Appendix A

Medication Dosing and Monitoring for pJIA CTPs

Glucocorticoids

A. Glucocorticoid exposure prior to starting on CTP

i. Intraarticular glucocorticoid injections

- IAS prior to starting on CTP is not an exclusion criterion, and number of joints injected and date(s) will be documented (dose, which joints will not be)

ii. Systemic glucocorticoids (oral)

- Allowed for an indication other than pJIA, but will document dose and when started
- Glucocorticoids need not be discontinued prior to starting

B. Glucocorticoid use during CTP

i. Systemic glucocorticoids

- Starting dose per provider's discretion, but encourage lowest possible dose for the shortest period of time
- Tapers per systemic JIA CTP rapid taper (1 month) (recommend but not required). See Appendix B.
- Encourage rapid taper (should be off or on very low dose steroid by 3 months)

ii. Intraarticular glucocorticoids injections

- IAS will be allowed during CTPs at provider's discretion (document number and date only)

Non-Biologic DMARDs

Methotrexate

A. Route[1-5]

- Oral or subcutaneous dosing allowed (reminder that subcutaneous route may have fewer side effects, better absorption and improved efficacy at doses greater than 10 mg/m^2)

B. Dose[1, 2, 6-10]

- Initial target dose should be reached by 6 weeks: 10-15 mg/m^2/week or 0.5 mg/kg/week
- Maximum recommended dose at any time: 25 mg
- Dose adjustments allowed based on response and tolerability after 4-8 weeks on therapy.

C. Toxicity monitoring[11, 12]

- Check CBC, LFTs (AST, ALT), and creatinine prior to initiation, approximately 1 month after initiation, approximately 1-2 months after an increase in dose, repeat every 3-4 months if prior results are normal and dose is stable.

- Consider hepatitis B screening at baseline
- Consider PPD or interferon gamma release assay prior to starting

D. Other issues:

Side effects to capture: nausea, vomiting, and abdominal pain

Leflunomide

A. Loading dose

- No loading dose recommended.

B. Maintenance dose[13-16]

- <20kg-10 mg every other day
- 20-30kg-10 mg/d
- 30-40kg-10mg/d alternating 20mg/d
- >40kg-20 mg/d

Target dose may be reached with incremental dosing over 4-6 weeks

C. Toxicity monitoring[12, 17]

Same as methotrexate:

- Check CBC, LFTs (AST, ALT), and creatinine prior to initiation, approximately 1 month after initiation, approximately 1-2 months after an increase in dose, repeat every 3-4 months if prior results are normal and dose is stable.

- Consider hepatitis B screening at baseline

D. Other issues

- Side effects to capture: diarrhea, hair loss

Sulfasalazine

A. Dosing[18-20]

- 30-50 mg/kg/day up to recommended dose of 2 grams/day (maximum 3 grams/day)

B. Toxicity monitoring:

Same as methotrexate:

- Check CBC, LFTs (AST, ALT) and creatinine prior to initiation, approximately 1 month after initiation, approximately 1-2 months after an increase in dose, repeat every 3-4 months if prior results are normal and dose is stable.
- Consider hepatitis B screening at baseline

Reminder that hemolytic anemia (associated with glucose-6-phosphate dehydrogenase deficiency), Stevens Johnson Syndrome, and DRESS syndrome* have been reported in patients taking SSZ.

*DRESS syndrome – Rash, eosinophilia at least one of the following: enlarged LN, hepatitis (transaminases or AST, ALT >2X

upper limit of normal), interstitial nephropathy, lung disease or myocardial involvement

Biologic DMARDs

General Guidelines

A. Dosing

Minimum starting doses provided. Adjustments at provider's discretion.

