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Tocilizumab in Pediatric Rheumatology: The Clinical Experience

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Abstract During the last two decades, clinical use of novel biological therapy has led to increased mechanistic understanding of complex rheumatological diseases. Conversely, basic and translational studies have led to development of new and varied therapeutic agents. These new medications which "target" specific steps in one or more immune pathways have the potential to control disease symptoms, improve quality of life and long-term prognosis, and perhaps in some, restore immunological tolerance. Use of these agents in clinical trials, combined with post-marketing surveillance, has revealed both the benefits and the undesirable side-effects of biological disease-modifying anti-rheumatic drugs (DMARDs). In this review we focus on the use of tocilizumab, a monoclonal antibody directed against the IL6 receptor (IL6R), which potently inhibits IL-6/IL6R signaling.

Keywords Interleukin 6 (IL-6) · Interleukin-6 receptor (IL-6R) · Tocilizumab · Systemic onset juvenile idiopathic arthritis (sJIA) · Children · Pediatrics · Pediatric rheumatology

Introduction

Systemic onset juvenile idiopathic arthritis (sJIA) was first recognized as an entity by Stills in 1897 [1]. SJIA affects both children and adults, and is characterized by fever in a quotidian pattern, with maximum temperatures in the late afternoon and sub-normal temperatures in the morning, and by an evanescent salmon-colored rash, serositis, leukocytosis, thrombocytosis, and a disuse anemia which may or may not be accompanied by arthritis. In adults, sJIA has been termed Still's disease. One-third of affected children may have a disease course characterized by persistent systemic symptoms, and 1/3 may develop polyarticular disease ("go polyarticular"); however, up to 1/3 have a much more benign form of the disease, which goes into remission with modest therapy.

Until the 1990s, systemic onset JIA (previously known as juvenile rheumatoid arthritis or JRA) had the highest morbidity and mortality of the JRA subtypes. Rheumatologists over age 40 will recall seeing children with cushingoid facies who were at risk of severe complications, including constrictive pericarditis, degenerative hip disease, short stature, and vertebral compression fractures, as the result of long-standing disease and of its therapy.

The last two decades have brought understanding of systemic onset JIA as an auto-inflammatory condition in which the failure to down-regulate pro-inflammatory cytokines, interleukin 1 (IL-1) and 6 (IL-6), results in perpetuation of inflammation. Improved prognosis for children with sJIA seems to relate to the capacity to modulate IL-6, either directly by interfering with the action of IL-6 to IL-6 receptors (IL-6R) or indirectly via upstream manipulation of IL-1 [2••, 3].

Brief History of IL-6

IL-6 was originally described as a T-cell-derived B-cell differentiation factor [4], on the basis of its function maturing B-cells into antibody-producing plasma cells [5, 6]. IL-6 was subsequently revealed to be produced by both "immune" and "non-immune" cells, resulting in a range of biological

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functions [7]. Labeled as a "pleiotropic" cytokine, because of the gene product's actions on multiple phenotypic states and/or functions, it was independently reported by several investigators, all of whom named it for its association with the tissue in which it was discovered or for its putative function at the time of its identification: names included interferon-beta 2, 26 kDa protein, hybridoma/plasmacytoma growth factor, and hepatocyte stimulating factor [7]. When it was realized that identical nucleotide sequencing coded for all these proteins, they were collectively named IL-6 [8, 9].

IL-6-dependent signals are transduced upon binding of IL-6 to the IL-6R. IL-6–IL-6R complexes activate JAK-1, JAK-2, or TYK-2 depending on tissue specificity, inducing phosphorylation of tyrosines in the cytoplasmic domain of gp130. Phosphorylation of gp130 recruits signal transducer and activator of transcription 3 (STAT-3) to STAT-3 phosphotyrosine residues, where STAT-3 itself is then phosphorylated, dimerized, and translocated to the nucleus [10–14]. In turn, STAT-3 induces expression target genes that are pro-inflammatory and of SOCS proteins (SOCS proteins are negative regulators of cytokine expression) [15]. Reported functions of IL-6 include inhibition of T regulatory (Treg) cells, differentiation of pro-inflammatory T helper 17 (Th17) cells [16], and induction of cytotoxic T-cells [17]. IL-6 production by hepatocytes contributes to fever and induces acute-phase proteins including C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin, fibrinogen, ferritin, and hepcidin [18, 19]. With IL-1, IL-6 has also been implicated in mediating anemia [20] (via induction of hepcidin and other proteins) and inducing thrombocytosis. Elevated levels of IL-6 have been reported in inflamed synovium [21] and in serum of sJIA, polyJIA, and RA patients [22–24].

