Appendix C. STOP-JIA Study Guide

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STOP-JIA GUIDE

CONSENSUS TREATMENT PLANS (CTP) FOR NEW ONSET POLYARTICULAR JIA

(pJIA) 1. Operational Case Definition

a. **Patients should have:**

- Age less than 19 at disease onset
- Age less than 19 at baseline[1] (if 18at enrollment, agrees to be followed for at least one year)
- Arthritis[2] (ACR definition)
  - Present in one joint for at least six weeks
  - >5 active joints are present at baseline ○

  May have any of the following:
  - RF+ polyarticular JIA
  - RF- polyarticular JIA
  - Extended oligoarticular JIA
  - Psoriatic JIA
  - Enthesitis related JIA
  - Undifferentiated JIA
- Contraception if sexually active (male and female)

b. **Patients MAY have:**

- Psoriasis
- Sacroiliitis
- Uveitis
- Enthesitis
- Past or current treatment with
  - NSAIDs
  - Intra-articular, topical and intra-ocular steroids
  - Hydroxychloroquine
  - IV/PO steroids if one of the below criteria are met:
    - iii. if treated < 3 months prior to baseline: treatment cannot exceed 2 weeks
    - iv. if treated > 3 months prior to baseline: any treatment course is permitted as long as treatment was completed 90 days prior to baseline
  - Methotrexate (started no more than 1 month prior to enrollment)
  - Biologics (allowed if patient has only received 1 dose within 1 week of enrollment)

c. **Patients should NOT have:**

- Systemic JIA
- Treatment with any medications for JIA aside from those listed above
- Known inflammatory bowel disease
- Known celiac disease
- Known Trisomy 21

- History of or current malignancy
- Concomitant serious active or recurrent chronic bacterial, fungal or viral infection
- Significant organ system disorder limiting use of treatments for pJIA
- Live vaccine within a month prior to baseline

[1]Patients may be enrolled up until their 19th birthday

[2]Swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, is observed by a physician, and which is not due to primarily mechanical disorders or to other identifiable causes.

2. CTP Choices

If the patient meets the operational case definition, and the treating physician feels that one of the CTPs is appropriate for the patient, one of the following CTPs should be chosen. d.

STEP-UP CTP

Initiation (baseline months)	Begin DMARD (methotrexate, sulfasalazine, or leflunomide) Optional:
	• Prednisone
	• Intra-articular corticosteroid injections
	• Unscheduled clinic visit at 1-2 months if no response or worsened to increase therapy.
Condition improved	If **JADAS ≤ 2.5 and off prednisone**, then no change in treatment from the prior visit is suggested.
Condition worsened or insufficient improvement	If **JADAS > 2.5 and/or *not off prednisone*** at any of the follow-up assessments, consider one of the following:
	• Change DMARD dose (if not at maximum)
	• Change DMARD
	• Add or change biologic
	Optional:
	• Intra-articular corticosteroids may be added at any time
	• Unscheduled visit at 9 months if biologic was added at the 6 month visit.

e. EARLY COMBINATION CTP

Initiation (up to 3 months)	Begin DMARD (methotrexate, sulfasalazine, or leflunomide) and biologic treatment **within one month of each other** Optional:
	• Prednisone
	• Intra-articular corticosteroid injections

	• Unscheduled clinic visit at 1-2 months if no response or worsened to increase therapy.
Condition improved	**If JADAS ≤ 2.5 and off prednisone**, then no change in treatment from the prior visit is suggested.
Condition worsened or insufficient	If **JADAS > 2.5 and/or *not* off prednisone** at any of the follow-up assessments, consider one of the following:
improvement	• Change DMARD dose (if not at maximum)
	• Change DMARD
	• Add or change biologic
	Optional:
	• Intra-articular corticosteroids may be added at any time
	• Unscheduled visit at 9 months if biologic was added at the 6 month visit.

f. BIOLOGIC FIRST CTP

Initiation (up to 3 months)	Begin Biologic treatment Optional:
	• Prednisone
	• Intra-articular corticosteroid injections
	• Unscheduled clinic visit at 1-2 months if no response or worsened to increase therapy.
Condition improved	If **JADAS ≤ 2.5 and off prednisone**, then no change in treatment from the prior visit is suggested.
Condition worsened	If **JADAS > 2.5 and/or *not* off prednisone** at any of the follow-up
or insufficient	up assessments, consider one of the following:
improvement	• Intra-articular corticosteroids at any time.
	• Unscheduled visit at 9 months if medication change was made at 9 months

MD Global & Juvenile Arthritis Disease Activity Score (JADAS) Guidelines

- The MD global should consider only children with PJIA as defined in the enrollment criteria (e.g. think about disease severity relative only to other children with PJIA, not across all categories of JIA).

