be a cohort of those previously reported with long-term follow-up.²²

Continuation rates were high, with 53 out of 67 patients entering a fourth year of continuous tocilizumab therapy. Nine patients discontinued treatment with eight of those discontinuing within nine weeks of initiation. At three-year assessment (n = 51) the proportion of patients meeting ACR Pedi 30, 50 and 70 were 96%, 96%, and 88% respectively. At the same point, 77% of patients were able to reduce their original steroid dose by at least half. Eight patients had tocilizumab ceased due to sustained remission although six subsequently resumed treatment due to relapse.²³

Ongoing studies

There is currently an ongoing UK-based study of tocilizumab in SoJIA. This study is being conducted at a London Hospital and recruitment is open to NHS North East patients although entry criteria are strict.²⁴

A trial of tocilizumab for the treatment of polyarticular JIA is still recruiting patients although completion is not expected until 2014.²⁵

Summary of the clinical evidence

To date only one phase III study and two phase II studies have been published in peer-reviewed journals.^{15,20,21} Within those studies, which were performed in predominantly Japanese populations with SoJIA refractory to conventional treatment, tocilizumab demonstrated high rates of clinical improvement according to accepted measures of response. A long-term extension study has demonstrated a sustained clinical improvement and a favourable risk-benefit profile with tocilizumab in this patient group.

Only a single unpublished non-comparative study provides evidence for the efficacy of tocilizumab in patients with polyarticular JIA.¹⁶⁻¹⁹

None of the studies have shown direct evidence of the effects of tocilizumab on joint destruction, a major disease manifestation and a significant determinant of future disability.

There are no direct comparisons of tocilizumab with other biological agents for the treatment of JIA such as etanercept and adalimumab. Extrapolation of efficacy results from studies in adults with rheumatoid arthritis is not appropriate because of the complexity and heterogeneity of juvenile arthritis.

The optimum dosing regimen for tocilizumab in paediatric patients is still to be determined. The dose used for the treatment of SoJIA in the published phase III study was 8 mg/kg every two weeks.¹⁵ In the TENDER study and the ongoing phase III study in polyarticular JIA, patients were randomised to receive tocilizumab at 8 mg/kg for patients weighing ≥ 30 kg or 12 mg/kg for patients weighing < 30 kg, also using a two week dose interval.^{16-19,25}

Longer-term evidence indicates that treatment must be maintained in order to maintain the clinical effect.

Safety

In the published Phase III study in patients with SoJIA two serious adverse events were reported during the lead-in phase; one anaphylactic reaction and one case of gastrointestinal haemorrhage.¹⁵ In the open-label extension phase of the study, serious adverse events occurred in 13 out of 50 patients, including bronchitis, gastroenteritis, and an anaphylactoid reaction. No deaths or cases of macrophage activation syndrome occurred. The majority of adverse events that arose during the study were mild or moderate in severity and similar to that observed for tocilizumab in adult studies. Adverse events frequently reported were upper-respiratory tract infections (URTIs) and gastroenteritis. In the double-blind phase, the incidence of gastroenteritis was similar in the tocilizumab and placebo groups (5% vs. 4%, respectively), whereas the occurrence of URTIs was increased in the placebo group (17% vs. 10%, respectively). The most common adverse events reported in the open-label extension were nasopharyngitis 55%, URTIs 34%, gastroenteritis 29%, and bronchitis 25%. Increases in specific liver enzymes occurred with frequency between 18 and 29%. Serious elevations in liver enzyme levels tended to occur early in treatment, generally within the first three to six months, and then tended to subside with continuation. In the published phase II studies the overall safety profile was consistent with that reported in the phase III study. The most common adverse events were infections, predominantly mild URTIs.^{20,21}

In the trial of tocilizumab in patients with polyarticular JIA, three of the 19 children were hospitalised due to adverse events during the study; two with gastroenteritis and one due to sensory disturbance.²³

Longer-term evidence of the safety of tocilizumab in paediatric populations is also reported, although in abstract only.