A link between IL-6 and inflammatory arthritis was suspected after reports of elevation of IL-6 in the lymphoproliferative disorder known as Castleman's disease. In Castleman's, IL-6 production is associated with anemia, leukopenia, fever, and elevation of acute phase reactants [25].

Mouse Data Implicate IL6/IL6R Signaling in Inflammatory Arthritis

The important function of IL-6 in arthritis is supported by data revealing that mice genetically engineered to have a point mutation in Tyr759 of the gp130 receptor portion of the IL6R develop RA-like disease. Tyr759 negatively regulates gp130: in the absence of this Tyr759 function excess signaling of IL-6 via gp130 occurs, leading to inflammatory arthritis [26]. The gp130 F759/F759 "knock-in" mouse model of arthritis is highly T-cell dependent; when crossed with mice that lack Rag-2, the arthritis phenotype is negated. Selective mutation of F759 in myeloid-derived cells (macrophages, synovial fibroblasts) confers disease even when not found in lymphocytes themselves. Taken together, the data suggest that T-cell mutations are required for the phenotype, but that mutation in myeloid but not T-cells is needed for development of arthritis. As might be expected, IL-6 deficient mice are resistant to collagen-induced arthritis [27, 28]. IL-6 induces osteoclastogenesis, and has been implicated in the erosive process observed in inflammatory arthritis [29].

Tocilizumab and IL-6 Blockade

Tocilizumab (TCZ) is a humanized monoclonal antibody (mAb) that targets components in the IL-6 signaling pathway (its complementary-determining regions from mouse anti-human IL-6R antibody are grafted to human IgG1) [30]. TCZ competes with IL-6 for both membrane-bound and soluble IL-6R [30], and blocks gp130 signal transduction [31]. Use of TCZ for RA improves clinical disease, halts radiological progression, and normalizes laboratory findings [32–40].

Systemic JIA and Tocilizumab (TCZ)

Yokota et al. first described use of IL-6 inhibition to treat sJIA in 2003 [31]. A phase II dose-ranging study of TCZ (2–8 mg/kg) to treat sJIA resulted in at least 30 % improvement after three doses at 2 mg/kg, although 8 mg/kg seemed to be the optimum dose for control of signs and symptoms of sJIA and of laboratory abnormalities. Doses higher than 8 mg/kg were not studied [41]. TCZ was also shown to be safe and effective in an open-label phase II single-dose study of tocilizumab in which, after demonstration of safety at a lower dose, a cohort of children received an increased dose [42].

A phase III trial of tocilizumab in sJIA reported achievement of ACR Pedi 30, 50, and 70 responses in 51/56 (91 %), 48/56 (86 %), and 38/56 (68 %), respectively, during the initial open-label phase [43]. Of the 56 patients enrolled in the open-label phase, 44 improved sufficiently with open-label drugs to make them eligible to participate in the randomized double-blind (DB) placebo-controlled withdrawal phase. In the DB phase, 43 of 44 eligible subjects were randomized to receive the drug or a placebo; ACR Pedi 30 responses were 16/20 (80 %) with TCZ versus 4/23 (17 %) with placebo, ACR50 16/20 (80 %) versus 4/23 (17 %), and ACR70 15/20 (75 %) versus 3/23 (13 %). For subjects whose symptoms worsened on placebo, most recaptured their initial TCZ response during the open-label extension: 47/48 (98 %) with an ACR30, 45/48 (94 %) with an ACR50 and 43/48 (90 %) with an ACR70. Radiography findings of children with sJIA showed less narrowing on Larsen score than at the start of study; significant improvement was found when comparing joint space narrowing before and after therapy ($p<0.05$) and also when

comparing subchondral bone cysts and erosion before and after therapy ($p<0.01$) [44].

