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BIOLOGIC THERAPY IN CHILDREN WITH ENTHESITIS-RELATED ARTHRITIS THE FIRST YEAR AFTER DISEASE ONSET

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ABSTRACT

Objective. There is scant evidence to guide physicians in the choice of one therapeutic agent or combination over another to treat children and adolescents with enthesites-related arthritis (ERA). Clinicians not only need to know about the efficacy of disease-modifying anti-rheumatic drugs (DMARDs) and biologic as stand-alone therapy versus placebo, but also how they work in combination and in comparison to one another.

The main objective of the study is to characterized the effective of biologic exposure in children with ERA over the first year after diagnosis.

Methods. We conduced a multicenter retrospective study of children diagnosed with ERA followed in several hospital: Children's Hospital of Philadelphia, Alabama Children's Hospital, Cincinnati Children's Hospital, Texas Scottish Rite Hospital for Children and Meyer Children's Hospital. We estimated the effect of biologic therapy on clinical parameters (active joint count, tender enthesis count, development of sacroiliitis), physician disease activity assessment, and patient-reported pain and global assessment of disease activity over the first year after diagnosis using a weighted repeated measures approach.

Results. During the study period, 218 newly diagnosed ERA patients had a total of 968 clinic visits the first year disease onset. 35 (16.1%), 70 (32.1%) and 56 (25.7%) were treated with biologic, DMARD monotherapy, or both, respectively during the first year after diagnosis. Over the first year after disease onset, use of a biologic was significantly

associated with less pain ($p=0.03$) and improved disease activity as measured by the JADAS-3 ($p=0.02$). Use of a biologic, versus no biologic, was associated with a significant greater negative slope (or faster change over the time) in tender entheses count ($p<0.01$).

Conclusion. During the first year after diagnosis, biologic exposure was associated with benefits for several clinically meaningful outcomes in children with enthesites-related arthritis.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatologic chronic condition in childhood. Enthesitis-related arthritis (ERA) is a JIA category that accounts for 10-20% of JIA [1-3], which preferentially affects boys, most frequently in the preadolescent and adolescent age group.

ERA is defined as arthritis and enthesitis of at least six weeks duration in a child younger than 16 years, or arthritis or enthesitis plus two of the following criteria: sacroiliac tenderness or inflammatory back pain, HLA-B27 positivity, onset of arthritis in a male older than six years, and family history of HLA-B27 associated disease [4]. The presence of HLA-B27 is often associated with this subset of JIA, even if it is not required for diagnosis.

The ERA category describes a clinically heterogeneous group of children including some that have predominantly enthesitis, enthesitis and arthritis, juvenile ankylosing spondylitis, or inflammatory bowel disease associated arthropathy. Enthesitis is defined as inflammation of an enthesis, which is a site where tendons, ligaments, or joint capsules attach to bone. Enthesitis is common in ERA and may not parallel the activity of arthritis.

Extra-articular manifestations (gastrointestinal, ocular, mucosal, and cutaneous) occur in variable portion of patients.

ERA causes comparable morbidities to the other JIA categories including articular destruction, functional decline, and uveitis. Additionally, this type of JIA may cause dactylitis, spinal involvement, and a subset of children will progress to

ankylosing spondylitis as adults, which is characterized by spinal and back pain, stiffness, and eventual fusion of vertebrae [5, 6]. Unlike adult ankylosis spondylitis, inflammatory back pain is rarely present at onset, even though sacroiliac and spinal involvement may occur in up to two-thirds of patients during the first 10 years of disease [7]. Observational studies suggest that ongoing disease activity for more than five years predicts disability and the disease remission occurs in less than 20% of children with ERA five years after diagnosis [8].

Up to now, there is scant evidence to guide physicians in the choice of one therapeutic agent or combination over another. Clinicians not only need to know about the efficacy of disease-modifying anti-rheumatic drugs (DMARDs) and biologic as stand-alone therapy versus placebo, but also how they work in combination and comparison to one another. Moreover, the comparative effectiveness and safety of different treatment algorithms for children with ERA remain unclear and without consensus.

Treatment regimens for ERA include monotherapy or combination therapy with non steroidal anti-inflammatory drugs (NSAIDs), DMARDs such as methotrexate, sulfasalazine, and leflunomide, or biologic agent such as etanercept, adalimumab, and infliximab.

There are only two randomized clinical trials focused on children with ERA [9, 10]; the majority of trials include ERA as one of several JIA categories. Both of the published ERA trials included only children with prevalent disease who had failure at least one NSAID and one DMARD and who had at least 3 active joints [9,10]. In both trials treat-

ment with biologic resulted in sustained clinical improvement. In another study, which included a subset of children with prevalent ERA disease (average disease duration 2 years) and at least 2 active joints, etanercept resulted in improvement in the pedi-ACR response criteria, tender entheses count, back pain, and back mobility [11]. There are no published trials of induction therapy for children with ERA. The choice of induction treatment algorithms for children with this type of JIA, according to the American College of Rheumatology (ACR) treatment recommendations, are based solely on the number of active joints [12]. Using this algorithms the earliest a child with ERA might be treated with a biologic is after 3 months of therapy with DMARD. The comparative efficacy of DMARD versus biologic therapy in children with the new onset of ERA remains unclear.