In the study of 128 patients receiving tocilizumab for SoJIA, adverse events occurred in 120 patients (94%) at a rate of 787 per 100 patient-years.²² The incidence rates of serious adverse events and serious infections were 37.2 and 14.5 per 100 patient-years, respectively. The most frequently reported serious infections were gastroenteritis (3.8/100 patient-years) and pneumonia (3.4/100 patient-years). In total eight patients were withdrawn from the study due to adverse events which included macrophage activation syndrome, anaphylactoid reaction (two patients), cardiac amyloidosis, duodenal perforation, gastrointestinal haemorrhage and infusion reaction (two patients). There were two fatalities. No cases of malignancy, tuberculosis or autoimmune disorders were reported.

In the study of 67 patients with median follow-up of three and a half years the most common adverse effects were nasopharyngitis, upper respiratory tract infections and gastroenteritis. The overall rate of serious adverse events was 35.5 per 100 patient years. The rate of serious infection was 13.6 per 100 patient years. There were no cases of opportunistic infection, malignancies, autoimmune diseases, or death.²³ These patients appear to be a cohort of the same group that have previously been reported with a shorter follow-up period.²²

Cost analysis

All costs include VAT at 17.5% where appropriate.

The application to use tocilizumab in paediatric patients specifies a dose of 8 mg per kg body mass which is the same dose as recommended for adult patients with arthritis. Thus the dose of drug will vary with body weight. Tocilizumab (RoActemra®) costs £1.50 per milligram and is available in 80, 200 and 400 mg vials. Table 1 demonstrates the dose and cost of drug treatment based on patient body mass.

Table 1. Dose and cost of tocilizumab therapy per patient for varying body masses ²⁶

Patient body mass (kg)	Dose required at 8 mg per kg	Total cost based on available packs	Actual purchase requirements
15	120	£188	2 x 80 mg vial
30	240	£282	3 x 80 mg vial
40	320	£423	1 x 200 mg vial 2 x 80 mg vial
50	400	£470	1 x 400 mg vial
60	480	£564	1 x 400 mg vial 1 x 80 mg vial

Patient doses, and thus cost, could be increased if higher doses are administered. There is currently a study underway investigating doses of 12 mg per kg in JIA.

In addition to drug cost, hospital admission costs will also be incurred. The application from the acute trust states that day-case admission will be required for each infusion of tocilizumab with administration every four weeks. Therefore 13 admissions would be required per patient per annum. The current payment-by-results day-case tariff price for 'inflammatory spine, joint or connective tissue disorders without complications or co-morbidities' (HRG code HD23C) is £471. However, specialised services for children attract at additional 78% of the tariff price therefore the cost for one day-case admission is £838. This figure does not include the market forces factor uplift rate which is typically about 1 to 2% for acute trusts within NHS North East, resulting in a total cost of about £850 per day-case paediatric admission for musculoskeletal conditions. ²⁷ Total annualised cost of drug treatment and administration based on various patient body masses are displayed in table 2.

Table 2. Annual cost of providing tocilizumab per juvenile patient based on various body masses ^{26,27}

Patient body mass (kg)	Dose required at 8 mg per kg	Total annual cost	Actual purchase requirements
15	120	£13,500	2 x 80 mg vial
30	240	£14,720	3 x 80 mg vial
40	320	£16,550	1 x 200 mg vial 2 x 80 mg vial
50	400	£17,160	1 x 400 mg vial
60	480	£18,380	1 x 400 mg vial 1 x 80 mg vial

The majority of the cost of providing tocilizumab for juvenile/paediatric patients is in administration, at about £11,050 per patient per annum. ²⁷

Some costs can be offset against the cost of tocilizumab. The application from the acute trust states that tocilizumab will only be offered to:

- Polyarticular JIA: children who had already failed to respond with the licensed aTNF treatments etanercept and adalimumab.
- Systemic-Onset JIA: as an alternative to anakinra in children who have failed aTNF treatment and who are not willing or unable to participate in the clinical study based in London. It is estimated that only 20% of SoJIA patients meet the inclusion criteria for the study. It is estimated that about 50% of children with SoJIA respond to anakinra and 50% have no response at all.

