Disease-modifying Antirheumatic Drug Use in the Treatment of Juvenile Idiopathic Arthritis: A Cross-sectional Analysis of the CARRA Registry

TIMOTHY BEUKELMAN, SARAH RINGOLD, TREVOR E. DAVIS, ESI MORGAN DeWITT, CHRISTINA F. PELAJO, PAMELA F. WEISS, and YUKIKO KIMURA, for the CARRA Registry Investigators

ABSTRACT. ***Objective.*** To characterize disease-modifying antirheumatic drug (DMARD) use for children with juvenile idiopathic arthritis (JIA) in the United States and to determine patient factors associated with medication use.

Methods. We analyzed cross-sectional baseline enrollment data from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry from May 2010 through May 2011 for children with JIA. Current and prior medication use was included. We used parsimonious backward stepwise logistic regression models to calculate OR to estimate associations between clinical patient factors and medication use.

Results. We identified 2748 children with JIA with a median disease duration of 3.9 years from 51 US clinical sites. Overall, 2023 (74%) had ever received a nonbiologic DMARD and 1246 (45%) had ever received a biologic DMARD. Among children without systemic arthritis, methotrexate use was most strongly associated with uveitis (OR 5.2, 95% CI 3.6–7.6), anticitrullinated protein antibodies (OR 4.5, 95% CI 1.7–12), and extended oligoarthritis (OR 4.1, 95% CI 2.5–6.6). Among children without systemic arthritis, biologic DMARD use was most strongly associated with rheumatoid factor (RF)-positive polyarthritis (OR 4.3, 95% CI 2.9–6.6), psoriatic arthritis (PsA; OR 3.0, 95% CI 2.0–4.4), and uveitis (OR 2.8, 95% CI 2.1–3.7). Among children with systemic arthritis, 160 (65%) ever received a biologic DMARD; tumor necrosis factor inhibitor use was associated with polyarthritis (OR 2.5, 95% CI 3.8–16), while interleukin 1 inhibitor use was not.

Conclusion. About three-quarters of all children with JIA in the CARRA Registry received nonbiologic DMARD. Nearly one-half received biologic DMARD, and their use was strongly associated with RF-positive polyarthritis, PsA, uveitis, and systemic arthritis. (J Rheumatol First Release Aug 1 2012; doi:10.3899/jrheum.120110)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS DISEASE-MODIFYING ANTIRHEUMATIC DRUG
DRUG TOXICITY

From the University of Alabama at Birmingham, Birmingham, Alabama; Seattle Children's Hospital, Seattle, Washington; Floating Hospital for Children at Tufts Medical Center, Boston, Massachusetts; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, New Jersey; The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; and Hospital Pequeño Príncipe, Curitiba, Brazil.

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry is supported by National Institutes of Health (NIH) grant RC2AR058934, the Arthritis Foundation, and Friends of CARRA. Dr. Beukelman was supported by NIH grant 5KL2 RR025776 through the University of Alabama at Birmingham Center for Clinical and Translational Science.

T. Beukelman, MD, MSCE, University of Alabama at Birmingham; S. Ringold, MD, MS, Seattle Children's Hospital; T.E. Davis, MD, Floating Hospital for Children at Tufts Medical Center; E. Morgan DeWitt, MD, MSCE, Cincinnati Children's Hospital Medical Center; C.F. Pelajo, MD, MSc, Hospital Pequeño Príncipe; P.F. Weiss, MD, MSCE, Children's Hospital of Philadelphia; Y. Kimura, MD, Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center.

Address correspondence to Dr. T. Beukelman, Division of Pediatric Rheumatology, University of Alabama at Birmingham, 1600 7th Ave. South, CPP 210, Birmingham, AL 35233-1711, USA. E-mail: tbeukelman@peds.uab.edu

Accepted for publication May 18, 2012.

The introduction of disease-modifying antirheumatic drugs (DMARD) for the treatment of juvenile idiopathic arthritis (JIA) over the last 2 decades has significantly improved clinical outcomes. First to be introduced were the nonbiologic DMARD, methotrexate (MTX) being chief among them[1]. Many years later the biologic DMARD were introduced. The tumor necrosis factor-α (TNF-α) inhibitors[2,3,4] were followed by several other biologic therapeutic agents with different mechanisms of action including inhibition of interleukin 1 (IL-1), IL-6, and T cell costimulation[5,6,7]. To date, the US Food and Drug Administration (FDA) has approved 3 biologic DMARD for the treatment of polyarticular JIA (etanercept, adalimumab, and abatacept) and 1 for the treatment of systemic arthritis (tocilizumab).