In this retrospective study we used a repeated measures design to evaluate the impact of biologic therapy on relevant clinical and patient-reported outcomes in children from 5 centers with new-onset ERA. Treatments were based upon provider and family preferences. The use of a weighted approach enable assessment of biologic effect in this cohort with balance in time-invariant cofounders.

METHODS

We performed a multicenter retrospective study in children who fulfilled the International League of Associations for Rheumatology (ILAR) criteria for ERA [4] and had at least 6 months of documented follow-up at a rheumatology clinic, at one of the following academic tertiary care referral centers: Children's Hospital of Philadelphia (CHOP, Philadelphia, PA), Children's of Alabama (Birmingham, Alabama), Cincinnati Children's Hospital Medical Center (Cincinnati, Ohio), Texas Scottish Rite Hospital for Children (Dallas, TX), and Meyer Children's Hospital (Florence, Italy). All children had to fulfill ILAR criteria for ERA within 6 months of disease onset. Children who met ERA criteria but had a first-degree relative with psoriasis were not excluded (n=7). Children and adolescente who transferred care from another institution and/or who were already receiving therapy at the time of initial evaluation were excluded.

Each institution queried their respective clinical database for all children diagnosed with ERA in the outpatient health record at the initial or subsequent follow-up visit. The range of diagnosis dates included from each institution varied depending upon availability of searchable medical records and are as: CHOP 2001-2012, Children's of Alabama 2007-2012, Cincinnati Children's Hospital Medical Center 2007-2012, Texas Scottish Rite Hospital for Children 1993-2011, and Meyer Children's Hospital 1995-2012.

Inclusion criteria were: males or females ages 2 to 18 years old, evaluated at a study site during the study period, affec-

ted by ERA according to ILAR criteria. Exclusion criteria were incomplete or missing data. All inclusion and exclusion criteria were verified by the coordinating center using the JIA Calculator [13]. The JIA Calculator is a web-based tool to help algorithmically classify children with according to ILAR criteria [4]; 39 children were excluded after this process.

The study was approved by the committees for the protection of human subjects at each of the participating institutions. CHOP served as the coordinating center.

Clinical characteristics

Baseline visit was defined as the first rheumatology visit at which the child presented with clinical signs of ERA, such as enthesitis, arthritis, acute uveitis or inflammatory back pain. The following clinical data were abstracted from the medical record: demographic (sex, age, race, disease onset and disease duration), personal and family history of HLA-B27 associated disease, clinical features (including development of new sacroiliitis demonstrated on MRI), laboratory data (including ANA, HLA-B27, rheumatoid factor, anti-citrullinated cyclic peptide, inflammatory markers), patient reported outcomes (disease activity assessment and pain), past and current medications. Disease activity at each visit was measured using physician disease activity assessment (range 0-10), the Juvenile SpondyloArthritis Disease Activity Index (JSpA DAI) (Table 1) [14], and the juvenile Arthritis Disease Activity Score 3 (JADAS-3) [15]. The JSpA DAI is a validated composite measure developed specifically for children with juvenile spondyloarthritis that include 8 items:

active joint count, active entheses count, pain, ERS or CRP related to juvenile spondyloarthropathy activity, morning stiffness, clinical sacroilitis, back mobility. The score has a range from 0-8 that is obtained by summing the total for each item (maximum total for item=1). A higher scores indicating a more disease activity [14].

The JADAS-3 is also a validated composite disease measure but it was specifically developed for all juvenile idiopathic arthritis category, and range from 0 (inactive disease) to 30 (highest disease activity). This index is very useful in the clinical practice also because ESR is excluded from the item [15].

All data were entered into a customized database (called REDCap) managed by the CHOP.

Statistical analysis

In order to assess which clinical factors impact the decision to treat with a biologic we fit a multilevel mixed-effects logistic regression model with adjustment for clustering by patient and site. Covariates tested included: study day, age, sex, race, HLA-B27 status, glucocorticoid use and presence of hip arthritis, wrist arthritis, sacroilitiis, or uveitis. The model include all visit up to and including the first visit where a biologic was prescribed. We used locally weighted scatterplot smoothing (Lowess) to also visually evaluate how disease activity scores influenced the probability of being prescribed biologic medication. JSpA DA scores were plotted against whether or not a biologic was prescribed at the visit or not.

Marginal structural models (MSMs) were used to estimate the casual effect of biologic treatment [16]. This approach appropriately controls for time-decedent confounders affected by prior treatment through creating a pseudo-population in which treatment is unconfounded by subject-specific characteristics and no censoring occurs. The model is fitted in a two-stage process. First at each time point each subject's probability of having their own treatment history and probability of being censored are derived as inverse-probability-of-treatment weight (IPTWs) and inverse-probability-of-censoring weight (IPCWs) respectively by pooled logistic regression. Next, the association between the treatment and outcome measured repeatedly is evaluated in a generalized estimating equation (GEE) model that is weighted using the IPTWs and IPCWs. Because of the weighting, the regression now takes places in the pseudo-population which assumes no unmeasured confounding and censoring, and results in unbiased estimate of the treatment effect and outcome.

