Treatment paradigm and landscape of products used in Polyarticular JIA

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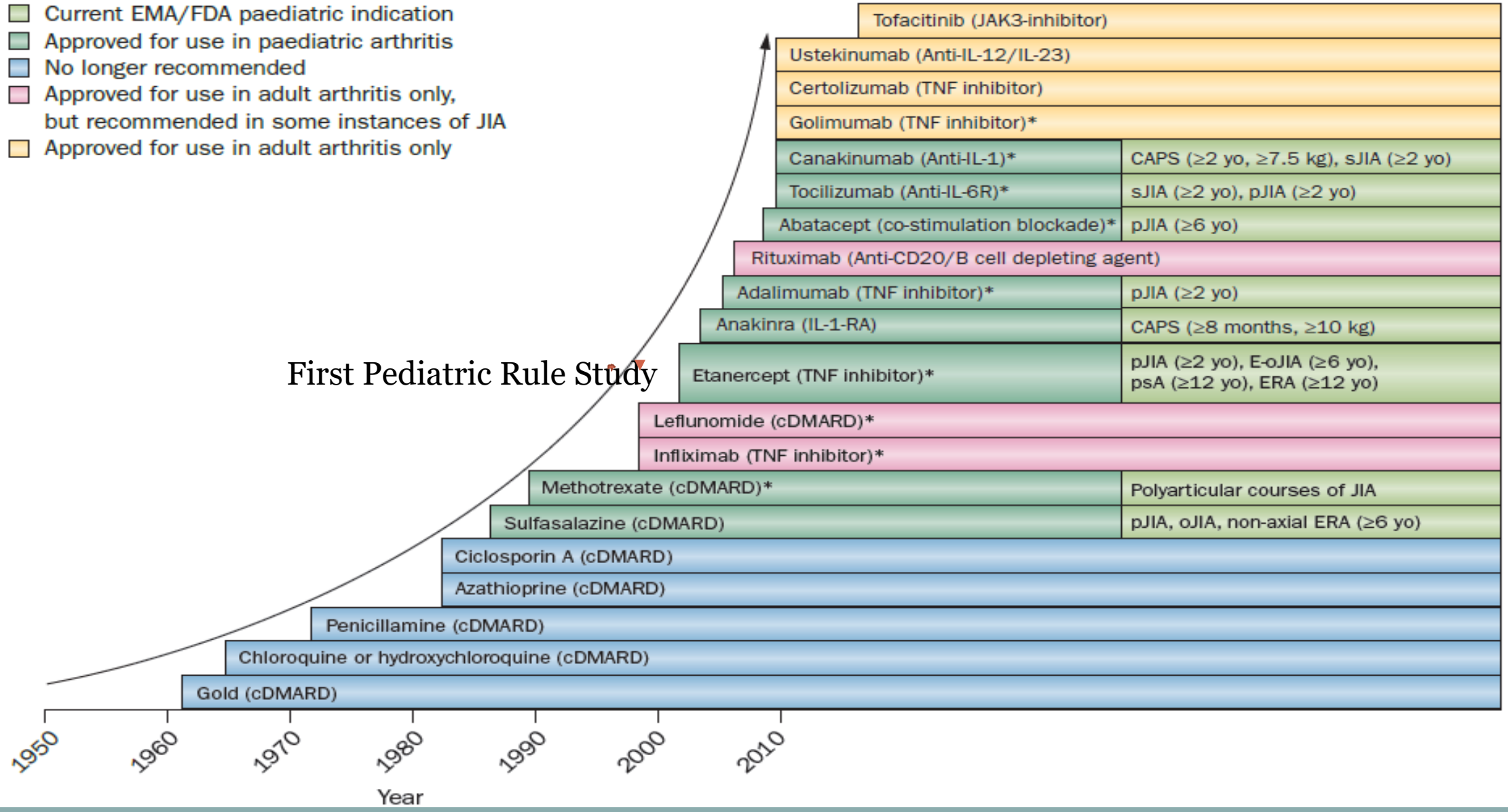
Presentation Topics