In response to these numerous advances in the treatment of JIA, the American College of Rheumatology issued the first evidence and consensus-based Recommendations for the Treatment of JIA in 2011 (ACR Recommendations)[8]. The ACR Recommendations used key clinical measures to define

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

patients and make specific recommendations about the appropriate initiation of biologic and nonbiologic DMARD. These key clinical measures included JIA treatment group (disease phenotype), prognostic features, disease activity, and current therapy. The ACR Recommendations were intended to reflect current clinical practice according to a panel of experts. Nevertheless, the actual use of DMARD in the treatment of JIA in clinical practice has not been well characterized and was the basis for our study.

In 2009, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) created an observational registry of pediatric rheumatology patients from throughout the US. In our study, we used enrollment data for children with JIA in the CARRA Registry to characterize DMARD use by pediatric rheumatologists on a national level and determine patient factors associated with medication use.

MATERIALS AND METHODS

Data source. The CARRA Registry is an observational longitudinal data capture study that encompasses all major pediatric rheumatic diseases and 51 active CARRA clinical sites that represent the majority of pediatric rheumatology centers from all major geographic regions of the US. Children are not systematically enrolled in the registry, but are recruited without regard to disease duration, disease severity, current disease activity status, or treatment received.

After obtaining Institutional Review Board approval, we analyzed cross-sectional baseline enrollment data for all children with a primary diagnosis of JIA as determined by the enrolling pediatric rheumatologist. We used data from all active US clinical sites from the start of the registry in May 2010 through May 2011. To maintain a limited dataset that did not contain any potential personal identifiers, we did not have access to the children's clinical site of enrollment.

Medications. Medication histories were obtained through family and patient recall, limited (not necessarily exhaustive) chart review, and provider recall at the discretion of the clinical site investigators. Use of individual nonbiologic DMARD and biologic DMARD was categorized as current, prior, never, or unknown. Use of intraarticular, intravenous pulse, and daily oral glucocorticoids was similarly categorized. Use of nonsteroidal antiinflammatory drugs (NSAID) was categorized as current daily use, not current daily use, or unknown. "Unknown" responses constituted < 1% of the data for the use of any one of the medications. For the purposes of our study, "ever use" encompassed all reported current and prior medication use, and nonbiologic DMARD comprised MTX, leflunomide (LEF), and sulfasalazine (SSZ; for children without systemic arthritis). The data do not contain information about medication doses or dates of initiation or discontinuation.

Analysis. We used logistic regression to calculate OR to estimate univariate associations between patient factors and medication use. Owing to fundamental differences between the treatment of systemic arthritis and the other categories of JIA[8], we analyzed medication use for children with systemic arthritis separately. We analyzed the following patient factors for children without systemic arthritis: International League of Associations for Rheumatology (ILAR) categories[9] [persistent oligoarthritis, extended oligoarthritis, rheumatoid factor-negative (RF–) polyarthritis, rheumatoid factor-positive (RF+) polyarthritis, psoriatic arthritis (PsA), enthesitis-related arthritis (ERA)], treatment groups from the ACR Recommendations[8] (history of arthritis of ≤ 4 joints and history of arthritis of ≥ 5 joints), HLA-B27 positivity, uveitis, inflammatory bowel disease (IBD), sacroiliac (SI) tenderness, enthesitis, psoriasis rash, anticitrullinated protein antibodies (ACPA), and radiographic joint damage (defined as presence of joint space narrowing, erosion, or ankylosis). Disease duration since the onset of symptoms was included as a potential confounding factor in all multivariable models. For children with systemic arthritis, we evaluated the following patient factors: history of polyarthritis (≥ 5 joints), serositis, and radiographic joint damage. We further analyzed patient factors that were significant in univariate analyses ($p < 0.10$) using stepwise backward selection multiple variable logistic regression models with removal of covariates at the level of $p > 0.05$ to create parsimonious models. The predictive value of the parsimonious multivariable models was analyzed by calculating the area under the curve (AUC) for the receiver-operating characteristic (ROC) curve. Models in which the AUC is ≥ 0.70 are considered to have acceptable discrimination[10]. Statistical analyses were performed using Stata 10.0 (StataCorp, College Station, TX, USA).

RESULTS

We identified 2748 children with JIA with available baseline enrollment data from 51 US clinical sites (Table 1). The median number of patients enrolled at each site was 35, and the interquartile range was 18 to 69 patients. Most children were diagnosed with JIA several years prior to enrollment in the CARRA Registry, with a median disease duration of 3.9 years. All categories of JIA were represented.

