

<b>DRUG PROFILE</b>
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**DRUGS IN PEDIATRIC RHEUMATOLOGY**

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**Abstract:** *Various factors, including disease activity and severity, co-morbidities and patient preference (including cost, route of administration and frequency of monitoring) need to be factored in deciding the optimal treatment of various rheumatic diseases in children. Non-steroidal anti-inflammatory drugs and steroids may be used to provide symptomatic relief whereas the arrest of progression of disease is achieved using disease modifying drugs. Treatment goals include achievement of remission or low disease activity, and the prevention of radiographic progression of the disease.*

**Keywords:** *Juvenile idiopathic arthritis, Rheumatic, NSAIDs, Steroids, Disease modifying anti rheumatic drugs, Methotrexate, Biologicals, Children.*

**Points to Remember**

- *Numerous medications are currently available for the treatment of rheumatic diseases apart from NSAIDs and steroids.*
- *NSAIDs and steroids can be used as a stopgap measures till optimum effects of disease modifying drugs start appearing.*
- *Methotrexate is the most commonly used agent for initial treatment of juvenile idiopathic arthritis.*
- *Combination therapy has been shown to have better outcome than monotherapy but the choice of medications should be tailored for each patient.*
- *Most of these medications require periodic monitoring by specialists for possible major adverse effects.*

**References**

1. Brown AG, Lapin WB, Ramirez AA, Rammel JL. Rheumatology. In: Naga O. (eds) Pediatric Board Study Guide. Springer, Cham. 2020 Available from [https://doi.org/10.1007/978-3-030-21267-4\\_15](https://doi.org/10.1007/978-3-030-21267-4_15) Accessed on 11<sup>th</sup> July 2020.
2. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res* 2018; 6:15. doi:10.1038/s41413-018-0016-9.
3. Kumar P, Banik S. Pharmacotherapy options in rheumatoid arthritis. *Clin Med Insights Arthritis Musculoskelet Disord*. 2013; 6:35-43.
4. Kim KN. Treatment of juvenile rheumatoid arthritis. *Korean J Pediatr* 2010; 53(11):936-941.
5. Joint Formulary Committee. *British National Formulary for children*. London: BMJ Group and Pharmaceutical Press, 2013-2014; 502-508.
6. Malattia C, Martini A. Glucocorticoids in juvenile idiopathic arthritis. *Ann NY Acad Sci*. 2014;1318: 65-70.
7. Castro, Monteiro de TC, Len TMT, Claudio, Hilário, Esteves MO. Treatment of refractory juvenile idiopathic arthritis via pulse therapy using methylprednisolone and cyclophosphamide. *Sao Paulo Med J* 2003; 121(3): 117-120.
8. Maksimov AA, Sha-kov AV, Speranski-AI, Solov'ev SK. Pulse therapy with methylprednisolone and