- How we got here
- Where we are currently
  - Overview of pJIA patient outcomes
  - Treatments Used
  - Dosing
- Potential Future Steps

New Treatments for JIA



First Pediatric Rule Study

Hinze, C. et al. Nat. Rev. Rheumatol. 11, 290–300 (2015)

JIA Clinical Trials of Biologics in pJIA

- ALL due to due to pediatric rule
- All international except etanercept
- One trial designed to satisfy BOTH FDA and EMA
- Advocate for continued access to treatment for participants beyond the end of the trial

	Centers	Countries	Patients
PRCSG/ PRINTO	248	39	3705

PRCSG-PRINTO Enrollment (3705 patients, 248 centers, 39 countries)

Trial	N. centers / countries	West Europe	East Europe	Latin America	North America	Others	Totals
Etanercept	9/2	0	0	0	69	0	69
Etanercept CLIPPER	38/19	43	75	5		4	127
Infliximab	31/14	62	10	28	23		123
Adalimumab	31/8	57	26		88		171
Abatacept iv	43/12	69	0	94	27		190
Abatacept sc	48/12	97	5	63	23	19	207
Tocilizumab syst iv	42/18	54	7	22	24	5	112
Tocilizumab poly iv	58/15	50	50	60	24	4	188
Tocilizumab syst sc	26/11	25	2	6	16	2	51
Tocilizumab poly sc	24/12	24	2	10	15	1	52
Canakinumab PII	5/5	23	0	0	0	0	23
Canakinumab PIII	63/22	128	27	16	19	0	190
Golimumab	33/13	69	46	30	28	0	173
Adalimumab registry	90/17	274	60	5	505	5	849
Abatacept registry	24/15	195	26	25	189	38	438
Rilonacept	59/22	134	35	82	69	7	327
Certolizumab Pegol	34/7	0	44	39	80	0	163
Tofacitinib poly	49/10	27	74	61	110	5	277
Tofacitinib syst	7/6	1	4	2	1	5	13
Secukinumab	33/10	59	18	0	6	0	83

Frequency of Inactive Disease

	Northern Europe (n=845)	Western Europe (n=832)	Southern Europe (n=2400)	Eastern Europe (n=2044)	North America (n=523)	Latin America (n=849)	Africa and Middle East (n=1209)	Southeast Asia (n=379)
Inactive disease								
Wallace criteria	218 (25·8%)	269 (32·3%)	1084 (45·2%)	378 (18·5%)	187 (35·8%)	294 (34·6%)	269 (22·2%)	101 (26·6%)
JADAS10 criteria	187 (29·4%; n=636)	173 (31·1%; n=556)	854 (45·1%; n=1893)	429 (23·6%; n=1815)	129 (34·5%; n=374)	264 (36·6%; n=721)	283 (26·3%; n=1075)	114 (32·8%; n=348)
cJADAS10 criteria	280 (33·1%)	297 (35·7%)	1161 (48·4%)	519 (25·4%)	216 (41·3%)	354 (41·7%)	335 (27·7%)	152 (40·1%)

Consolaro A, et al. Lancet Child Adolesc Health. 2019 Apr;3(4):255-263. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study.

Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN)

PEDIATRIC RHEUMATOLOGY PR-COIN CARE & OUTCOMES IMPROVEMENT NETWORK

PR Coin

- 14 Pediatric Rheumatology Centers in US and Canada providing data in JIA patients
- Data from 2011- 2016 in Polyarticular JIA patients (Poly RF +/- and Extended Oligoarticular)
- Inactive Disease (i.e. cJADAS10 score ≤ 2.5)
  - 43.5 % (715/1645) demonstrated Inactive Disease
- Normal Functional Ability (i.e. CHAQ score = 0)
  - 56.5% (783/1392) demonstrated normal functional ability
- Best Possible Patient Overall Well Being (i.e. Patient/Parent VAS score = 0)
  - 43.9% (789/1797) demonstrated excellent overall well being