Overall medication use. Among all patients with JIA, 2023 (74%) had ever received a nonbiologic DMARD (Table 2), including MTX (ever used by 95% of nonbiologic DMARD users), SSZ (11%), and LEF (5%). By contrast, the current users of nonbiologic DMARD at enrollment numbered 1400 (51%). Most MTX users (74%) had received it through the subcutaneous route of administration during their treatment course. Many SSZ users (35%) had not ever received MTX; only 5% of LEF users had not received MTX. Among current SSZ users, 20% were concurrent users of MTX.

Among all patients with JIA, 1246 (45%) had ever received a biologic DMARD (Table 2). By contrast, the current users of biologic DMARD at enrollment numbered 1050 (38%). TNF inhibitors were ever used by 96% of all biologic users. Etanercept was the most commonly used TNF inhibitor (ever used by 81% of all TNF inhibitor users), followed by adalimumab (32%) and infliximab (18%). Among users of adalimumab or infliximab, 43% did not ever receive etanercept. Among users of infliximab, 54% did not have uveitis or inflammatory bowel disease (IBD). Many children treated with TNF inhibitors received > 1 anti-TNF agent; 22% received 2 and 6% received 3 or more different TNF inhibitors. Few abatacept users (8% of total) had never used a TNF inhibitor. Children with systemic arthritis were 86% of all IL-1 inhibitor users.

Among all children, 1258 (46%) ever received an intraarticular glucocorticoid injection and 1041 (38%) ever received systemic glucocorticoid to treat JIA. The majority of children (57%) who ever received intravenous pulse glucocorticoids had systemic arthritis. About one-half of all children (51%) were currently receiving daily NSAID.

There was clinically important variation in medication use according to the JIA ILAR categories and ACR treatment groups (Table 3). Not surprisingly, DMARD use was less common among children with oligoarthritis or a history of ≤ 4 active joints; intraarticular glucocorticoid use was more common among these patients. More than 20% of children with

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

Table 1. Characteristics of the study patients (N = 2748). For time-varying characteristics (e.g., sacroiliac tenderness), current and prior presence are included.

Characteristic	
Median age, yrs (IQR)	12.0 (7.7–15.4)
Female, n (%)	1996 (73)
Median disease duration, yrs (IQR)	3.9 (1.8–7.2)
ILAR JIA categories, n (%)	
Systemic arthritis	246 (9)
Persistent oligoarthritis	724 (26)
Extended oligoarthritis	224 (8)
RF– polyarthritis	802 (29)
RF+ polyarthritis	200 (7)
Enthesitis-related arthritis	286 (10)
Psoriatic arthritis	170 (6)
Undifferentiated arthritis	62 (2)
Missing or "other"	34 (1)
HLA-B27-positive, n (%)	210 (8)
ACPA-positive, n (%)	114 (4)
Sacroiliac tenderness, n (%)	264 (10)
Ethesitis, n (%)	324 (12)
Uveitis, n (%)	304 (11)
Inflammatory bowel disease, n (%)	53 (2)
Psoriasis rash, n (%)	143 (5)
Radiographic joint damage, n (%)	588 (21)
ACR treatment groups, n (%)	
History of arthritis of ≤ 4 joints	1045 (38)
History of arthritis of ≥ 5 joints	1443 (53)
Systemic arthritis	246 (9)

IQR: interquartile range; ILAR: International League of Associations for Rheumatology; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor; ACPA: anticitrullinated protein antibody; ACR: American College of Rheumatology.

systemic arthritis and RF+ polyarthritis were currently receiving systemic glucocorticoids. There was no marked variation in current daily NSAID use among the JIA categories or ACR treatment groups.

Overall, there were 304 (11%) children with a history of uveitis. Most of these children had received treatment with MTX (88%) and many had received TNF inhibitors (57%). Children with uveitis who received TNF inhibitors were much more likely to ever receive a monoclonal antibody TNF inhibitor (adalimumab, infliximab, or golimumab) compared to children who received TNF inhibitors and did not have uveitis (OR 10, 95% CI 6.7–16).

Use of nonbiologic DMARD among children without systemic arthritis. There were multiple patient factors independently associated with the use of MTX (Table 4). Not surprisingly, a history of ≥ 5 active joints and its associated ILAR categories (extended oligoarthritis, RF– polyarthritis, and RF+ polyarthritis) were associated with more MTX use. PsA remained associated with MTX use when adjusted for a history of ≥ 5 active joints and other factors. SI tenderness was associated with less use of MTX. Uveitis was strongly associated with the use of MTX. The patient factors in the parsimonious multivariable model demonstrated a modest predictive value overall for treatment with MTX with an AUC of the ROC curve of 0.79.

In multivariable analysis, SSZ use was most strongly associated with IBD (OR 2.8, 95% CI 1.3–5.8) and ERA (OR 2.1, 95% CI 1.3–3.6) compared to oligoarthritis. The parsimonious multivariable model for any nonbiologic DMARD use (MTX, LEF, or SSZ) was similar to the MTX model, with the exception that SI tenderness had no association with use of any nonbiologic DMARD.