Anakinra (Kineret®) pre-filled syringes cost £30.82 each. As daily administration is required the annual cost of anakinra treatment is £11,250 not including any outpatient check-ups or other follow-up. ²⁶

The application states that the only remaining treatment option for these patients would be a 'bone-marrow transplant', assumed to refer to an autologous stem-cell transplant. A local tariff agreement lists the price for a paediatric autologous bone marrow transplant as £46,000. ²⁸ Such treatment can induce remission in a proportion of patients although there is a relatively high mortality risk. ¹² This must be compared to likely ongoing treatment with tocilizumab which currently has an unknown long-term safety profile in paediatric patients. The application states an initial treatment period of six months, after which it is assumed that treatment will only be continued if an acceptable degree of efficacy is obtained. Criteria for treatment efficacy are not defined.

It is estimated that within NHS North East only one or two paediatric patients per annum would require treatment with tocilizumab and that this represents the total patient cohort. It is not known how many stem-cell transplants can be successfully avoided through use of tocilizumab or whether its effect is only to delay progression to stem-cell transplant.

Points to consider

There is a well-developed and robust clinical evidence base supporting the use of tocilizumab for SoJIA. Evidence for the use of tocilizumab in polyarticular JIA is not as well developed. Much of the evidence is not yet available in peer reviewed publications and data reports relating to longer-term follow-up are poor. Nonetheless, the evidence consistently demonstrates that tocilizumab can produce meaningful outcomes in a large proportion of patients, many of whom were refractory to prior treatment options. In-line with its sought place in therapy, all tocilizumab studies have been against a placebo control or there has not been a control group.

Tocilizumab is not licensed for paediatric patients. Roche expects to file for EMEA approval for this indication in 2012.¹⁷ In April 2008 tocilizumab was approved by Japanese authorities for the treatment of JIA.¹⁷ NICE anticipate commencing the appraisal process for tocilizumab in JIA in November 2010.³⁰ The Newcastle Drug and Therapeutics Committee have previously approved the use of anakinra for the treatment of SoJIA, also an off-license indication.

There are no definitive data relating to the duration of tocilizumab therapy in children. It is anticipated that a significant proportion of those receiving treatment will require continuation of treatment into adult life. It is possible that in future greater doses may be recommended for paediatric patients than those currently indicated from clinical studies.

Alternatives to tocilizumab treatment in this patient group identified are anakinra or stem-cell transplant. Only around half of patients with SoJIA respond to treatment with anakinra. It has a short half-life and requires daily subcutaneous injections compared with four-weekly administration of tocilizumab. For certain patients a stem-cell transplant may result in disease remission. However this is an expensive procedure and is associated with significant morbidity and mortality. There is some pharmacological plausibility for using tocilizumab subsequent to etanercept or adalimumab and in place of anakinra as it has a distinct pharmacological mode of action and different cellular target. However this hypothesis has not been evaluated in any active-comparator studies.

The safety profile of tocilizumab in paediatric patients appears to be predictable and favourable given the severity of the underlying condition. However the long-term effects in paediatric populations are not known. In addition, the inclusion and exclusion criteria applied to studies may not be representative of use in practice.

Tocilizumab is a costly treatment, with the cost of acute care and administration being greater than the drug cost. Total annual costs will vary depending on the age of the child but will range from £13,000 to about £18,500. This represents an additional £2,000 to £6,000 compared with anakinra. Treatment is likely to be required indefinitely if efficacy is confirmed. If a stem-cell transplant can be avoided, the off-set savings will be nearly £50,000 per patient.

Author's declarations: The authors have no relevant interests to declare.

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Appendix 1. Juvenile rheumatoid arthritis response criteria

The standard primary outcome measure of response in JIA to treatment with biological agents such as tocilizumab is the ACR Pedi 30. This is defined as at least a 30% response to at least three out of the following six variables with worsening of 30% or more in no more than one of the six variables. The ACR Pedi 50, 70 and 90 outcomes are the same except that the 30% level is replaced with either 50, 70 or 90% respectively.

- Clinician global assessment of disease severity
- Patient/parent global assessment of overall well-being
- Number of active joints (joints with swelling not due to deformity or joints with limitation of motion with pain, tenderness or both)
- Number of joints with limitation of motion
- Functional ability based on the Child Health Assessment Questionnaire
- Erythrocyte sedimentation rate, a surrogate but reliable biological marker for inflammatory activity

Reference: Technology Appraisal Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. NICE www.nice.org.uk/nicemedia/live/11446/32321/32321.pdf