PEDIATRIC RHEUMATOLOGY PR-COIN CARE & OUTCOMES IMPROVEMENT NETWORK

Treatment Patterns- Biologic Treatments

	Northern Europe (n=845)	Western Europe (n=832)	Southern Europe (n=2400)	Eastern Europe (n=2044)	North America (n=523)	Latin America (n=849)	Africa and Middle East (n=1209)	Southeast Asia (n=379)
Biological medications	389 (46·0%)	254 (30·5%)	815 (34·0%)	514 (25·1%)	202 (38·6%)	275 (32·4%)	295 (24·4%)	80 (21·1%)
Etanercept	295 (34·9%)	138 (16·6%)	571 (23·8%)	384 (18·8%)	134 (25·6%)	152 (17·9%)	199 (16·5%)	35 (9·2%)
Infliximab	105 (12·4%)	26 (3·1%)	61 (2·5%)	19 (0·9%)	22 (4·2%)	40 (4·7%)	17 (1·4%)	12 (3·2%)
Adalimumab	140 (16·6%)	98 (11·8%)	225 (9·4%)	97 (4·7%)	56 (10·7%)	63 (7·4%)	81 (6·7%)	0
Abatacept	23 (2·7%)	16 (1·9%)	24 (1·0%)	10 (0·5%)	15 (2·9%)	19 (2·2%)	8 (0·7%)	0
Anakinra	19 (2·2%)	25 (3·0%)	79 (3·3%)	2 (0·1%)	7 (1·3%)	3 (0·4%)	36 (3·0%)	0
Canakinumab	0	12 (1·4%)	25 (1·0%)	6 (0·3%)	1 (0·2%)	5 (0·6%)	3 (0·2%)	0
Tocilizumab	17 (2·0%)	29 (3·5%)	54 (2·3%)	65 (3·2%)	9 (1·7%)	58 (6·8%)	36 (3·0%)	40 (10·6%)

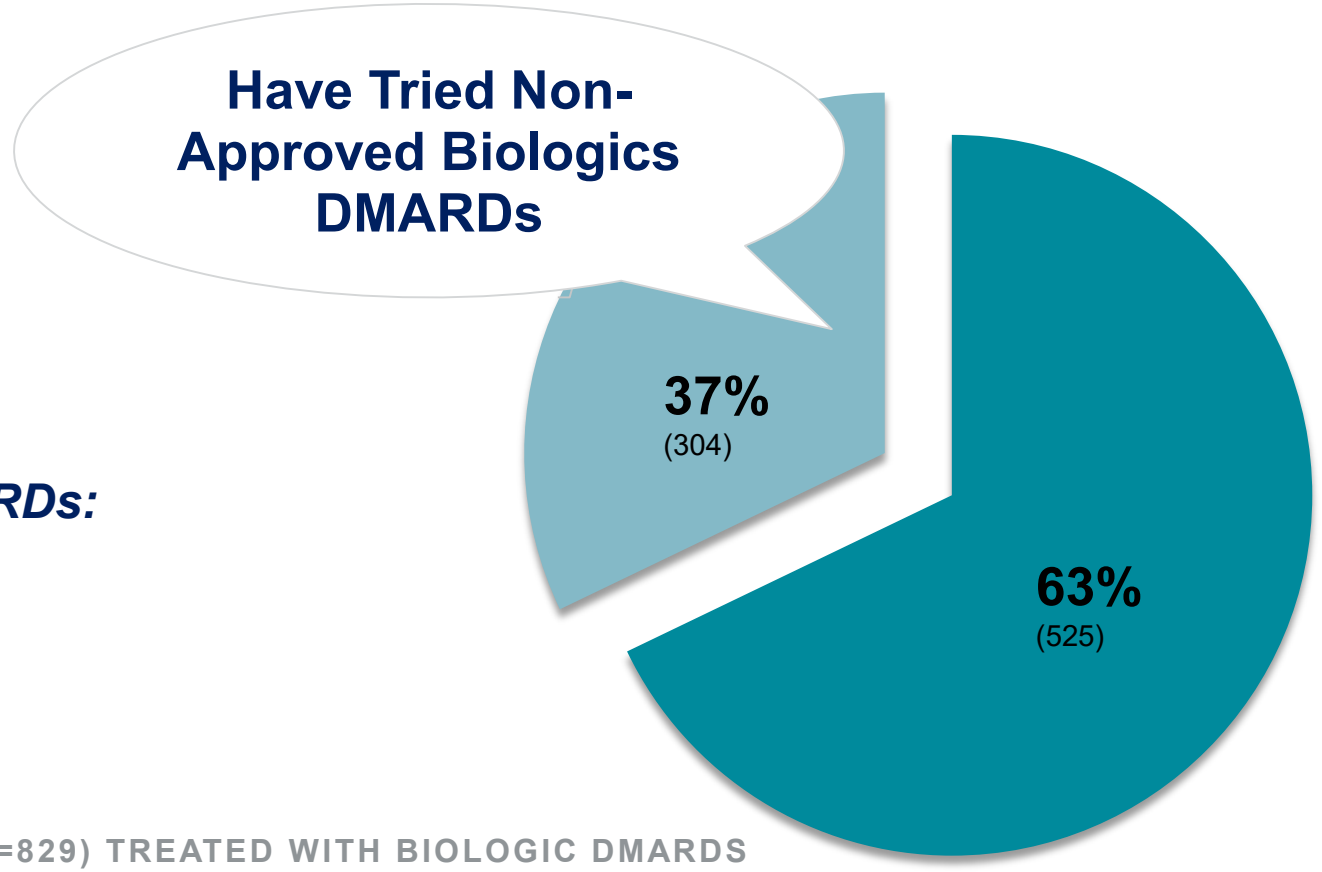
Consolaro A, et al. Lancet Child Adolesc Health. 2019 Apr;3(4):255-263.