B. Toxicity Monitoring

- Complete blood count, liver enzymes, serum creatinine prior to initiation
    - Repeat approximately every 4- 6 months if prior results normal and dose stable
- TB screen prior to initiation (PPD or TB quantiferon gold)
    - Repeat approximately once yearly
    - If positive, need chest Xray and treatment per infectious diseases prior to initiating treatment (usually at least 4-6 weeks of treatment)
- Consider screening for hepatitis B prior to initiation

C. Other recommendations

- Avoid live vaccinations while on biologic agents
- Avoid combinations of biologic agents

Tumor necrosis factor-α inhibitors

A. Dosing

- Etanercept - 0.4 mg/ kg sq twice weekly (maximum 25 mg)/ or 0.8 mg/ kg sq weekly (maximum 50 mg)[21, 22]
- Infliximab - 5-10 mg/kg iv 0,2,6 q 4-8 weekly[17, 23]
- Adalimumab[24]
    - 15-30 kg -- 20 mg sq every other week
    - ≥ 30 kg -- 40 mg sq every other week
- Certolizumab[25] - Dose in RA may be used for those 18yr or older
    - 400 mg/dose at 0,2 and 4 week then 200 mg sc every 2 week

      Or
    - 400mg/dose at 0, 2, 4 week then 400 mg sc every 4 weeks
- Golimumab[26] - Dose in RA may be used for those 18yr or older
    - 50 mg monthly subcutaneous injection

      **will update when pediatric trial results available

B. Special monitoring recommendations for tumor necrosis factor-α inhibitors

- Consider screening for histoplasmosis, blastomycosis, coccidiomycosis in endemic areas

C. Special other considerations for tumor necrosis factor-α inhibitors

- Recommend discussion of the FDA malignancy risk warning as part of routine counseling prior to initiation of therapy
- DMARD use is recommended but not required with infliximab to avoid human antichimeric antibody development

Abatacept

A. Dosing[27, 28]

- IV
    - 10mg/kg up to 1000mg Q2 weeks for 3 doses, then Q4 weeks
    - Children above 75kg -- follow adult dosing schedule below.
    - Adult dosing—
        - <60kg 500mg
        - 60-100kg-750mg
        - >100kg-100mg
- SQ (based on RA dosing)[29]
    - Loading IV dose as above (for weight), then 125 mg SC within a day, followed by 125 mg SC once a week
    - Dose recommendations from pediatric trial will be added when available.

Rituximab

A. Dosing[30]

- 750 mg/m2/dose iv infusion every 2 weeks X 2 doses (max 1 gm), repeat every 4-8 months

B. Special toxicity monitoring[17, 31]

- Consider monitoring serum IgG and IgM levels, circulating B cell numbers
- Consider IVIG replacement therapy if hypogammaglobulinemia develops

C. Special other considerations

- Consider vaccination of children prior to initiation of therapy due to poor ability to mount immune response once therapy started, avoid live vaccines on therapy
- Consider re-dosing based on response in 4-8 months

Tocilizumab

A. Dosing[32]

- <30 kg -- 10 mg/kg q 4 weeks
- >30 kg -- 8 mg/kg q 4 weeks

B. Special Toxicity Monitoring

- Total neutrophil count, platelets, ALT and AST at the time of the 2nd infusion and then monthly
- Lipid level (Total cholesterol, HDL, LDL, triglycerides) monitoring 1-2 months following initiation of therapy, then at 6 month intervals.

REFERENCES

1. Cespedes-Cruz A, Gutierrez-Suarez R, Pistorio A, et al. Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. *Ann Rheum Dis.* Mar 2008;67(3):309-314.

2. Ruperto N, Murray KJ, Gerloni V, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum.* Jul 2004;50(7):2191-2201.

3. Ravelli A, Gerloni V, Corona F, et al. Oral versus intramuscular methotrexate in juvenile chronic arthritis. Italian Pediatric Rheumatology Study Group. *Clin Exp Rheumatol.* Mar-Apr 1998;16(2):181-183.

4. Alsufyani K, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Malleson PN. The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. *J Rheumatol.* Jan 2004;31(1):179-182.

5. Tukova J, Chladek J, Nemcova D, Chladkova J, Dolezalova P. Methotrexate bioavailability after oral and subcutaneous dministration in children with juvenile idiopathic arthritis. *Clin Exp Rheumatol.* Nov-Dec 2009;27(6):1047-1053.