- **MD Global of 0** should be used to indicate that the child has no evidence of arthritis, uveitis, enthesitis or tenosynovitis based on information from the current clinic visit that is available during the visit; this may include clinical exam, imaging studies and labs.

- **MD Global of 10** should be used to indicate severe, diffuse active arthritis, as well as severity of uveitis and enthesitis or tenosynovitis based on clinical exam and/or imaging studies associated with the current clinic visit, if available during the clinic visit.

Calculating the cJADAS10:
The **cJADAS10** should be calculated at the point of care. It is a simple sum of:

MD Global + Total Active Joint Count (10 maximum) + Parent Global =

Disease activity cut-offs:

- Low disease activity ≤ 2.5
- Moderate disease activity 2.51-8.5
- High disease activity > 8.5

Caveats:

- Patients may achieve moderate disease activity if MD Global = 0, AJC=0, and Parent Global >2.5.
- Clinical judgment still required for interpretation of values.

Suggested Glucocorticoid dosing and tapering tables

All doses at each time point are suggested targets. It is anticipated that tapering of dose to reach the next target will occur between time points. Each suggested option below illustrates discontinuation of steroids before or at 3 months.

		Option 1 LOW DOSE: Starting dose 0.25 mg/kg with 2 week taper					
Weight in kg	**10-<20**	**20-<30**	**30-<40**	**40-<50**	**50-<60**	**≥60**	**Weight-based target dose**
0 weeks	2.5	5	7.5	10	12.5	20	0.25 mg/kg (max 20 mg)
1 week	1.5	2.5	5	7.5	10	15	0.125 mg/kg
11/2 week	0.5	1	1.5	2	2.5	3	0.05 mg/kg
2 weeks	0	0	0	0	0	0	off
		Option 2 MEDIUM DOSE: Starting dose 0.5 mg/kg with one month taper					
Weight in kg	**10-<20**	**20-<30**	**30-<40**	**40-<50**	**50-<60**	**≥60**	**Weight-based target dose**
0 weeks	5	10	15	20	25	30	0.5 mg/kg (max 30 mg)
1 weeks	4	7.5	12.5	15	20	25	0.4 mg/kg
2 weeks	2.5	5	7.5	10	12.5	15	0.25 mg/kg
3 weeks	1	2	3	4	5	6	0.1 mg/kg
4 weeks	0	0	0	0	0	0	off
		Option 3 HIGH DOSE FAST TAPER: Starting dose 1 mg/kg with 1 month taper					
Weight in kg	**10-<20**	**20-<30**	**30-<40**	**40-<50**	**50-<60**	**≥60**	**Weight-based target dose**
0 weeks	10	20	30	40	50	60	1 mg/kg (max 60 mg)
1 weeks	7.5	15	22.5	30	37.5	45	0.75 mg/kg
2 weeks	5	10	15	20	25	30	0.5 mg/kg

3 weeks	2.5	5	7.5	10	12.5	15	0.25 mg/kg
4 weeks	0	0	0	0	0	0	off
		Option 4 HIGH DOSE SLOW TAPER: Starting dose 1mg/kg with 3 month taper					
Weight in kg	**10-<20**	**20-<30**	**30-<40**	**40-<50**	**50-<60**	**≥60**	**Weight-based target dose**
0 weeks	10	20	30	40	50	60	1 mg/kg (max 60mg)
2 weeks	7.5	15	22.5	30	37.5	45	0.75 mg/kg
1 month	5	10	15	20	25	30	0.5 mg/kg
2 months	2.5	7.5	7.5	10	12.5	15	0.25 mg/kg
3 months	0	0	0	0	0	0	off

2. SCHEDULE OF ASSESSMENTS

	Baseline	3 +/-1mo	6 +/-1mo	9 +/-1mo	12 +/-1	Unscheduled
Physician Assessments						
Pre-existing conditions	x					
Comorbid conditions		x	x	x	x	x
Medication history	x					
Concomitant Meds	x	x	x	x	x	x
Physician Assigned ILAR JIA category	x	x	x	x	x	x
JIA Disease Manifestations	x	x	x	x	x	x
Height & weight	x	x	x	x	x	x
Active Joint Count	x	x	x	x	x	x
# of Joints with LROM	x	x	x	x	x	x
# of Joints with Swelling	x	x	x	x	x	x
Physician Global Assessment of Disease	x	x	x	x	x	x
Morning Stiffness	x	x	x	x	x	x
Uveitis assessment	x	x	x	x	x	x
Adverse events		x	x	x	x	x

Intended CTP	x					
Actual CTP followed		x	x	x	x	x
JADAS	x	x	x	x	x	x
Imaging results (if obtained)	x	x	x	x	x	x
Parent/Subject						
Demographics	x	x	x	x	x	x
Global Health	X	X	X	X	X	x
Functional Ability	x	x	x	x	x	x
Pain	x	x	x	x	x	x
Fatigue	x		x		x	
Depression	x				x	
Anxiety	x				x	
Other medication side effects	x	x	x	x	x	x
Family Impact	x				x	
Standard of Care Labs						
Serologies	x	x	x	x	x	x
HLA-B27	x	x	x	x	x	x
ESR and/or CRP	x	x	x	x	x	x
Labs for medication safety depends on medications (see section 5: pp 10-14)	X	X	X	X	X	X
	x	x	x	x	x	

3. PATIENT REPORTED OUTCOME MEASURES

To be completed by parent/proxy for children < 8 and by children ≥ 8 years.