Use of biologic DMARD among children without systemic arthritis. There were multiple patient factors independently associated with the use of biologic DMARD (Table 5). Again, not surprisingly, a history of ≥ 5 active joints and RF+ and RF– polyarthritis were associated with more biologic DMARD use. Nevertheless, biologic DMARD were used by 20% of children with persistent oligoarthritis, and only 41% of these children had a history of uveitis. In the multivariable model, some clinical features typically associated with ERA (enthesitis, SI tenderness) remained associated with biologic DMARD use, while the ERA category as a whole did not. The patient factors in the parsimonious multivariable model demonstrated a modest predictive value overall for treatment with biologic DMARD, with an AUC of the ROC curve of 0.77.

Among 1056 children who received TNF inhibitors, only 82 (8%) did not receive prior or current nonbiologic DMARD. In multivariable analysis of all patient factors, this medication usage pattern was most strongly associated with ERA (OR 3.2, 95% CI 1.9–5.4) compared to patients with other categories of JIA.

We separately analyzed biologic DMARD use among patients with the JIA ILAR categories that may be associated with more or less than 4 affected joints. Restricted to children with ERA, several patient factors were associated with the use of biologic DMARD in a multivariable parsimonious model: IBD (OR 8.8, 95% CI 2.4–33), radiographic damage (OR 4.6, 95% CI 2.4–9.0), enthesitis (OR 2.4, 95% CI 1.4–4.4), and history of ≥ 5 joints (OR 1.7, 95% CI 1.0–2.8). Restricted to children with PsA, several patient factors were associated with the use of biologic DMARD in a multivariable parsimonious model: HLA-B27 (OR 5.4, 95% CI 1.1–27), radiographic damage (OR 3.3, 95% CI 1.2–9.4), and history of ≥ 5 joints (OR 2.5, 95% CI 1.2–5.2).

Nonbiologic medication use by children with systemic arthritis. There were 246 children (9%) with systemic arthritis. Among these children, 80% had received MTX, 13% cyclosporine, 4% cyclophosphamide, 3% LEF, 3% mycophenolate mofetil, 2% SSZ, and 2% tacrolimus. MTX use was more common in children with polyarthritis (Table 6). Cyclosporine use was more common in children with radiographic damage (Table 6).

Biologic DMARD use by children with systemic arthritis. Among children with systemic arthritis, 160 (65%) had received any biologic; 46% had received any TNF inhibitor,

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

Table 2. Medication use among all patients with juvenile idiopathic arthritis (n = 2748).

Medication	Medication Users, n (% of total)
Any nonbiologic DMARD	2023 (74)
Methotrexate	1939 (71)
Sulfasalazine	228 (8)
Leflunomide	96 (3)
Any biologic DMARD	1246 (45)
TNF inhibitors	1196 (44)
Etanercept	972 (35)
Adalimumab	378 (14)
Infliximab	220 (8)
Golimumab	17 (1)
Certolizumab	8 (< 1)
IL-1 inhibitors	111 (4)
Anakinra	106 (4)
Rilonacept	13 (< 1)
Canakinumab	7 (< 1)
Abatacept	77 (3)
Rituximab	19 (1)
Tocilizumab	16 (1)
Intraarticular glucocorticoid	1258 (46)
Systemic glucocorticoid	1041 (38)
Oral glucocorticoid	1031 (38)
Intravenous pulse glucocorticoid	132 (5)
Current daily NSAID	1393 (51)

DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor-α; IL-1: interleukin 1; NSAID: nonsteroidal antiinflammatory drug.

39% any IL-1 inhibitor, 5% tocilizumab, 5% abatacept, and 1% rituximab. TNF inhibitor use was more common in children with radiographic damage (Table 6). IL-1 inhibitor use was more common in children with radiographic damage compared to children without radiographic damage. Only 21 (13%) of the ever biologic users did not ever use MTX or cyclosporine.

DISCUSSION

Using cross-sectional data for 2748 children with prevalent JIA enrolled in the CARRA Registry at 51 different clinical sites throughout the US, we observed that 74% of all patients had ever received nonbiologic DMARD and 45% had ever received biologic DMARD in clinical practice. The use of systemic glucocorticoids (38% ever use) and NSAID (51% current daily use) was also common. In addition, we identified several patient factors that were strongly and independently associated with particular medication usage.