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- cyclophosphamide in systemic juvenile rheumatoid arthritis: the results of an open, parallel, controlled, randomized, 12-month study. *Ter Arkh.* 1992;64(5):47-51.
9. Leow OM, Lim LK, Ooi PL, Shek LP, Ang EY, Son MB. Intra-articular glucocorticoid injections in patients with juvenile idiopathic arthritis in a Singapore hospital. *Singapore Med J.* 2014; 55(5): 248-252.
  10. Vannucci G, Cantarini L, Giani T. Glucocorticoids in the management of systemic juvenile idiopathic arthritis. *Pediatr Drugs.* 2013; 15(5):343-349.
  11. Tian K, Cheng H, Zhang J, Chen K. Intra-articular injection of methylprednisolone for reducing pain in knee osteoarthritis: A systematic review and meta-analysis. *Medicine (Baltimore).* 2018; 97(15): e0240.doi:10.1097/MD.00000000000010240.
  12. Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewé R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann. Rheum. Dis.* 2014; 73(1):3-5.
  13. Benjamin O, Bansal P, Goyal A, Lappin SL. Disease Modifying Anti-Rheumatic Drugs (DMARD) [Updated 2020 Feb 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK507863/>Last accessed 11<sup>th</sup> July 2020.
  14. Nelson RP, Ballou M. Immunomodulation and immunotherapy: Drugs, cytokines, cytokine receptors and antibodies. *J Allergy Clin Immunol* 2003; 111(2 Suppl): S720-732.
  15. Blazina S, Markelj G, Avramovic MZ, Toplak N, Avèin T. Management of juvenile idiopathic arthritis: a clinical guide. *Paediatr Drugs* 2016; 18:397-412.
  16. Ferrara G, Mastrangelo G, Barone P, La Torre F, Martino S, Pappagallo G, et al. Rheumatology Italian Study Group. Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting. *PediatrRheumatol Online J* 2018; 16(1): 46. doi:10.1186/s12969-018-0255-8
  17. Ramanan AV, Whitworth P, Baildam EM. Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child* 2003; 88:197-200.
  18. Harris JG, Kessler EA, Verbsky JW. Update on the treatment of juvenile idiopathic arthritis. *Curr Allergy Asthma Rep* 2013; 13(4): 337-346.
  19. Van Rossum MA, Fiselier TJ, Franssen MJ, Zwinderman AH, ten Cate R, van Suijlekom-Smit LW, et al. Sulfasalazine in the Treatment of Juvenile Chronic Arthritis: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. *Dutch Juvenile Chronic Arthritis Study Group. Arthritis Rheum* 1998; 41(5): 808-816.
  20. Huang JL, Chen LC. Sulphasalazine in the Treatment of Children With Chronic Arthritis. *Clin Rheumatol.* 1998; 17(5): 359-363. DOI: 10.1007/BF01450892.
  21. Silverman E, Strand V. Leflunomide in juvenile idiopathic arthritis. *Future Rheumatol* 2006; 1(6): 673-682.
  22. Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, et al. Leflunomide or Methotrexate for Juvenile Rheumatoid Arthritis. *N Engl J Med* 2005; 352:1655-1666.
  23. Kim KN. Treatment of juvenile rheumatoid arthritis. *Korean J Pediatr* 2010; 53(11):936-941.
  24. Goebel JC, Roesel M, Heinz C, Ganser G, Heiligenhaus A. Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. *Br J Ophthalmol* 2011; 95:209-213.
  25. Kvien TK, Hoyeraal HM, Sandstad B. Gold Sodium Thiomalate and D-penicillamine. A Controlled, Comparative Study in Patients with Pauciarticular and Polyarticular Juvenile Rheumatoid Arthritis. *Scand J Rheumatol* 1985; 14(4):346-354.
  26. Kerrigan SA, McInnes IB. JAK Inhibitors in Rheumatology: Implications for Pediatric Syndromes? *Curr Rheumatol Rep* 2018; 20(12):83. doi:10.1007/s11926-018-0792-7
  27. Ghoreschi K and Massimo Gadina M. Jakpot. New small molecules in autoimmune and inflammatory diseases. *Exp Dermatol.* 2014 Jan; 23(1):7-11. DOI: 10.1111/exd.12265.
  28. Ruperto N, Brunner HI, Zuber ZTzaribachev N, Kingsbury DJ, Foeldvari I, Horneff G, et al. Pediatric Rheumatology International Trials Organization (PRINTO); Pediatric Rheumatology Collaborative Study Group (PRCSG). Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study. *PediatrRheumatol* 2017; 15, 86.doi: 10.1186/s12969-017-0212-y.PMID: 29282090.
  29. Huang Z, Lee PY, Yao X, Zheng S, Li T. Tofacitinib Treatment of Refractory Systemic Juvenile Idiopathic Arthritis. *Pediatrics* 2019; 143(5) e20182845; DOI: 10.1542/peds 2018-2845.
  30. Genovese MC, Kremer JM, Kartman CE, Schlichting DE, Xie L, Carmack T, et al. Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. *Rheumatology (Oxford)* 2018; 374:1243-1249.
  31. Vanoni F, Minoia F, Malattia C. Biologics in Juvenile Idiopathic Arthritis: A Narrative Review. *Eur J Pediatr* 2017; 176(9):1147-1153.
  32. Prince FHM, Dorai Raj AK, Otten MH, Cheung PPM, Tymms KE, van Suijlekom-Smit LWA, et al. TNFalpha inhibitors for juvenile idiopathic arthritis. *Cochrane Database Syst Rev* 2018; 2018(8):CD008598.
  33. Semeraro F, Arcidiacono B, Nascimbeni G, Angi M, Parolini B, Costagliola C. Anti-TNF therapy for juvenile idiopathic arthritis-related uveitis. *Drug Des Devel Ther* 2014; 8:341-348.