In the PRINTO/PRCSG multi-center registration study of tocilizumab for sJIA, 112 subjects 2–17 years old with recalcitrant sJIA for at least six months (mean disease duration 5.2 years) were randomized to TCZ or placebo infusion every two weeks by use of a 2:1 randomization scheme. Using a different approach from earlier trials, children <30 kg received a dose of 12 mg/kg whereas those ≥30 kg received 8 mg/kg [2••]. Seventy-five patients received TCZ (8 mg/kg for patients ≥30 kg, and 12 mg/kg for those <30 kg), and 37 patients received placebo. The primary end point (definition of improvement: afebrile state and minimum of a JIA ACR30) was measured at 12 weeks; 64/75 (85 %) in the TCZ compared with 9/37 (24 %) in the placebo group met the definition of improvement, $p<0.001$ [2••]. An "early out" into an open-label TCZ group was offered to non-responders; 54 % of placebo and 1 % of TCZ subjects discontinued participation in the DB phase and entered the open-label continuation. Subjects who completed the double-blind phase were offered open-label tocilizumab at week 12 of the double-blind phase. Patients were eligible to remain in the open-label continuation until TCZ was clinically available for treatment of sJIA. At study week 52, one-third of the patients had inactive disease, and 52 % no longer required glucocorticoids.

In 2011 the FDA and EMEA approved TCZ for use for sJIA in children aged two years and above. TCZ for sJIA was approved after publication of the 2011 American College of Rheumatology recommendations for treatment of sJIA, meaning these recommendations do not include TCZ [45••]. However, TCZ is included in consensus protocols published by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) [46••].

An open-label study of children less than two years old with active sJIA is currently in progress; it focuses on TCZ safety, pharmacokinetics, and pharmacodynamic outcomes for this age group [47•].

Use of TCZ remains off-label for adult-onset Still's disease (AOSD), though TCZ is indicated for RA and for sJIA. Successful use of TCZ has been reported for 14 French patients with refractory AOSD [48]. Eleven Israeli patients with AOSD who were successfully treated with TCZ experienced a reduction in number of swollen and tender joints, resolution of systemic symptoms (rash and fevers), and a reduction in acute-phase reactants [49].

Adverse Events

Serious adverse events (SAEs) in the pediatric population were described with each study and are summarized in Table 1. De Benedetti et al. reported a 25 % risk of an SAE and an 11 % risk of a serious infection per year of treatment from a large phase II registration study of sJIA children with moderate to severe disease [2••]. The cumulative number of infections in that study was 3.0 per patient-year, and the number of serious infections was 0.11 per patient-year. Tuberculosis and opportunistic infection were not reported, but macrophage activation syndrome occurred in three of the patients (one episode was attributed to varicella infection as an initiator whereas the other two cases were attributed to withdrawal of TCZ). Death was reported for six of the 112 study patients; three patients were still in the study and receiving TCZ at the time of death. One death was attributed to MVA, one to spontaneous tension pneumothorax, and one to infection—streptococcal sepsis. The three other deaths occurred 6, 12, and 13 months after withdrawal from the study, and were probably secondary to macrophage activation syndrome (MAS) in one patient and to pulmonary hypertension in the other two [2••].

Table 1 Summary of SAEs associated with TCZ

Common SAE ≥5 %	Uncommon SAE ≥1–<5 %	Rare SAE <1 %
URI	MAS	Anaphylaxis
Nasopharyngitis	Infusion reaction	
Diarrhea		
HA		
Neutropenia		Thrombocytopenia
↑ ALT		
Hyperlipidemia		

ALT = alanine aminotransferase, HA = headache, MAS = macrophage activation syndrome, SAE = serious adverse events. URI = upper respiratory infection, yr = year

Whether tocilizumab contributed to or hindered development of MAS is still the subject of active investigation. The clinical findings of MAS were low in comparison with those for patients not treated with IL-6 blockade, but it has been hypothesized that tocilizumab may partially-treat MAS, potentially masking symptoms and increasing the difficulty of diagnosing MAS [50•, 51]. Monitoring of lipids is required during TCZ therapy, although whether TCZ contributes to increase in levels of medium-size pro-inflammatory LDLs or larger non-inflammatory LDLs is unknown.

Other Uses in the Pediatric Population

he CHERISH study was designed to show the efficacy and safety of TCZ for patients with active polyarticular juvenile idiopathic arthritis (polyJIA) who did not respond to methotrexate [52, 53]. The safety profile in CHERISH did not find new SAEs apart from those previously described for sJIA patients treated with TCZ. Children with methotrexate-resistant polyarticular disease also seemed to benefit from treatment with TCZ [54]. The FDA approved TCZ for

treatment of poly JIA on May 1, 2013 and EMA approval is anticipated later in 2013.