The development of the weights at each visit took into account demographics, time-invarant clinical variables including HLA-B27 positivity and year of diagnosis (dichotomized as before or after biologic approval for JIA by FDA), and time-varying clinical variables that might influence the use of biologic therapy, including glucocorticoid use, hip arthritis, wrist arthritis, sacroiliitis (demonstrated on imaging), and acute anterior uveitis. Stability of the weights was assessed graphically at intervals of 60 study days.

For the weighted GEE model, the primary outcome was the active joint count measured over the time. Secondary out-

comes assessed included repeated measures of the tender entheses count, physician disease activity assessment, JSpA DAI, JADAS-3, patient assessment of disease activity, patient-reported pain, and development of sacroiliitis after diagnosis. A negative binomial distribution with log link was assumed to account for the over dispersion for active joint count and tender entheses count due to the number of zero counts. Normal distribution with identity link was used for the remainder of outcomes. The models for active joint count, physician disease activity assessment, JSpA DAI, JADAS-3, patient assessment of disease activity, and patient-reported pain included the following variables: biologic use, DMARD use, age, sex, study day, an interaction between study day and biologic use, and accounted for clustering within site and weighted inverse probability of biologic use (from step 1). The model for tender entheses count included the same variables with the addition of HLA-B27 since our prior work has shown HLA-B27 status is a predictor of tender entheses course.

Data regarding development of new sacroiliitis was only available for 4 sites. The association of development of new sacroiliitis and biologic use at these 4 sites was tested using chi-square analysis.

All analyses were run using Stata (StataCorp. 2015, Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) or SAS software 9.3 (Copyright ⓒ 2011, SAS Institude Inc., Cary, NC, USA).

RESULTS

Subjects

During the study period, 218 newly diagnosed ERA patients had a total of 968 outpatient visits the first year after disease onset. The median age for the records was 11.6 years. Demographics and clinical characteristics of the cohort are shown in Table 2.

176 (80.7%), 22 (10.1%), 20 (9.2%) of children had arthritis and enthesitis, arthritis plus 2 or more additional ILAR criteria, or enthesitis plus 2 or more additional ILAR criteria, respectively. The population was predominantly male and 58% were HLA-B27 positive.

Sixty-four (32%) had a polyarticular course. The treating provider performed imaging for sacroilitiis based on clinical suspicion. Twenty-one children (14%) had evidence of sacroiliitis on imaging at diagnosis and an additional 14 (11%) developed sacroiliitis over the first year of follow-up. Of the 35 with sacroiliitis at some point during the first year, 21 (60%) were HLA-B27 positive.

Medication use

33 (15.1%), 73 (33.5%), and 52 (23.9%) were treated with biologic monotherapy, DMARD monotherapy, or simultaneous DMARD and biologic therapy, respectively during the first year after disease onset. Two patients (1%) were switched from a DMARD to a biologic without any overlap in the medications. Adalimumab, etanercept, and infliximab accounted for 17 (19.5%), 63 (72.4%), and 7 (8.1%) of bio-

logic use, respectively. Seventy-nine (91%) of children who started a biologic remained on biologic therapy for the duration of follow-up. Nine (10%) biologic users switched biologic during the course therapy. The median time to biologic switch was 155 days (IQR: 62, 163). Of the 8 children who stopped the biologic before the end of follow-up, 1 had previously tried a different biologic.

We evaluated whether the severity of disease and certain disease manifestations were associated with the probability to prescribe a biologic. In a multilevel mixed-effects logistic analysis, the presence of wrist, hip, or sacroiliac arthritis were all associated with increased odds of biologic exposure (Table 3). This type of bias often results in the exposure being errantly associated with poorer outcomes [17]. As disease activity increased for JSpA DAI, the probability of receiving biologic also increased, a finding consistent with confounding by indication (Figure 1).

One hundred (78.7%), 26 (20.5%), and 1 (0.8%) of the patient were treated with methotrexate, sulfasalazine, and leflunomide, respectively. Of the 127 children treated with any DMARD, 27 (20%) discontinued DMARD use before the end of follow-up. One hundred and eighty-nine (86.7%) and 58 (26.6%) were treated with continuous NSAIDs or systemic glucocorticoids, respectively. Sixty-two (28.4%) received at lest 1 joint injection. The median number of joint injections in patient who underwent the procedure was 1 (IQR: 1, 2).

Outcomes

Results of the weighted GEE model, which adjusted for the confounding and censoring through weighting, are shown in Table 4. Over the first year after disease onset, patients who received a biologic were more likely to have a lower JADAS-3 ($p=0.02$) and less pain ($p=0.03$), when holding a covariates constant. Use of a biologic was associated with improvement, albeit statistically insignificant, in all other clinical, disease activity, and patient assessment. Use of a DMARD was associated with significantly lower tender entheses count ($p=0.01$) and physician disease activity assessment ($p=0.03$). DMARD use, similar to biologic use, was associated with improvement, albeit statistically insignificant in all other outcomes; the magnitude of the estimate, however, was dampened for all outcomes in comparison to the estimate for biologic use.