NEW MEDICATIONS ARE NEEDED FOR CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

- Hermine I Brunner, Laura E Schanberg, Yukiko Kimura, Anne Dennos, Guy Eakin, Dominic Co, Robert Colbert, Robert Fuhlbrigge, Ellen Goldmuntz, Daniel Kingsbury, Sandra Mintz, Karen Onel, Cathy Patty-Resk, Lisa Rider, Rayfel Schneider, Allen Watts, Emily Von Scheven, Daniel J Lovell, Timothy Beukelman for the PRCSG Advisory Council and the CARRA Registry Investigators.

- Data collection from the CARRA JIA Registry (n = 7,379) and the Cincinnati Children's Hospital Medical Center JIA Registry (n = 1,599)

Every Third Child requiring advanced therapy with a biologic DMARD or targeted synthetic DMARD have tried a treatment that has not been approved for JIA



Unapproved Biologic DMARDs:

- *Tofacitinib*
- *Golimumab IV/SC*
- *Secukinumab*
- *Ustekinumab*
- *Anakinra*
- *Infliximab*
- *Rituximab*

(N=829) TREATED WITH BIOLOGIC DMARDS

	CCHMC (N=1599)	CARRA (N=7379)
Treatment without bDMARDs		
Never received DMARD	435 (27%)	870 (11%)
Conventional DMARD only‡	335 (20%)	1743 (24%)
Treatment using bDMARDs¶		
1 bDMARD	342 (21%)	2992 (41%)
2 bDMARDs	239 (15%)	1129 (15%)
3 bDMARDs	174 (11%)	428 (6%)
4 bDMARDs	49 (3%)	130 (1.8%)
5 or more bDMARDs	25 (1.6%)	87 (1.2%)
Any bDMARD	829 (53%)	4766 (65%)