Patients with JIA-associated uveitis refractory to therapy may benefit from TCZ treatment, as may adults with non-JIA-associated inflammatory eye disease [55•]. An open-label trial is in progress to investigate the safety and efficacy of TCZ for children (2–17 years) with vision-threatening JIA-associated uveitis that is refractory to other systemic immunosuppressive therapy [56]. Data from an open-label phase I trial on adult systemic lupus erythematosus (SLE), also suggest that TCZ may be an effective therapy [57].

Other IL-6 Inhibitors

Currently, TCZ is the only commercially-available IL-6 inhibitor. Other IL-6 blockers are in various stages of development. Centocor (Horsham, Pennsylvania, USA, a subsidiary of Johnson and Johnson, New Brunswick, New Jersey, USA), developed Sirukumab (previously CNTO-136). Sirukumab is a human anti-IL-6 monoclonal antibody which binds to IL-6, preventing further signal transduction and activation of the IL-6 pathway, and is in the Janssen/GSK pipeline for treatment of RA [58]. The same company developed Siltuximab (previously CNTO-328), an anti-IL-6 chimeric antibody with high affinity for IL-6, which is in development for multiple myeloma and other malignancies [59]. Bristol–Myers Squibb and Alder Biopharmaceuticals developed BMS945429 (ALD518), a humanized monoclonal antibody directed against IL-6; promising results were obtained from a phase II study of methotrexate-resistant rheumatoid arthritis patients [60].

Conclusions

The challenging complexity of understanding the mechanism of sJIA is compounded by the lack of an appropriate animal model. Despite this, the science of sJIA has evolved: we now know that IL-6 inhibition with TCZ reduces symptoms for children with sJIA, and that it seems to be of therapeutic value in clinical trials and in real world experience.

However, understanding of the mechanism(s) of a particular therapy often lags behind use in the clinic. Recent data suggest that TCZ is clinically effective for many but not all children with systemic juvenile idiopathic arthritis (sJIA); sJIA is currently regarded as an auto-inflammatory disease that may arise as a result of defective signaling or failure to down-regulate innate immune signaling. IL-6 seems to work in part by amplifying innate immune signals that contribute to inflammation; an IL-6 blocker acts by attenuating these pro-inflammatory signals. Questions remain about the relationships between defective phosphorylation of IL-18 receptor β-chain [61] in sJIA and IL-6 and whether CCL20 is an important downstream mediator of inflammation in sJIA. Also uncertain is whether the dyserythropoesis observed in sJIA children can contribute to activation of the innate immune system, stimulating innate immunity via iron that is not incorporated into hemoglobin. Although tocilizumab has been shown to be effective for sJIA, little information is available on whether this therapy, steroids, or therapy directed at interruption of IL-1 signaling should be used early in the disease (first), and whether any of this therapy, if used early, can prevent the evolution of sJIA into a chronic disease for those whose disease is not naturally limited to a single episode. Because it can be hard to determine the short and long-term safety of serial and concomitant agents for all users, designing and performing late-effect studies using disease-specific registers should also be high on our agenda.

Conflict of Interest Reut Gurion declares that he has no conflict of interest.

Nora G. Singer has been a site PI on clinical trials of tocilizumab in RA (Genentech/Roche), has received an unrestricted CME grant for the Cleveland Society of Rheumatology Annual Meeting (2012) from Genentech/Roche, has received reimbursement for travel to investigator meetings from Genentech/Roche, and has received reimbursement/honoraria for participation in conference from the Vienna Medical Academy.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Still GF. On a form of chronic joint disease in children. Med Chir Trans. 1897;80:47–60.
2. •• De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367(25):2385–95. doi:10.1056/NEJMoa1112802. *The 12 week double blind phase comparing response between tocilizumab and placebo showed that tocilizumab was effective in sJIA. This clinical trial completed the basis for FDA and EMEA labeling of tociluzimab as an effective agent in sJIA.*
3. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367(25):2396–406. doi:10.1056/NEJMoa1205099.
4. Yoshizaki K, Nakagawa T, Fukunaga K, Tseng LT, Yamamura Y, Kishimoto T. Isolation and characterization of B cell differentiation factor (BCDF) secreted from a human B lymphoblastoid cell line. J Immunol. 1984;132(6):2948–54.
5. Muraguchi A, Kishimoto T, Miki Y, Kuritani T, Kaieda T, Yoshizaki K, et al. T cell-replacing factor- (TRF) induced IgG secretion in a human B blastoid cell line and demonstration of acceptors for TRF. J Immunol. 1981;127(2):412–6.
6. Hirano T, Taga T, Nakano N, Yasukawa K, Kashiwamura S, Shimizu K, et al. Purification to homogeneity and characterization of human B-cell differentiation factor (BCDF or BSFp-2). Proc Natl Acad Sci U S A. 1985;82(16):5490–4.