Interestingly, female sex was associated with significantly higher tender enthesis count ($p=0.03$), higher JADAS-3 ($p <0.01$), higher patient disease activity assessment ($p <0.01$), and more pain ($p <0.01$).

Fourteen children were diagnosed with sacroiliitis by imaging over the course of follow-up. Twelve (86%) of these children were not being treated with a biologic at the time of sacroiliitis diagnosis ($p <0.01$). Three of these children were subsequently started on biologic therapy. When stratified by HLA-B27 status, lack of biologic exposure remained significantly associated with development of new sacroiliitis (both $p <0.01$).

Use of a biologic, versus no biologic, was significantly associated with a faster change over the time in tender enthe-

ses count ($p < 0.01$). The change over time in all outcomes in children treated with biologic monotherapy, biologic plus DMARD, DMARD monotherapy, and supportive care only (NSAIDs, glucocorticoids, intra-articular joint injections) are shown in Figure 2 and 3. For all outcomes the rate of change was fastest for those children treated with both biologic and DMARD, followed by biologic status; those patients who were HLA-B27 negative started with significantly higher baseline tender entheses count than those who were HLA-B27 positive.

DISCUSSION

According to the ACR recommendations for the treatment of JIA [12], initiation of TNF α inhibitor is recommended more readily for patients with active sacroiliac arthritis than for patients without this joint affected. The beginning of biologic treatment was recommended for subjects with active sacroiliac arthritis who have received an adequate trial of NSAIDs and have high disease activity and features of poor prognosis (Table 5). Moreover, anti-TNF is also recommended for patients who have received 3 months of methotrexate and have high disease activity, irrespective of prognostic factors, or moderate disease activity with features of poor prognosis, or 6 months of methotrexate and moderate disease activity without features of poor prognosis. Also, initiation of a TNF-α inhibitor has been supported for patients who have received 3 months of sulfasalazine and have moderate or high disease activity, or 6 months of sulfasalazine and low disease activity with features of poor prognosis [12, 18, 19].

In our multicenter observational study we reported the effect of biologic exposure in children with newly diagnosed ERA over the first year after disease onset. Our data suggest that biologic treatment is associated with statistically significant improvement in disease activity and pain over the first year after diagnosis. Furthermore, the direction of our estimates was consistent across all outcomes measures. DMARD therapy, as expected, also improved outcomes measures. The

magnitude of estimated effect, however, was uniformly greater in children treated with a biologic versus a DMARD. However, in our study design we haven't assessed if there was a difference statistically significant between a particular type of DMARDs (i.e. methotrexate or sulfasalazine) or a particular type of biologic (i.e. etanercept or adalimumab) into determinate an improvement of disease. Further studies are needed to investigate this aspect.

Moreover, several findings warrant additional discussion. First, as with any observational of therapeutic intervention, the possibility of confounding-by-indication bias must be considered. This bias arises when children with more severe disease manifestation are more likely to receive the exposure of interest and experience poorer outcomes. In this study, we did find evidence that children with higher disease activity and more severe disease manifestations (cervical, axial, ocular inflammation) were more likely to receive biologic therapy within first 3 months, as demonstrated in Table 3 and Figure 1. Our weighted GEE model, which adjusted for the confounding and censoring through weighting, likely minimized but did not remove this bias. Since we demonstrated that the children who received biologics had a greater magnitude of beneficial effect than children who receive DMARDs, and that the slope of change was greatest in children who received a biologic with or without a DMARD, the possibility exists that biologics have an even greater positive effect on clinical and patient-reported outcomes than we were able to demonstrate.

Second, this study was not designed to systematically evaluate for the presence of axial arthritis. Imaging for suspi-

cion of axial disease was done as per the treating physician. Interestingly, 11% of children had axial involvement recognized on MRI evaluation at some point during the first year after disease onset. Of these, 86% were not being treated with biologic. It is unclear if early biologic use was "protective" against development of axial arthritis in those treated with biologic or if early use of a biologic suppressed axial disease symptoms and therefore the need for subsequent imaging. Prior studies have shown that in children with newly diagnosed JSpA and MRI evidence of sacroiliitis (both active and chronic lesion), up 2/3 may not have symptoms. Without the use of universal screening to detect subclinical sacroiliitis the true efficacy of biologics for this disease manifestation will remain unknown. The role of early biologic use in JSpA remains unclear and has not been systematically evaluated.

In summary, this study supports the effectiveness of biologics within the first year after disease onset in everyday clinical practice. Children treated with biologics had improvement in all clinical features and patient-reported outcomes, albeit some statistically insignificant. Next steps should include efficacy trials of early biologic use versus traditional DMARDs in regards to time to inactive disease, risk treatment of sacroiliitis, patient-reported outcomes, and cost saving.