Definitions for Treatment Failures

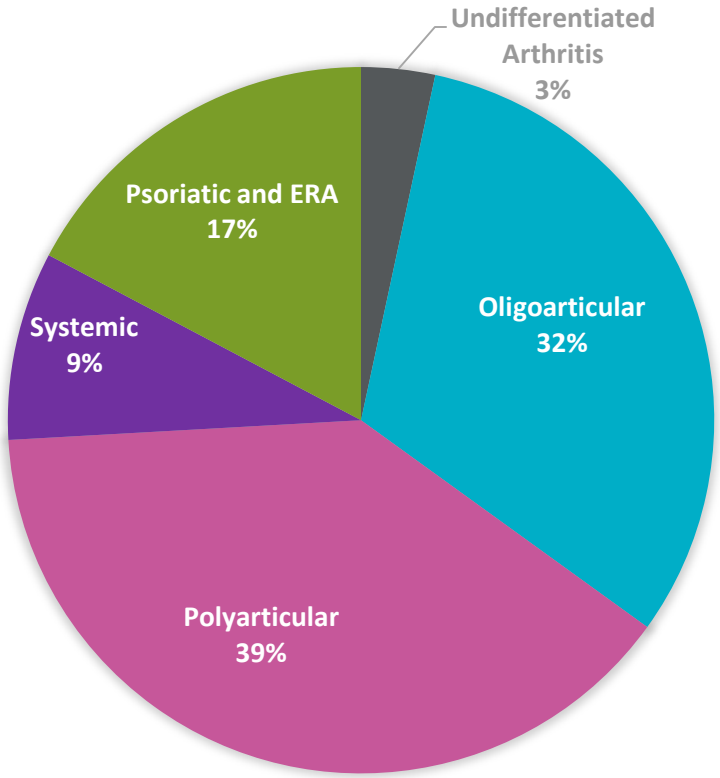
- Definition #1: At Least Moderate Disease Activity
  - MD-global $\geq$3 OR AJC $\geq$ 3 OR Pat-global $\geq$3
- Definition #2: Not in Inactive Disease
  - MD-global $\geq$1 OR AJC$\geq$1 OR Pat-global$\geq$1

	CCHMC JIA Registry – assessed over time			CARRA Registry – assessed at most recent visit only		
Patients	Total N	Failure by Definition 1 N (%)	Failure by Definition 2 N (%)	Total N	Failure by Definition 1 N (%)	Failure by Definition 2 N (%)
ALL JIA (with complete failure definition variables)	487	255 (52%)	375 (77%)	1,159	527 (45%)	859 (74%)
Number of bDMARDs						
2 bDMARDs used	239 (48%)	113 (47%)	174 (73%)	731 (63%)	283 (39%)	507 (69%)
3 bDMARDs used	174 (37%)	97 (56%)	137 (79%)	282 (24%)	149 (53%)	225 (80%)
4 bDMARDs used	49 (10%)	31 (63%)	43 (88%)	87 (8%)	56 (64%)	72 (83%)
≥ 5 bDMARDs used	25 (5%)	14 (56%)	21 (84%)	59 (5%)	39 (66%)	55 (93%)

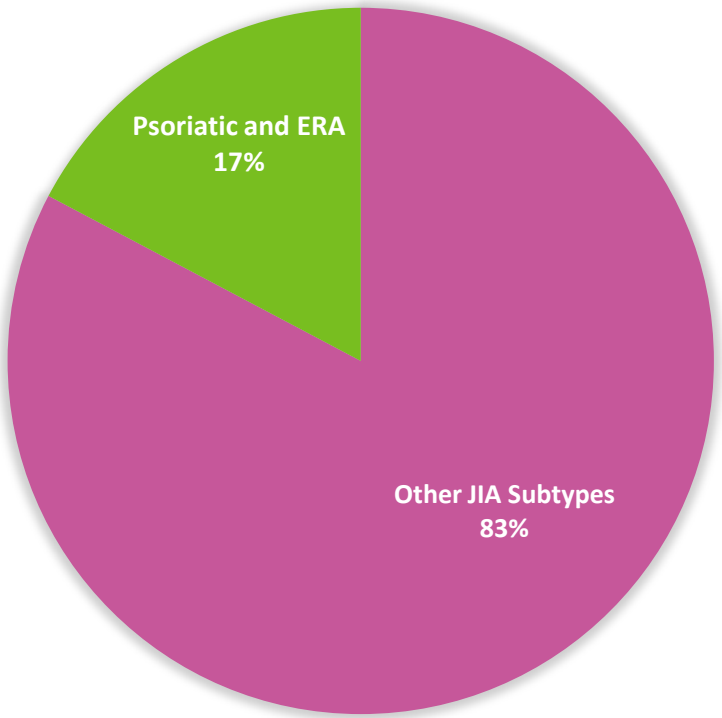
JPsA + ERA Population = 17% of all JIA Patients