7. Kishimoto T. The biology of interleukin-6. Blood. 1989;74(1):1–10.
8. Van Damme J, Cayphas S, Van Snick J, Conings R, Put W, Lenaerts JP, et al. Purification and characterization of human fibroblast-derived hybridoma growth factor identical to T-cell-derived B-cell stimulatory factor-2 (interleukin-6). Eur J Biochem. 1987;168(3):543–50.
9. Poupart P, Vandenabeele P, Cayphas S, Van Snick J, Haegeman G, Kruys V, et al. B cell growth modulating and differentiating activity of recombinant human 26-kd protein (BSF-2, HuIFN-beta 2, HPGF). EMBO J. 1987;6(5):1219–24.
10. Lutticken C, Wegenka UM, Yuan J, Buschmann J, Schindler C, Ziemiecki A, et al. Association of transcription factor APRF and protein kinase Jak1 with the interleukin-6 signal transducer gp130. Science. 1994;263(5143):89–92.
11. Stahl N, Boulton TG, Farruggella T, Ip NY, Davis S, Witthuhn BA, et al. Association and activation of Jak-Tyk kinases by CNTF-LIF-OSM-IL-6 beta receptor components. Science. 1994;263(5143):92–5.
12. Matsuda T, Yamanaka Y, Hirano T. Interleukin-6-induced tyrosine phosphorylation of multiple proteins in murine hematopoietic lineage cells. Biochem Biophys Res Commun. 1994;200(2):821–8. doi:10.1006/bbrc.1994.1525.
13. Berger LC, Hawley TS, Lust JA, Goldman SJ, Hawley RG. Tyrosine phosphorylation of JAK-TYK kinases in malignant plasma cell lines growth-stimulated by interleukins 6 and 11. Biochem Biophys Res Commun. 1994;202(1):596–605. doi:10.1006/bbrc.1994.1970.
14. Zhang X, Blenis J, Li HC, Schindler C, Chen-Kiang S. Requirement of serine phosphorylation for formation of STAT-promoter complexes. Science. 1995;267(5206):1990–4.
15. Naka T, Kishimoto T. Joint disease caused by defective gp130-mediated STAT signaling. Arthritis Res. 2002;4(3):154–6.
16. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006;441(7090):235–8. doi:10.1038/nature04753.
17. Okada M, Kitahara M, Kishimoto S, Matsuda T, Hirano T, Kishimoto T. IL-6/BSF-2 functions as a killer helper factor in the in vitro induction of cytotoxic T cells. J Immunol. 1988;141(5):1543–9.
18. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J. 1990;265(3):621–36.
19. Siewert E, Bort R, Kluge R, Heinrich PC, Castell J, Jover R. Hepatic cytochrome P450 down-regulation during aseptic inflammation in the mouse is interleukin 6 dependent. Hepatology. 2000;32(1):49–55. doi:10.1053/jhep.2000.8532.
20. Raj DS. Role of interleukin-6 in the anemia of chronic disease. Semin Arthritis Rheum. 2009;38(5):382–8. doi:10.1016/j.semarthrit.2008.01.006.
21. Sack U, Kinne RW, Marx T, Heppt P, Bender S, Emmrich F. Interleukin-6 in synovial fluid is closely associated with chronic synovitis in rheumatoid arthritis. Rheumatol Int. 1993;13(2):45–51.
22. De Benedetti F, Massa M, Robbioni P, Ravelli A, Burgio GR, Martini A. Correlation of serum interleukin-6 levels with joint involvement and thrombocytosis in systemic juvenile rheumatoid arthritis. Arthritis Rheum. 1991;34(9):1158–63.