Table 1. JSpA DAI items (N=610 visits)

1. **Active joint count**: includes any involved joint to a maximum of 10. There is no weighting of particular joints; mean ± SD	0 joints=0 1-2 joints= 0.5 >2 joints= 1	1.4 ±3.0
2. **Active enthesitis count:** includes any involved enthesis to a maximum of 10. There is no weighting of particular entheses; mean ± SD	0 entheses=0 1-2 entheses= 0.5 >2 entheses= 1	1.3 ± 2.1
3. **Pain:** patient reported pain over the past week, recorded on a visual analogue scale (0, 10); mean ± SD	0=0 1-4= 0.5 5-10= 1	2.4 ± 2.7
4. **ESR or CRP related to JSpA activity;** N(%)	Normal =0 1-2 times normal=0.5 >2 times normal=1	473 (77) 83 (14) 54 (9)
5. **Morning stiffness:** Morning stiffness for greater than 15 minutes; N(%)	Absent= 0 Present=1	307 (50) 303 (50)
6. **Clinical sacroiliitis:** defined as the presence of 2 or more of the following: tenderness on examination, positive Patrick or FABER's test and inflammatory back pain; N(%)	Absent= 0 Present=1	529 (87) 81 (13)
7. **Uveitis:** Presence of any uveitis (including acute/ symptomatic and chronic/asymptomatic disease); N(%)	Absent=0 Present=1	594 (97) 16 (3)
8. **Back mobility:** Abnormal back mobility defined as modified Schober's < 20 cm; N(%)	Normal=0 Abnormal=1	594 (97) 16 (3)

Legend. JSpA DAI Items.*Score is obtained by summing the total for each item (maximum total per item=1). Range of possible scores is 0 to 8, with higher scores indicating more disease activity. SD= Standard deviation

from: Development and retrospective validation of the juvenile spondyloarthritis disease activity index.

Authors: Weiss PF, Colberti RA, Xiao R, Feudtner C, Beukelman T, DeWitt EM, **Pagnini I**, Wright TB, Wallace CA.

Arthritis Care Research (Hoboken). 2014;66(12):1775-82.

Table 2. Patient Characteristics at Diagnosis

	N=218
Demographics	
Age, Median (IQR)	11.6 (9.6, 13.8)
Sex (male), N (%)	157 (72)
Race, Caucasian, N (%)	182 (83.5)
ILAR ERA criteria, N (%)	
Arthritis	187 (85.8)
Enthesitis	145 (66.5)
Sacroiliac joint tenderness and/or inflammatory spinal pain	70 (32.1)
Acute, symptomatic uveitis	14 (6.5)
Onset of arthritis in a male >6 years	132 (60.6)
Family history of HLA-B27+ associated disease in a first degree relative	36 (16.7)
Clinical Features and Patient Reported Outcomes at Diagnosis, Median (IQR)	
Active Joint Count	2 (1, 4)
Tender Enthesis Count	2 (0, 3)
Physician disease activity (VAS 0-10)	2.4 (2, 4)
Juvenile Spondyloarthritis Disease Activity Index (JSpADA) (0-8)	3 (2, 3.5)
Patient/parent pain (VAS 0-10)	4 (2, 7)
Patient/parent disease activity (VAS 0-10)	4 (2, 6)

Legend. Patient characteristics at diagnosis. * Imaging results only available for 4 sties (N-152)

Table 3. Factors associated with first biologic prescription

Disease manifestation	Odds Ratio (95% CI)	p-value
Hip arthritis	3.9 (1.7, 8.9)	0.001
Wrist arthritis	2.8 (1.4, 5.7)	0.003
Sacroiliitis	4 (1.5, 10.3)	0.005
Uveitis	2.1 (0.7, 5.9)	0.18
HLA-B27 positivity	1.25 (0.7, 2.3)	0.45

Legend. Results of multilevel mixed-effects logistic modeling to determine factors associated with prescription of first biologic.