34. Yokota S, Imagawa T, Murata T, Tomiita M, Itoh Y, Fujikawa S, et al. Response to Baricitinib Based on Prior Biologic Use in Patients With Refractory Rheumatoid Arthritis. *Mod Rheumatol* 2012; 22(4):491-497.
35. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and Safety of Adalimumab as the First and Second biologic agent in juvenile idiopathic arthritis: the German Biologics JIA Registry. *Arthritis Rheumatol* 2014; 66(9):2580-2589.
36. Torre FL, Cattalini M, Teruzzi B, Meini A, Moramarco F, Iannone F. Efficacy of Adalimumab in Young Children With Juvenile idiopathic arthritis and chronic uveitis: a case series. *BMC Res Notes* 2014; 7: 316. doi: 10.1186/1756-0500-7-316.
37. Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, et al. Long-term Efficacy and Safety of Etanercept in Children With Polyarticular-Course Juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 2003; 48(1):218-226. doi:10.1002/art.10710
38. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in Children with Polyarticular Juvenile Rheumatoid Arthritis. *Pediatric Rheumatology Collaborative study group. N Engl J Med* 2000;342:763-769. doi:10.1056/NEJM200003163421103.
39. Wilkinson N, Jackson G, Gardner-Medwin J. Biologic therapies for juvenile arthritis. *Arch Dis Child* 2003;88: 186-191.
40. Tynjälä P, Lahdenne P, Vähäsalo P, Kautiainen H, Honkanen V. Impact of anti-TNF treatment on growth in severe juvenile idiopathic arthritis. *Ann Rheum Dis* 2006; 65(8):1044-1049. doi:10.1136/ard.2005.047225.
41. Lahdenne P, Vähäsalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Ann Rheum* 2003; 62:245-247.
42. Semeraro F, Arcidiacono B, Nascimbeni G, Angi M, Parolini B, Costagliola C. Anti-TNF therapy for juvenile idiopathic arthritis-related uveitis. *Drug Des Devel Ther* 2014; 8:341-348.
43. Goldzweig O, Hashkes PJ. Abatacept in the treatment of polyarticular JIA: development, clinical utility, and place in therapy. *Drug Des Devel Ther.* 2011; 5:61-70.
44. Hara R, Umebayashi H, Takei S, Okamoto N, Iwata N, Yamasaki Y, et al. Intravenous abatacept in Japanese patients with polyarticular-course juvenile idiopathic arthritis: results from a phase III open-label study. *Pediatr Rheumatol* 2019; 17(1), 17. doi:10.1186/s12969-019-0319-4
45. Sepah YJ, Sadiq MA, Chu DS. Primary (month-6) outcomes of the STOP-uveitis study: evaluating the safety, tolerability, and efficacy of tocilizumab in patients with noninfectious uveitis. *Am J Ophthalmol* 2017; 183: 71-80.
46. Quesada-Masachs E, Caballero CM. Subcutaneous tocilizumab may be less effective than intravenous tocilizumab in the treatment of juvenile idiopathic arthritis-associated uveitis. *J Rheumatol* 2017; 44:260-261.
47. Ramanan AV, Dick AD, Guly C, McKay A, Jones AP, Hardwick B, et al. Tocilizumab in Patients With anti-TNF Refractory Juvenile Idiopathic Arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial. *Lancet Rheumatol* 2020; 2(3):e135-e141.
48. Actemra (tocilizumab) [package insert]. South San Francisco: Genentech, Inc; 2013. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/125276s092lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125276s092lbl.pdf). Accessed on 11.07. July 2020.
49. Orrock JE, Ilowite NT. Canakinumab for the treatment of active systemic juvenile idiopathic arthritis. *Expert Rev Clin Pharmacol* 2016; 9(8):1015-1024.
50. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat NM, Horneff G, et al. Pediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. *Ann Rheum Dis* 2018; 77(12):1710-1719.
51. Ilaris (canakinumab) [product monograph]. Dorval, Quebec, Canada: Novartis Pharmaceuticals Canada Inc; February 22018. Available from [https://www.novartis.ca/sites/www.novartis.ca/files/ilaris\\_scrip\\_e\\_0.pdf](https://www.novartis.ca/sites/www.novartis.ca/files/ilaris_scrip_e_0.pdf). Accessed on 11<sup>th</sup> July, 2020.
52. Hedrich CM, Bruck N, Fiebig B, Gahr M. Anakinra: A Safe and Effective First-Line Treatment in Systemic Onset Juvenile Idiopathic Arthritis (SoJIA). *Rheumatol Int* 2012; 32(11):3525-3530.
53. Woo P. Anakinra treatment for systemic juvenile idiopathic arthritis and adult onset Still disease. *Annals of the Rheumatic Diseases* 2008; 67:281-282.
54. Dewitt EM, Kimura Y, Beukelman T. Juvenile Idiopathic Arthritis Disease-specific Research Committee of Childhood Arthritis Rheumatology and Research Alliance. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2012; 64(7):1001-1010.
55. Autmizguine J, Cohen-Wolkowicz M, Ilowite N; RAPPORT Investigators. Rilonacept pharmacokinetics in children with systemic juvenile idiopathic arthritis. *J Clin Pharmacol* 2015; 55(1):39-44. doi: 10.1002/jcph.372.
56. Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. *Arthritis Rheum* 2013; 65(9):2486-2496. doi:10.1002/art.38042.
57. Ilowite NT, Prather K, Lokhnygina Y, Schanberg LE, Elder M, Milojevic D, et al. Randomized, double-blind,

placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. *Arthritis Rheumatol* 2014;66(9): 2570-2579. Doi: 10.1093/rheumatology/key306.

58. Kearsley-Fleet L, Sampath S, McCann LJ, Baildam E, Beresford MW, Davies R, et al. Use and effectiveness of rituximab in children and young people with juvenile idiopathic arthritis in a cohort study in the United Kingdom. *Rheumatology (Oxford)* 2019; 58(2): 331-335.
59. Sakamoto AP, Pinheiro MM, Barbosa CM, Fraga MM, Len CA, Terreri MT. Rituximab use in young adults diagnosed with juvenile idiopathic arthritis unresponsive to conventional treatment: report of 6 cases. *Rev Bras Rheumatol* 2015; 55(6): 536-541. doi:10.1016/j.rbr.2014.12.015.