Outcome	Measure	Timing	Source
Global Health	PROMIS®r pediatric global health measure (PGH-7)	Every study visit	• Parent-proxy report if child < 8 years • Child self-report (children ≥ 8 years)
Functional Abilit	PROMIS® physical function mobility and upper extremity short forms	Every study visit	• Parent-proxy report if child < 8 years • Child self-report (children ≥ 8 years)
Pain	Visual analog scales and FACES scale; PROMIS®	Every study visit	• Parent-proxy report if child < 8 years • Child self-report (children ≥ 8 years)

	pediatric pain interference		
Fatigue	PROMIS® pediatric fatigue; short form	Baseline, 6 months, end of study	• Parent-proxy report if child < 8 years • Child self-report (children ≥ 8 years)
Depression	PROMIS® pediatric emotional distress – depression; short form	Baseline, end of study	• Parent-proxy report if child < 8 years • Child self-report (children ≥ 8 years)
Anxiety	PROMIS® pediatric emotional distress – anxiety short form	Baseline, end of study	• Parent-proxy report if child < 8 years • Child self-report (children ≥ 8 years)
Other medication effects	Juvenile Arthritis Multidimensional Arthritis Report (question #11)(57)	All visits (All patients)	• Parent-proxy report if child < 8 years • Child self-report (children ≥ 8 years)
Family Impact	PedsQL™ Family Impact Module(92)	Baseline, end of study	• Parent-proxy report (for all children)

5. Medication Dosing and Monitoring for pJIA CTPs

Glucocorticoids

A. Steroid exposure *prior* to starting on CTP

i. Intraarticular corticosteroid injections (IAS)

- IAS will be allowed at any time prior to starting on CTP, and number of joints injected and date(s) will be documented (dose, which joints, etc. will not be)

ii. Systemic steroids (PO)

- May be allowed prior to starting CTP, if subject has taken steroids for < 2 weeks prior to baseline

B. Steroid use *during* CTP

i. Systemic steroids

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

ii. Intraarticular corticosteroid injections

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

Non-Biologic DMARDs

Methotrexate

A. Route

- 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

- 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 (study visit not required).

C. Toxicity monitoring

- Check CBC, LFTs (AST, ALT), 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
- PPD prior to starting?

D. Will capture additional tolerability variables such as:

- Nausea*
- Vomiting*
- Abdominal pain*

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Leflunomide

B. **Loading dose** No loading dose recommended.

C. Maintenance dose

- <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

Same as methotrexate:

Check CBC, LFTs (AST, ALT), 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 effect to capture: diarrhea, hair loss

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Sulfasalazine

A. Dosing

- 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), 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 (>2X), interstitial nephropathy, lung disease or myocardial involvement

Biologic DMARDs

C. General Dosing Minimum starting doses provided. Adjustments at provider's discretion.

D. General 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 general recommendations

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

Anti-TNF

E. A. Dosing

- **Etanercept -** 0.4 mg/ kg sc twice weekly (max 25 mg)/ or 0.8 mg/ kg sc weekly (max 50 mg)
- **Infliximab -** 5-10 mg/kg iv 0,2,6 q 4-8 weekly
- **Adalimumab**
  - 15-30 kg -- 20 mg sc every other week
  - ≥ 30 kg -- 40 mg sc q every other week
- **Certolizumab **** - Dose in adult 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**** - Dose in adult 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 TNF antagonists

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

C. Special other considerations for TNF antagonist

- 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 HACA

Tocilizumab

F. Dosing

- <25 kg -- 4-8 mg/kg q 4 weeks diluted in sterile saline to total volume 50 ml as IV infusion over 1 hour every 4 weeks
- >25 kg -- 4-8 mg/kg q 4 weeks diluted in sterile saline to total volume 100 ml as IV

infusion over 1 hour every 4 weeks

- Will adopt pediatric doses of 8-10mg/kg once data are available

F.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.

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Rituximab

F. Dosing

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

C. Special toxicity monitoring

- 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

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Abatacept

A. Dosing

- I V
  - 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
- S Q
  - Dose recommendations from pediatric trial:
    - Body Weight of Patient Dose (once weekly)
    - 10 to less than 25 kg 50 mg
    - 25 to less than 50 kg 87.5 mg
    - 50 kg or more 125 mg