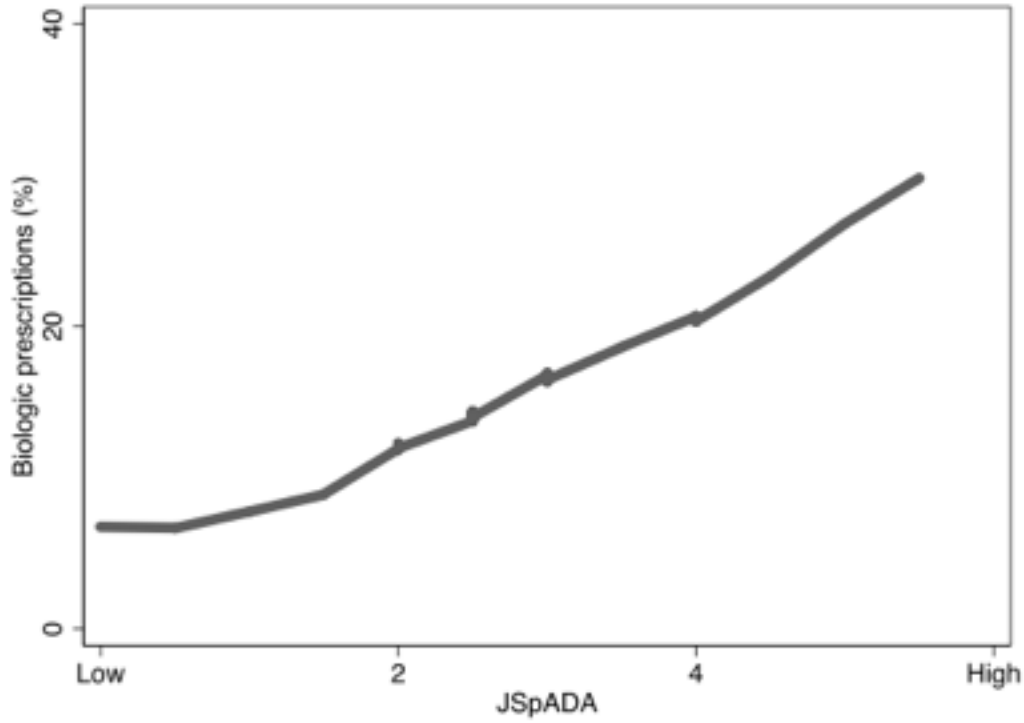

Figure 1. Lowess plot to evaluate confounding by indication between prescription of a biologic and Juvenile Spondyloarthritis Disease Activity (JSpA DA). Disease activity scores up to and including the first prescription of a biologic were plotted against a binary variable defining if a patient was prescribed a biologic at that time point or not.

Table 4. Results of weighted GEE analysis for outcomes.

Outcome (over time)	Variable	Estimate (95% CI)	p-value
Active joint count	Biologic	-0.70 (-1.58, 0.18)	0.12
	DMARD	-0.20 (-0.54, 0.15)	0.27
	Age	0.06 (-0.02, 0.13)	0.13
	Female Sex	-0.81 (-1.33, -0.29)	<0.01
Tender entheses count	Biologic	-0.04 (-0.53, 0.45)	0.87
	DMARD	-0.27 (-0.49, -0.06)	0.01
	Age	0.06 (0.01, 0.10)	<0.001
	Female Sex	0.31 (0.02, 0.60)	0.03
	HLA-B27 -	0.66 (0.39, 0.94)	<0.01
Physician disease activity (0,10)	Biologic	-0.58 (-1.45, 0.30)	0.20
	DMARD	-0.56 (-1.07, -0.06)	0.03
	Age	0.04 (-0.02, 0.11)	0.17
	Female Sex	0.32 (-0.26, 0.89)	0.28
JSpADA (0, 8)	Biologic	-0.89 (-1.94, 0.16)	0.10
	DMARD	-0.15 (-0.74, 0.44)	0.62
	Age	0.06 (0.06, 0.17)	0.35
	Female Sex	0.27 (-0.38, 0.92)	0.41
JADAS-3 (0, 30)	Biologic	-2.30 (-4.28, -0.32)	0.02
	DMARD	-0.68 (-0.56, 1.20)	0.48
	Age	0.18 (-0.16, 0.53)	0.30
	Female Sex	3.20 (1.06, 5.34)	<0.01
Patient-reported disease activity (0, 10)	Biologic	-0.10 (-1.23, 1.04)	0.87
	DMARD	-0.01 (-0.90, 0.88)	0.98
	Age	0.07 (-0.11, 0.26)	0.45
	Female Sex	2.59 (1.39, 3.80)	<0.01

Patient-reported pain (0, 10)	Biologic	-1.47 (-2.79, -0.16)	0.03
	DMARD	-0.20 (-1.02, 0.62)	0.63
	Age	0.09 (-0.12, 0.29)	0.41
	Female Sex	2.88 (1.68, 4.09)	<0.01

Legend. Results from repeated measures multivariate models. Higher scores for physician disease activity, JSPA DAI, JADAS-3, patient-reported disease activity, and patient reported pain indicate poorer outcomes.