We found that a considerable proportion of children with JIA are treated with biologic agents by pediatric rheumatologists in the US. Among children with the systemic arthritis and RF+ polyarthritis categories of JIA, about two-thirds of patients had ever received biologic DMARD. Even among children with the persistent oligoarthritis category and without uveitis, 12% had received biologic DMARD, a practice that has been recommended for refractory disease[8] but has not been the subject of any controlled studies. To our knowledge, there are not similar published reports of the use of biologic DMARD among all children with JIA from other countries with which to compare our results.

For children without systemic arthritis, the current ACR Recommendations generally specify a variable trial of nonbiologic DMARD prior to initiation of TNF inhibitors[8]. Correspondingly, we observed that the vast majority of children (92%) without systemic arthritis who received TNF inhibitors had also received nonbiologic DMARD. Children who received TNF inhibitors in the absence of nonbiologic DMARD use were significantly more likely to have ERA, suggesting that some pediatric rheumatologists may believe that nonbiologic DMARD are less effective in the treatment of ERA. This opinion may be based, in part, on the fact that nonbiologic DMARD have not been shown to be efficacious in the treatment of adults with ankylosing spondylitis[11]. Accordingly, the ACR Recommendations specify a lower threshold for the initiation of TNF inhibitors for children with active SI arthritis compared to children without SI arthritis[8]. Nevertheless, when we restricted our analyses of the ever use

Table 3. Medication use by juvenile idiopathic arthritis International League of Associations for Rheumatology categories and American College of Rheumatology treatment groups. Counts for nonbiologic DMARD, biologic DMARD, and intraarticular GC include ever use. Data are n (%).

Classification	Nonbiologic DMARD	Biologic DMARD	Intraarticular GC	Any Systemic GC	Current Systemic GC	Current Daily NSAID
Oligoarthritis	387 (53)	143 (20)	467 (65)	118 (16)	14 (2)	370 (51)
Extended oligoarthritis	200 (89)	104 (46)	157 (70)	61 (27)	6 (3)	108 (48)
RF– polyarthritis	666 (83)	431 (54)	313 (39)	340 (42)	79 (10)	400 (50)
RF+ polyarthritis	181 (91)	136 (68)	73 (37)	125 (63)	43 (22)	118 (59)
ERA	181 (63)	132 (46)	77 (27)	103 (36)	21 (7)	162 (57)
Psoriatic	142 (84)	99 (58)	60 (35)	56 (33)	10 (6)	72 (42)
Systemic	202 (82)	160 (65)	82 (33)	204 (83)	62 (25)	114 (46)
Undifferentiated	40 (65)	23 (37)	21 (34)	22 (35)	3 (5)	36 (58)
History of ≤ 4 active joints	594 (57)	270 (26)	573 (55)	223 (21)	35 (3)	536 (51)
History of ≥ 5 active joints	1219 (84)	812 (56)	600 (42)	609 (42)	144 (10)	738 (51)

DMARD: disease-modifying antirheumatic drug (methotrexate, leflunomide, or sulfasalazine); GC: glucocorticoid; NSAID: nonsteroidal antiinflammatory drug; RF: rheumatoid factor; ERA: enthesitis-related arthritis.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

Table 4. Patient factors associated with the use of methotrexate among children without systemic arthritis (n = 2502).

Patient Factor	Univariate OR (95% CI)	Multivariable OR (95% CI)
Extended oligoarthritis*	7.3 (4.7–11)	3.8 (2.3–6.3)
RF– polyarthritis*	4.7 (3.7–5.9)	2.6 (1.9–3.7)
RF+ polyarthritis*	9.5 (5.8–15)	3.9 (2.2–7.1)
Psoriatic arthritis*	4.5 (2.9–6.8)	3.5 (2.2–5.5)
ERA*	0.9 (0.7–1.2)	—
History ≥ 5 joints	4.4 (3.7–5.3)	2.0 (1.5–2.8)
HLA-B27	0.6 (0.4–0.8)	—
Uveitis	3.5 (2.5–5.0)	4.4 (3.0–6.5)
IBD	2.1 (1.0–4.4)	3.4 (1.3–8.6)
Sacroiliac tenderness	0.5 (0.4–0.7)	0.5 (0.4–0.7)
Enthesitis	0.6 (0.5–0.8)	—
Psoriasis rash	2.0 (1.3–3.1)	—
ACPA	9.9 (4.0–24)	4.9 (1.9–13)
Radiographic damage	2.3 (1.8–2.9)	1.8 (1.3–2.4)
Disease duration, yrs	1.1 (1.1–1.2)	1.1 (1.0–1.1)

* Compared to oligoarthritis category. RF: rheumatoid factor; ERA: enthesitis-related arthritis; IBD: inflammatory bowel disease; ACPA: anticitrullinated protein antibodies.

Table 5. Patient factors associated with the use of biologic DMARD among children without systemic arthritis (n = 2502).