6. Becker ML, Rose CD, Cron RQ, Sherry DD, Bilker WB, Lautenbach E. Effectiveness and toxicity of methotrexate in juvenile idiopathic arthritis: comparison of 2 initial dosing regimens. *J Rheumatol.* Apr 2010;37(4):870-875.

7. Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. *N Engl J Med.* Apr 16 1992;326(16):1043-1049.

8. Reiff A, Shaham B, Wood BP, Bernstein BH, Stanley P, Szer IS. High dose methotrexate in the treatment of refractory juvenile rheumatoid arthritis. *Clin Exp Rheumatol.* Jan-Feb 1995;13(1):113-118.

9. Tynjala P, Vahasalo P, Tarkiainen M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis.* Sep 2011;70(9):1605-1612.

10. Wallace CA, Giannini EH, Spalding SJ, et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis Rheum.* Dec 19 2011.

11. Kocharla L, Taylor J, Weiler T, Ting TV, Luggen M, Brunner HI. Monitoring methotrexate toxicity in juvenile idiopathic arthritis. *J Rheumatol.* Dec 2009;36(12):2813-2818.

12. Beukelman T, Patkar NM, Saag KG, et al. 2011 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).* Apr 2011;63(4):465-482.

13. Silverman E, Mouy R, Spiegel L, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med.* Apr 21 2005;352(16):1655-1666.

14. Silverman E, Spiegel L, Hawkins D, et al. Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum.* Feb 2005;52(2):554-562.

15. Foeldvari I, Wierk A. Effectiveness of leflunomide in patients with juvenile idiopathic arthritis in clinical practice. *J Rheumatol.* Aug 1 2010;37(8):1763-1767.

16. Shi J, Kovacs SJ, Wang Y, Ludden TM, Bhargava VO. Population pharmacokinetics of the active metabolite of leflunomide in pediatric subjects with polyarticular course juvenile rheumatoid arthritis. *J Pharmacokinet Pharmacodyn.* Aug 2005;32(3-4):419-439.

17. Cassidy JT, Petty RE, Laxer RM, Lindsley CB. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia, PA: Saunders Elsevier; 2010.

18. Ansell BM, Hall MA, Loftus JK, et al. A multicentre pilot study of sulphasalazine in juvenile chronic arthritis. *Clin Exp Rheumatol.* Mar-Apr 1991;9(2):201-203.

19. Huang JL, Chen LC. Sulphasalazine in the treatment of children with chronic arthritis. *Clin Rheumatol.* 1998;17(5):359-363.

20. Burgos-Vargas R, Vazquez-Mellado J, Pacheco-Tena C, Hernandez-Garduno A, Goycochea-Robles MV. A 26 week randomised, double blind, placebo controlled exploratory study of sulfasalazine in juvenile onset spondyloarthropathies. *Ann Rheum Dis.* Oct 2002;61(10):941-942.

21. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med.* Mar 16 2000;342(11):763-769.

22. Lovell DJ, Giannini EH, Reiff A, 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.* Jan 2003;48(1):218-226.

23. Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum.* Sep 2007;56(9):3096-3106.

24. Lovell DJ, Ruperto N, Goodman S, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med.* Aug 21 2008;359(8):810-820.

25. http://www.cimzia.com/pdf/Prescribing_Information.pdf. Accessed July 23, 2013.

26. http://www.simponi.com/prescribing-information.pdf. Accessed July 23, 2013.

27. Ruperto N, Lovell DJ, Quartier P, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. *Arthritis Rheum.* Jun 2010;62(6):1792-1802.

28. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet.* Aug 2 2008;372(9636):383-391.

29. http://packageinserts.bms.com/pi/pi_orencia.pdf. Accessed July 23, 2013.

30. Alexeeva EI, Valieva SI, Bzarova TM, et al. Efficacy and safety of repeat courses of rituximab treatment in patients with severe refractory juvenile idiopathic arthritis. *Clin Rheumatol.* Sep 2011;30(9):1163-1172.
31. Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis.* Jun 2011;70(6):909-920.
32. http://www.gene.com/download/pdf/actemra_prescribing.pdf. Accessed July 23, 2013.