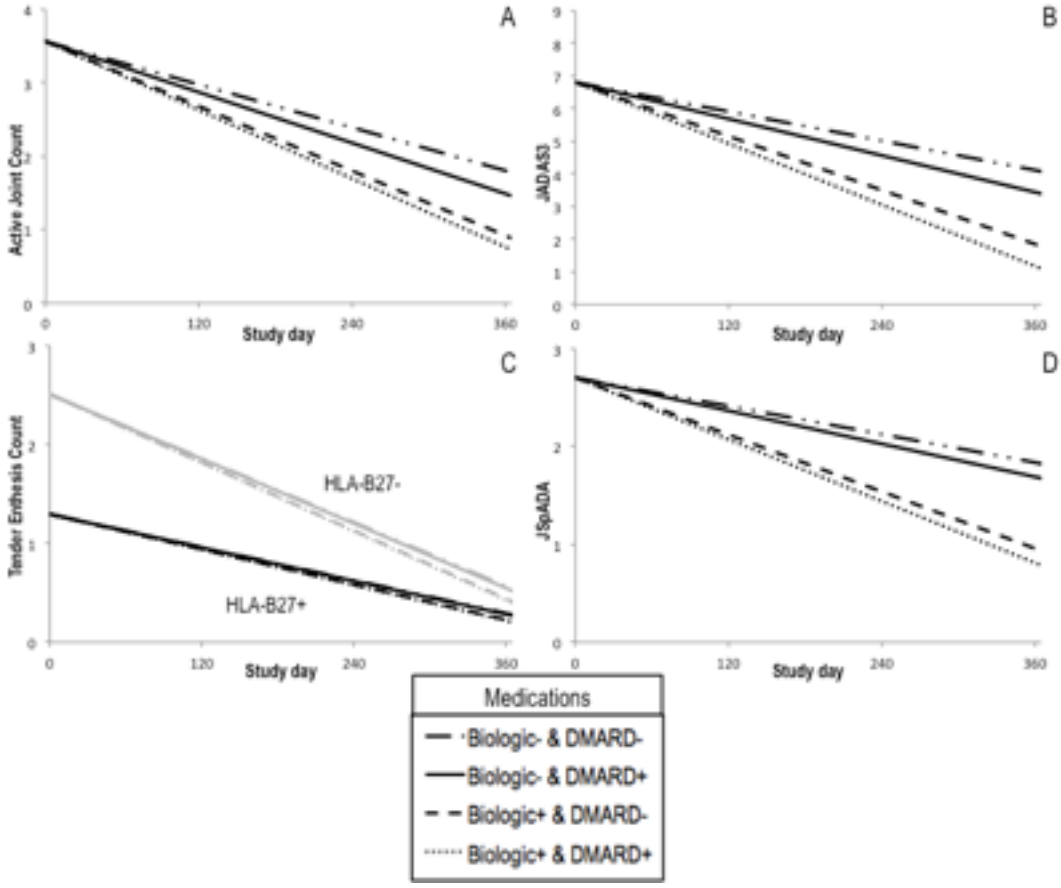

Figure 2. Patient disease manifestations and disease activity trajectories by treatment medication over the first year following initial diagnosis of enthesitis-related arthritis modeled using marginal structural models. Trajectories during the first year following diagnosis of (A) active joint count, (B) JADAS-3, (C) tender enthesis count (stratified by HLA-B27 status; gray=negative, black=positive), and (D) JSpA DAI for patients treated with neither biologic nor DMARD, DMARD monotherapy, biologic monotherapy, and dual DMARD plus biologic therapy.

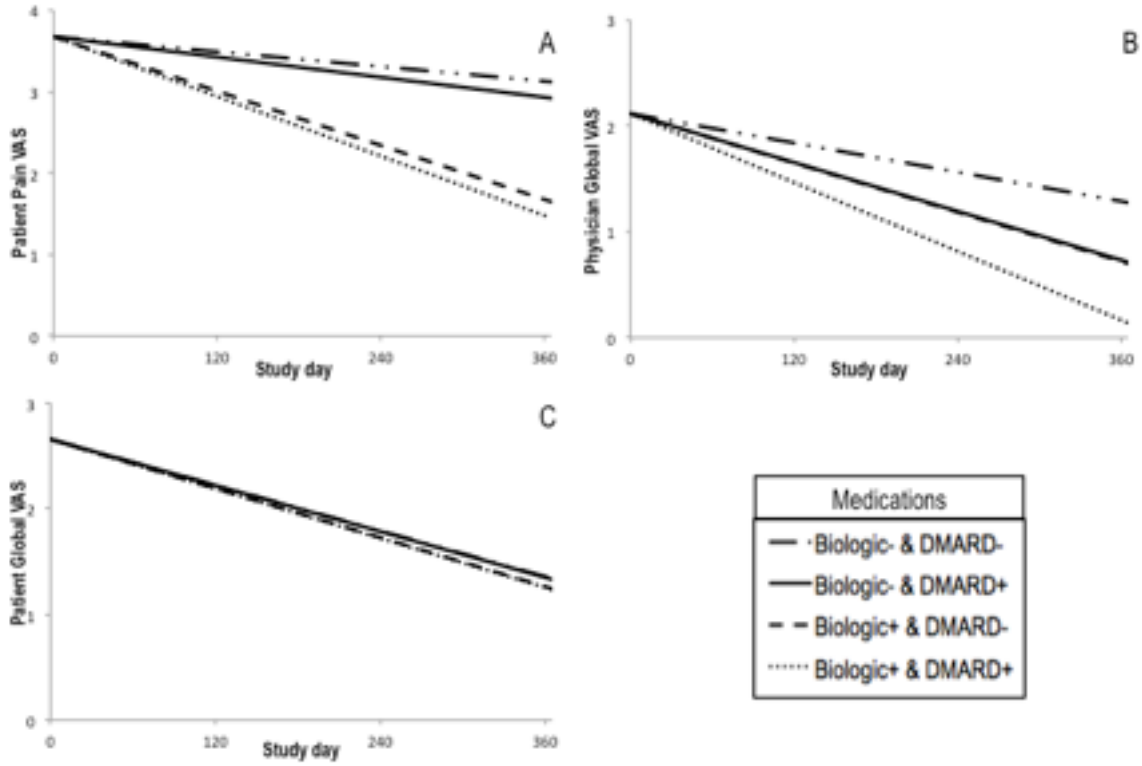

Figure 3. Patient disease manifestation and disease activity trajectories by treatment medication over the first year following initial diagnosis of enthesitis-related arthritis modeled using marginal structural models. Trajectories during the first year following diagnosis of (A) patient pain scores, (B) physician global disease activity scores, and (C) patient reported disease activity scores for those treated with neither biologic nor DMARD, DMARD monotherapy, biologic monotherapy, and dual DMARD plus biologic therapy.