Patient Factor	Univariate OR (95% CI)	Multivariable OR (95% CI)
Extended oligoarthritis*	3.5 (2.6–4.8)	—
RF– polyarthritis*	4.7 (3.8–5.9)	1.9 (1.5–2.5)
RF+ polyarthritis*	8.6 (6.1–12)	3.4 (2.2–5.2)
Psoriatic arthritis*	5.7 (4.0–8.1)	2.7 (1.8–3.9)
ERA*	3.5 (2.6–4.7)	—
History ≥ 5 joints	3.7 (3.1–4.4)	2.3 (1.8–2.9)
HLA-B27	1.3 (1.0–1.8)	—
Uveitis	1.8 (1.4–2.3)	2.3 (1.7–3.0)
IBD	3.3 (1.8–6.0)	3.0 (1.4–2.6)
Sacroiliac tenderness	1.9 (1.4–2.4)	1.7 (1.2–2.4)
Enthesitis	1.6 (1.3–2.1)	1.9 (1.4–2.6)
Psoriasis rash	2.0 (1.4–2.8)	—
ACPA	3.4 (2.3–5.2)	1.9 (1.1–3.2)
Radiographic damage	3.0 (2.5–3.7)	2.2 (1.7–2.8)
Disease duration, yrs	1.1 (1.1–1.2)	1.1 (1.1–1.1)

* Compared to oligoarthritis category. DMARD: disease-modifying antirheumatic drug; RF: rheumatoid factor; ERA: enthesitis-related arthritis; IBD: inflammatory bowel disease; ACPA: anticitrullinated protein antibodies.

of biologic DMARD to children with ERA, we did not find a significant association with SI tenderness. The reason for this result is unclear, but it is possible that not all patients with reported SI tenderness had clinically important SI arthritis.

Our results support the importance of the number of affected joints (rather than the ILAR category) in clinical decision-making, as presented in the ACR Recommendations[8]. A history of arthritis of ≥ 5 joints remained strongly and independently associated with biologic DMARD use when controlling for other patient factors. It was also strongly and independently associated with biologic DMARD use among children with ERA and PsA, the ILAR categories that may be associated with more or less than 4 affected joints. There was not a marked difference in the proportion of patients who received biologic DMARD in the extended oligoarthritis versus RF– polyarthritis categories (46% vs 54%; p = 0.053). Also consistent with the ACR Recommendations, the presence of radiographic damage or ACPA was associated with biologic DMARD use. We were unable to assess other prognostic features reported in the ACR Recommendations (e.g., hip or cervical spine arthritis).

TNF inhibitors are not always completely effective or universally tolerated, which may lead to switching among agents for individual patients. In our study, 28% of TNF inhibitor users had received > 1 anti-TNF agent during their disease course. This proportion is higher than about 10% reported from biologics registries in the United Kingdom[12] and the Netherlands[13], but is lower than the about 35% reported from Finland[14]. These differences likely reflect, in part, the relative availability of different biologic agents in the respective countries and the time periods of the studies.

Etanercept was the most commonly received TNF inhibitor, most likely because it was the first TNF inhibitor studied and approved for the treatment of JIA by the FDA[2]. However, infliximab was received by a significant proportion of children with JIA, including those without uveitis or IBD, and has not received an FDA-approved label for this indication. In a randomized clinical trial in JIA, infliximab failed to demonstrate efficacy for the primary endpoint versus placebo[4], despite convincing evidence of clinical effectiveness during open-label use[15,16,17]. We observed that the monoclonal antibody TNF inhibitors are used more among children with uveitis. This medication usage pattern is supported by numerous observational studies[18,19,20], although no randomized studies have been reported. These TNF inhibitor usage patterns suggest that pediatric rheumatologists do not rely solely on the results of controlled clinical trials or FDA-approved labeling when making treatment decisions for children with JIA.

MTX represented the vast majority of nonbiologic DMARD use, and we identified several patient factors that were independently associated with its use. The strongest associations with MTX use were uveitis, ACPA, RF+ polyarthritis, and extended oligoarthritis. Most users of MTX received it through the subcutaneous route at some time in their disease course. This is not surprising because subcutaneous administration of higher doses of MTX has been suggested to be more efficacious than doses typically administered through the oral route in children with JIA[21]. In adults with rheumatoid arthritis, one study found that subcutaneous administration was more efficacious than identical doses of orally administered MTX[22]. It cannot be known from these data how many children initiated oral MTX and subsequently failed to respond. Based on the results of one survey published in 2007, most pediatric rheumatologists in the US and Canada

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

Table 6. Patient factors associated with medication use for children with systemic arthritis (n = 246).