23. De Benedetti F, Robbioni P, Massa M, Viola S, Albani S, Martini A. Serum interleukin-6 levels and joint involvement in polyarticular and pauciarticular juvenile chronic arthritis. Clin Exp Rheumatol. 1992;10(5):493–8.
24. Hirano T, Matsuda T, Turner M, Miyasaka N, Buchan G, Tang B, et al. Excessive production of interleukin 6/B cell stimulatory factor-2 in rheumatoid arthritis. Eur J Immunol. 1988;18(11):1797–801. doi:10.1002/eji.1830181122.
25. Jourdan M, Bataille R, Seguin J, Zhang XG, Chaptal PA, Klein B. Constitutive production of interleukin-6 and immunologic features in cardiac myxomas. Arthritis Rheum. 1990;33(3):398–402.
26. Atsumi T, Ishihara K, Kamimura D, Ikushima H, Ohtani T, Hirota S, et al. A point mutation of Tyr-759 in interleukin 6 family cytokine receptor subunit gp130 causes autoimmune arthritis. J Exp Med. 2002;196(7):979–90.
27. Alonzi T, Fattori E, Lazzaro D, Costa P, Probert L, Kollias G, et al. Interleukin 6 is required for the development of collagen-induced arthritis. J Exp Med. 1998;187(4):461–8.
28. Sasai M, Saeki Y, Ohshima S, Nishioka K, Mima T, Tanaka T, et al. Delayed onset and reduced severity of collagen-induced arthritis in interleukin-6-deficient mice. Arthritis Rheum. 1999;42(8):1635–43. doi:10.1002/1529-0131(199908)42:8<1635::AID-ANR11>3.0.CO;2-Q.
29. Wong PK, Quinn JM, Sims NA, van Nieuwenhuijze A, Campbell IK, Wicks IP. Interleukin-6 modulates production of T lymphocyte-derived cytokines in antigen-induced arthritis and drives inflammation-induced osteoclastogenesis. Arthritis Rheum. 2006;54(1):158–68. doi:10.1002/art.21537.
30. Sato K, Tsuchiya M, Saldanha J, Koishihara Y, Ohsugi Y, Kishimoto T, et al. Reshaping a human antibody to inhibit the interleukin 6-dependent tumor cell growth. Cancer Res. 1993;53(4):851–6.
31. Yokota S. Interleukin 6 as a therapeutic target in systemic-onset juvenile idiopathic arthritis. Curr Opin Rheumatol. 2003;15(5):581–6.
32. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987–97. doi:10.1016/S0140-6736(08)60453-5.
33. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63(3):609–21. doi:10.1002/art.30158.
34. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12–9. doi:10.1007/s10165-008-0125-1.
35. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2004;50(6):1761–9. doi:10.1002/art.20303.
36. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66(9):1162–7. doi:10.1136/ard.2006.068064.
37. Yazici Y, Curtis JR, Ince A, Baraf H, Malamet RL, Teng LL, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Ann Rheum Dis. 2012;71(2):198–205. doi:10.1136/ard.2010.148700.
38. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968–80. doi:10.1002/art.23940.
39. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus

methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69(1):88–96. doi:10.1136/ard.2008.105197.

40. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516–23. doi:10.1136/ard.2008.092932.
41. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M, et al. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2005;52(3):818–25. doi:10.1002/art.20944.
42. Woo P, Wilkinson N, Prieur AM, Southwood T, Leone V, Livermore P, et al. Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement. Arthritis Res Ther. 2005;7(6):R1281–8. doi:10.1186/ar1826.
43. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008;371(9617):998–1006. doi:10.1016/S0140-6736(08)60454-7.
44. Inaba Y, Ozawa R, Imagawa T, Mori M, Hara Y, Miyamae T, et al. Radiographic improvement of damaged large joints in children with systemic juvenile idiopathic arthritis following tocilizumab treatment. Ann Rheum Dis. 2011;70(9):1693–5. doi:10.1136/ard.2010.145359.
45. •• Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011;63(4):465–82. doi:10.1002/acr.20460. *These recommendations were formulated before FDA approval of tociluzimab for SJIA and hence do not evaluate the use of tociluzimab in sJIA.*
46. •• DeWitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2012;64(7):1001–10. doi:10.1002/acr.21625. *The 2012 consensus treatment plans which include biologics discusses the proceedings of how consensus plans for sJIA were developed including a tociluzimab pathway.*
47. • NCT01455701. A phase 1 pharmacokinetic and safety study of Tocilizumab (TCZ) in patients less than 2 years old with active Systemic Juvenile Idiopathic Arthritis (sJIA). http://www.clinicaltrials.gov/ct2/show/NCT01455701?term=NCT01455701&rank=1. Accessed 2/1/13. *This study which is ongoing and listed on the Clinical Trials.gov website will provide useful data about dosing if tociluzimab is used off label in those sJIA patients who are less than two years of age.*
48. Puechal X, DeBandt M, Berthelot JM, Breban M, Dubost JJ, Fain O, et al. Tocilizumab in refractory adult still's disease. Arthritis Care Res (Hoboken). 2011;63(1):155–9. doi:10.1002/acr.20319.
49. El-Kayam O, Jiries N, Dranitzki Z, Kivity S, Lidar M, Levy O, et al. Tocilizumab in adult Still's disease: the Israeli experience. Arthritis Rheum. 2012;64(10 (Supplement)):S83.
50. • Shimizu M, Nakagishi Y, Kasai K, Yamasaki Y, Miyoshi M, Takei S, et al. Tocilizumab masks the clinical symptoms of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome: the diagnostic significance of interleukin-18 and interleukin-6. Cytokine. 2012;58(2):287–94. doi:10.1016/j.cyto.2012.02.006. *In this discussion the authors discuss whether tociluzimab effectively treats subclinical MAS and thus makes MAS more difficult to diagnose*.
51. Yokota S, Tanaka T, Kishimoto T. Efficacy, safety and tolerability of tocilizumab in patients with systemic juvenile idiopathic arthritis. Ther Adv Musculoskelet Dis. 2012;4(6):387–97. doi:10.1177/1759720X12455960.
52. NCT00988221. A 24 week randomized, double-blind, placebo-controlled withdrawal trial with a 16 week open-label lead-in phase, and 64 week open-label follow-up, to evaluate the effect on clinical response and the safety of tocilizumab in patients with active polyarticular-course juvenile idiopathic arthritis.
53. Brunner HI, Ruperto N, Zuber Z, Keane K, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular juvenile idiopathic arthritis: data from a phase 3 trial. Arthritis Rheum. 2012;64(10 (Supplement)):S682.
54. Imagawa T, Yokota S, Mori M, Miyamae T, Takei S, Imanaka H, et al. Safety and efficacy of tocilizumab, an anti-IL-6-receptor monoclonal antibody, in patients with polyarticular-course juvenile idiopathic arthritis. Mod Rheumatol. 2012;22(1):109–15. doi:10.1007/s10165-011-0481-0.
55. • Tappeiner C, Heinz C, Ganser G, Heiligenhaus A. Is tocilizumab an effective option for treatment of refractory uveitis associated with juvenile idiopathic arthritis? J Rheumatol. 2012;39(6):1294–5. doi:10.3899/jrheum.120010. *Tocilizumab has been reported off-label for use in JIA associated uveitis (which is not a feature of sJIA) and may become a second-line therapy.*
56. NCT01603355. An open-label trial to assess the efficacy and safety of tocilizumab in the management of juvenile idiopathic arthritis associated vision-threatening uveitis that is refractory to other modes of systemic immunosuppression.
57. Illei GG, Shirota Y, Yarboro CH, Daruwalla J, Tackey E, Takada K, et al. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum. 2010;62(2):542–52. doi:10.1002/art.27221.
58. Xu Z, Bouman-Thio E, Comisar C, Frederick B, Van Hartingsveldt B, Marini JC, et al. Pharmacokinetics, pharmacodynamics and safety of a human anti-IL-6 monoclonal antibody (sirukumab) in healthy subjects in a first-in-human study. Br J Clin Pharmacol. 2011;72(2):270–81. doi:10.1111/j.1365-2125.2011.03964.x.
59. Van Zaanen HC, Lokhorst HM, Aarden LA, Rensink HJ, Warnaar SO, van der Lelie J, et al. Chimaeric anti-interleukin 6 monoclonal antibodies in the treatment of advanced multiple myeloma: a phase I dose-escalating study. Br J Haematol. 1998;102(3):783–90.
60. Mease P, Strand V, Shalamberidze L, Dimic A, Raskina T, Xu LA, et al. A phase II, double-blind, randomised, placebo-controlled study of BMS945429 (ALD518) in patients with rheumatoid arthritis with an inadequate response to methotrexate. Ann Rheum Dis. 2012;71(7):1183–9. doi:10.1136/annrheumdis-2011-200704.
61. De Jager W, Vastert SJ, Beekman JM, Wulffraat NM, Kuis W, Coffer PJ, et al. Defective phosphorylation of interleukin-18 receptor beta causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2782–93. doi:10.1002/art.24750.