Table 5. Features of poor prognosis and disease activity for active sacroiliac arthritis

FEATURE OF POOR PROGNOSIS

Radiographic damage of any joint (erosions or joint space narrowing by radiograph)

DISEASE ACTIVITY LEVELS

Low disease activity (must satisfy all)

- normal back flexion
- erythrocyte sedimentation rate or C-reactive protein level normal
- physician global assessment of overall disease activity < 4 of 10
- patient/parent global assessment of overall well-being < 2 of 10

Moderate disease activity (does not satisfy criteria for low or high activity)

- 1 or more features greater than low disease activity level AND fewer than 2 features of high disease activity

High disease activity (must satisfy at least 2)

- erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal

- physician global assessment of overall disease activity ≥ 7 of 10
- patient/parent global assessment of overall well-being ≥ 4 of 10

from: 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.

Authors: Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM; Lovell DJ, Martini A, Rabinovich CE, Rupert N. Arthritis Care Res. 2011;63(2):465-482.

REFERENCES:

1. Solau-Gervais E, Robin C, Gambert C, Troller S, Danner S, Gombert B, et al. Prevalence and distribution of juvenile idiopathic arthritis in a region of Western France. Joint Bone Spine. 2010;77(1):47-49.

2. Oen K, Tucker L, Huber AM, Miettunen P, Scuccimarri R, Campillo S, et al. Predictors of early inactive disease in a juvenile idiopathic arthritis cohort: results of a Canadian multicenter, prospective inception cohort study. Arthritis Rheumatology. 2009;61(8):1077-1086.

3. Yilmaz M, Kendirli SG, Altintas DU, Karakoc GB, Inal A, Killivìc M. Juvenile idiopathic arthritis profile in Turkish children. Pediatric Int. 2008;50(2):154-158.

4. Petty RE, Southward 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(2):390-392.

5. Burgos-Vargas R, Pacheco-Tena C, Vazquez-Mellado J. The juvenile-onset spondyloarthropaties: rationale for clinical evaluation. Best Pract Res Clin Rheumatol. 2002;16(4):551-572;.

6. Burgos-Vargas R, Vazquez-Mellado J, Cassis N, Duarte C, Casarin J, Cifuentes M, et al. Genuine ankylosing spondylitis in children: a case control study of patients with early definite disease according to adult onset criteria. J Rheumatol. 1996;23(12):214-217.

7. Pagnini I, Savelli S, Matucci-Cerinic M, Fonda C, Cimaz R, Simonini G. Early predictors of juvenile sacroiliitis in enthesitis-related Arthritis. J Rheumatol. 2010(11); 37:2395-2401.

8. Flato B, Aslant A, Vinje O, Forre O. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthropathy. J Rheumatol. 1998;25(2):366-375.

9. Burgos-Vargas R, Tse SM, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with Enthesites-Rhelated Arthritis. Arthritis Care Res (Hoboken). 2015;67(11):1503-1512.

10. Horneff G, Foeldvari I, Minden K, Trazeddel R, Kümmerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesites-rhelated arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis and Rheumatology. 2015;67(8):2240-2249.

11. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari i, Vojinovic J, Chasnyk VG, et al. Efficacy and safety of

open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. Ann Rheum Dis. 2014;73(6):1114-1122.

12. 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 Rese (Hoboken) 2011;63(4):465-482.

13. Behrens EM, Beukelman T, Cron RQ. Juvenile Idiopathic Arthritis classification criteria: loopholes and diagnosis software. J Rheumatol. 2007;34(1):234; author reply 234-235.

14. Weiss PF, Colbert RA, Xiao R, Feudtner C, Beukelman T, DeWitt EM, et al. Development and retrospective validation of the juvenile spondyloarthritis disease activity index. Arthritis Care Res (Hoboken). 2014;66(12): 1775-1782.

15. McErlane F, Beresford MW, Balidam EM, Chieng SE, Davidson JE, Foster HE, et al. Validity of a three-variable juvenile arthritis disease activity score in children with new-onset juvenile idiopathic arthritis. Ann Rheum Dis. 2013;72(12):1983-1988.

16.Robins JM, Hernan MA, Brumback B. Marginal structural models and casual inference in epidemiology. Epidemiology. 2000;11(5):550-560.

17.Czimadi I, Collet J. Bias and confounding in pharmacoepidemiology. Textbook of Pharmacoepidemiology. Chichester, United Kingdom: Wiley; 2006;261-275.

18.Schmeling H, Horneff G. Infliximab in two patients with juvenile ankylosing spondylitis. Rheumatoid Int. 2004; 24(3):173-176;.

19.McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systemic review and economic evaluation. Health Techonol Assess. 2007; 11(28):1-58, iii-iv.