Medication	Patient Factor	Univariate OR (95% CI)	Multivariate OR (95% CI)
Methotrexate	Polyarthritis	5.5 (2.8–11)	4.0 (2.0–8.3)
	Serositis	1.9 (0.8–4.9)	—
	Radiographic damage	4.5 (1.5–13)	—
	Disease duration, yrs	1.2 (1.1–1.3)	1.2 (1.0–1.3)
Cyclosporine	Polyarthritis	1.9 (0.8–4.6)	—
	Serositis	2.3 (1.0–5.1)	—
	Radiographic damage	3.5 (1.6–7.4)	3.9 (1.8–8.6)
	Disease duration, yrs	1.1 (1.1–1.2)	—
TNF inhibitor	Polyarthritis	3.0 (1.7–5.4)	—
	Serositis	1.7 (0.9–3.2)	—
	Radiographic damage	8.6 (4.3–18)	4.7 (2.2–10)
	Disease duration, yrs	1.2 (1.2–1.3)	1.2 (1.1–1.3)
IL-1 inhibitor	Polyarthritis	1.3 (0.8–2.3)	—
	Serositis	1.9 (1.0–3.5)	—
	Radiographic damage	2.6 (1.5–4.7)	4.7 (2.2–10)
	Disease duration, yrs	1.0 (0.9–1.0)	0.9 (0.8–1.0)

TNF: tumor necrosis factor-α; IL-1 interleukin 1.

would have recommended the oral route of administration for children with oligoarthritis in whom they were initiating therapy with MTX[23]. In contrast, results from a recent clinical trial suggested that using subcutaneous MTX at 0.5 mg/kg/week (maximum 40 mg) at initiation of therapy for polyarthritis may be a superior approach[24]. The most appropriate dose and route of administration for the initiation of MTX therapy remains uncertain.

SSZ was used by a minority of patients, most of whom had ERA or concurrent IBD. In the ACR Recommendations, SSZ use was recommended under some circumstances for children with ERA, but was uncertain for children without ERA[8]. LEF has been shown to be efficacious in the treatment of JIA[8,25]. Nevertheless, we found that LEF was used sparingly in the treatment of JIA and very infrequently in the absence of prior therapy with MTX. This suggests that LEF was likely reserved for instances of MTX intolerance or failure.

The use of DMARD for children with systemic arthritis demonstrated some associations with patient factors, but we were unable to examine most of the poor prognostic features found in the ACR Recommendations[8], such as hip arthritis or a 6-month duration of significant active systemic disease. A history of polyarthritis was associated with MTX use, but was not associated with cyclosporine, TNF inhibitor, or IL-1 inhibitor use. Radiographic damage was strongly associated with all DMARD except MTX and likely represents a marker of severe refractory disease.

Despite the widespread use of DMARD, the use of systemic glucocorticoids was common. More than one-third of patients with JIA received systemic glucocorticoids during their disease course and > 20% of children with RF+ polyarthritis or systemic arthritis were current users at the time of enrollment. Nevertheless, there are almost no published studies of systemic glucocorticoids in the treatment of JIA, and consequently the ACR Recommendations remained silent on the appropriateness of their use[8]. Clearly, rigorous studies of the safety and effectiveness of systemic glucocorticoids in the treatment of JIA are needed[26].

Uveitis may occur in the context of any of the ILAR categories of JIA, although it is most common among children with oligoarthritis[27]. In multivariable models, uveitis was strongly and independently associated with nonbiologic and biologic DMARD use. Uveitis disease activity is commonly independent of arthritis disease activity[28]. This implies that uveitis may frequently be the determining factor in the systemic treatment of children with JIA. Nevertheless, there are no published sizable randomized studies of the systemic treatment of uveitis in children[29]; clearly, more research about the most appropriate treatment for uveitis is needed.

Our study had limitations. Patients enrolled in the CARRA Registry represent a convenience sample of children with prevalent JIA cared for at pediatric rheumatology centers. It is not known whether children who were not enrolled in the CARRA Registry had different disease severity or received different treatment than children who were enrolled at the same clinical site. However, selection bias in patient enrollment was likely to be idiosyncratic and center-specific and therefore minimized by the large number of contributing centers. The distribution of JIA categories in the CARRA Registry is similar to those found in recently published JIA inception cohorts[30,31], with the notable exception of fewer patients with persistent oligoarthritis. Children with less severe disease (e.g., oligoarthritis) are likely clinically evaluated less frequently, and it is possible that they may have fewer opportunities to be recruited to the registry. In addition, it is likely that children who receive care at pediatric rheumatology centers may have more severe disease than children who receive care elsewhere. Medication histories were not

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

systematically obtained, but were recorded by the local study investigators from several sources, including family report, physician recollection, and limited medical record review. It is not known how this nonsystematic data collection may have influenced our results, including the potential for recall bias. Laboratory and radiographic studies were performed at the discretion of the treating physicians as part of routine clinical care. We accepted the JIA ILAR category as assigned by the treating pediatric rheumatologist and did not attempt to reclassify patients based on the data collected in the registry, although there are recognized difficulties in implementing the ILAR categorization system in the routine clinical setting[32]. Our cross-sectional study design prevented us from making any causal inferences. For example, it cannot be known from the data whether radiographic damage occurred before or after the initiation of a biologic DMARD. The data did not contain some important clinical factors potentially associated with medication usage, such as the specific joints involved and historical disease activity and severity measures.