Cincinnati Children's
changing the outcome together

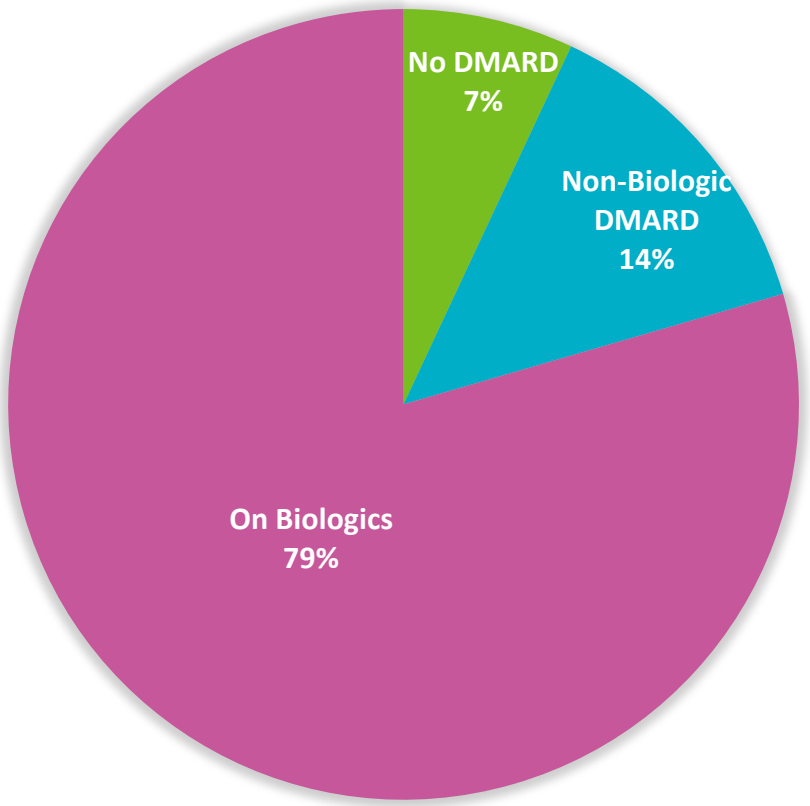
JIA POPULATION AT CCHMC (N=1,599)



JPSA OR ERA SUBTYPES (N=1,599)



JPsA + ERA Population Treatments



Biologic DMARDs:

- Etanercept
- Infliximab
- Canakinumab
- Rituximab
- Adalimumab
- Tocilizumab SC/IV
- Anakinra
- Abatacept SC/IV
- Secukinumab
- Ustekinumab
- Golimumab SC/IV
- Tofacitinib

Non-Biologic DMARDs

- Methotrexate
- Sulfasalazine
- Leflunomide

CLINICAL DOSING OF FDA APPROVED BIOLOGICS IN POLY JIA

- Data from the New CARRA Registry
- Cross-sectional assessment of current dose of approved biologics at most recent data entry for patients with RF+ polyarthritis, RF- polyarthritis, and extended oligoarthritis

Analysis directed by Timothy Beukelman, MD, MSCE

Etanercept Treated (n = 783 Current Users)

- **FDA Approved Dose: 0.4 mg/kg twice weekly OR 0.8 mg/kg once weekly, maximum weekly dose of 50 mg in patients at least 2 years of age**
- **< 2 years old at initial use: 2.8% of ever users**