We found that nonbiologic and biologic DMARD were frequently used in the treatment of JIA and were associated with several specific patient factors. These associated factors were largely in agreement with published ACR Recommendations for the treatment of JIA. Our study results also highlighted several areas in significant need of further clinical investigation, in particular the appropriate management of uveitis with systemic immunosuppression and the best use of systemic glucocorticoids for the treatment of JIA.

REFERENCES

1. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, 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 1992;326:1043-9.
2. 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;342:763-9.
3. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 2008;359:810-20.
4. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007;56:3096-106.
5. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: A randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008;372:383-91.
6. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis 2011;70:747-54.
7. 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;371:998-1006.
8. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, 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 2011;63:465-82.
9. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
10. Hosmer DW, Lemeshow S. Assessing the fit of the model. In: Applied logistic regression. 2nd ed. New York: John Wiley & Sons; 2000:143-202.
11. Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC Jr, Dijkmans B, et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2006;65:442-52.
12. Southwood TR, Foster HE, Davidson JE, Hyrich KL, Cotter CB, Wedderburn LR, et al. Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis patients. Rheumatology 2011;50:189-95.
13. Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: The Dutch national register. Ann Rheum Dis 2009;68:635-41.
14. Tynjala P, Vahasalo P, Honkanen V, Lahdenne P. Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis. Ann Rheum Dis 2009;68:552-7.
15. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: An open label study. Ann Rheum Dis 2003;62:245-7.
16. Gerloni V, Pontikaki I, Gattinara M, Desiati F, Lupi E, Lurati A, et al. Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: Results of an open-label prospective study. Arthritis Rheum 2005;52:548-53.
17. Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, Wouters C, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: Findings from an open-label treatment extension. Ann Rheum Dis 2010;69:718-22.
18. Foeldvari I, Nielsen S, Kummerle-Deschner J, Espada G, Horneff G, Bica B, et al. Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: Results of a multinational survey. J Rheumatol 2007;34:1146-50.
19. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol 2007;91:319-24.
20. Tynjala P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis 2007;66:548-50.
21. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SK, Falcini F, 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 2004;50:2191-201.
22. Braun J, Kastner P, Flaxenberg P, Wahrisch J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: Results of a six-month,

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org

multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum 2008;58:73-81.
23. Beukelman T, Guevara JP, Albert DA, Sherry DD, Burnham JM. Variation in the initial treatment of knee monoarthritis in juvenile idiopathic arthritis: A survey of pediatric rheumatologists in the United States and Canada. J Rheumatol 2007;34:1918-24.
24. Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum 2011 Dec 19 [E-pub ahead of print].
25. 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;352:1655-66.
26. Huppertz HI. Recommendations for juvenile idiopathic arthritis by the American College of Rheumatology: Comment on the article by Beukelman et al. Arthritis Care Res 2011;63:1354-5; author reply 1355-6.
27. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: Suggested modification of the current screening guidelines. Rheumatology 2007;46:1015-9.
28. Grassi A, Corona F, Casellato A, Carnelli V, Bardare M. Prevalence and outcome of juvenile idiopathic arthritis-associated uveitis and relation to articular disease. J Rheumatol 2007;34:1139-45.
29. Heiligenhaus A, Michels H, Schumacher C, Kopp I, Neudorf U, Niehues T, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int 2012;32:1121-33.
30. Hyrich KL, Lal SD, Foster HE, Thornton J, Adib N, Baildam E, et al. Disease activity and disability in children with juvenile idiopathic arthritis one year following presentation to paediatric rheumatology. Results from the Childhood Arthritis Prospective Study. Rheumatology 2010;49:116-22.
31. Oen K, Duffy CM, Tse SM, Ramsey S, Ellsworth J, Chedeville G, et al. Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort. Arthritis Care Res 2010;62:527-36.
32. Behrens EM, Beukelman T, Cron RQ. Juvenile idiopathic arthritis classification criteria: Loopholes and diagnosis software. J Rheumatol 2007;34:234; author reply 234-5.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 24, 2024 from www.jrheum.org