- **Receiving High Dose (> 0.880 mg/kg per week): 22%**
- **Receiving Low Dose (< 0.720 mg/kg per week): 45%**

Adalimumab Treated (n = 786 current users)

- **FDA Approved Dose: 10 kg to less than 15 kg: 10 mg subcutaneously (SC) every 2 weeks; 15 kg to less than 30 kg: 20 mg SC every 2 weeks; 30 kg and greater: 40 mg SC every 2 weeks in children ≥ 2 years old**

- **< 2 years old at initial use: 0.5% of ever users**
- **Receiving High Dose: 21%**
- **Receiving Low Dose: 7%**
- **Receiving weekly dosing: 15%**
- **Dosing longer than every 2 weeks: 3%**

IV Abatacept Treated (n = 66 current users)

- **FDA Approved Dose: 10 mg/kg (maximum dose 1000 mg) every 4 weeks**
  - **Getting infusions > than every 4 weeks: 8%**
  - **Getting infusions < than every 4 weeks: 11%**

  - **Receiving High Dose (>11 mg/kg/infusion): 27%**
  - **Receiving Low Dose (<9 mg/kg/infusion): 41%**

SQ Abatacept Dosing (n = 74 current users)

- FDA approved dose: Weekly dosing, 10-< 25 kg 50 mg; 25-< 50 kg 87.5 mg; ≥ 50 kg 125 mg

  - Getting injections at > 1-week intervals: 5%

  - Receiving High Dose: 12%
  - Receiving Low Dose: 5%

IV Tocilizumab Dosing (n = 112 current users)

- FDA approved dose: every 4 weeks; in < 30 kg then 10 mg/kg, for ≥ 30 kg 8 mg/kg in those ≥ 2 yrs. of age

  - < 2 years old at initial use: <1% of ever users
  - Receiving High Dose: 26%
  - Receiving Low Dose: 39%
  - Getting infusions < every 4 weeks: 16%
  - Getting infusions > every 4 weeks: 6%

SQ Tocilizumab Dosing (n = 88 current users)

- FDA Approved Dose: 162 mg per dose; < 30 kg every 3 weeks, ≥ 30 kg every 2 weeks in those ≥ 2 years of age

  - <2 years old at first use: 0%
  - Receiving High Dose: 33%
  - Receiving Low Dose: 5%

POTENTIAL FUTURE STEPS

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- Develop clear guidelines for studies of new agents in proven therapeutic approaches
  - E.g. IL-6 inhibition with Sarilumab or Sirukumab
- New therapeutic approaches
  - JAK/STAT Inhibitors
    - Challenging as different agents are NOT equal in relative inhibition of JAK 1 vs JAK 2 vs JAK 3
    - Undefined safety profile in both adults and children
    - Tofacitinib study in pJIA has completed enrollment

POTENTIAL FUTURE STEPS

- **Expansion of Pediatric Rule to include psoriatic JIA and ERA including revision of the list of "Automatic Full Waivers" under PREA (https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea)**

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics*
These conditions qualify for waiver because studies would be impossible or highly impractical.

  - **Juvenile Psoriatic Arthritis, Psoriatic Arthritis and Axial Spondyloarthropathies including Ankylosing Spondylitis are all on this list**
  - **As shown previously large unmet medical need and frequent off label use**
  - **Number of agents being developed specifically for psoriatic arthritis and spondyloarthropathy in adults but not tested in US but tested in JIA patients in ROW due to EMA requirement**

POTENTIAL FUTURE STEPS

- **Investigation of agents for new FDA indication "non-radiographic axial spondyloarthritis"**
  - **902 children with JSpA currently in the CARRA Registry (*Data shown with permission of CARRA, provided by Tim Beukelman, MD*)**
    - **522 (58%) with ERA and 380 (42%) with JPsA**
    - **Sacroiliitis by imaging and/or clinical exam in 40% of ERA and 12% of those with JPsA**
    - **Biologic therapy used in 81% with sacroiliitis and 65% without sacroiliitis**