**Arthritis Care & Research**
Vol. 72, No. 10, October 2020, pp 1420–1430
DOI 10.1002/acr.24044


American College of Rheumatology
*Empowering Rheumatology Professionals*

# Safety and Effectiveness of Adalimumab in Patients With Polyarticular Course of Juvenile Idiopathic Arthritis: STRIVE Registry Seven-Year Interim Results

Hermine I. Brunner,[1] Kabita Nanda,[2] Mary Toth,[3] Ivan Foeldvari,[4] John Bohnsack,[5] Diana Milojevic,[6] C. Egla Rabinovich,[7] Daniel J. Kingsbury,[8] Katherine Marzan,[9] Elizabeth Chalom,[1] Gerd Horneff,[10] Rolf-Michael Kuester,[11] Jason A. Dare,[12] Maria Trachana,[13] Lawrence K. Jung,[14] Judyann Olson,[15] Kirsten Minden,[16] Pierre Quartier,[17] Mareike Bereswill,[18] Jasmina Kalabic,[18] Hartmut Kupper,[18] Daniel J. Lovell,[1] Alberto Martini,[19] and Nicolino Ruperto,[19] for the Paediatric Rheumatology International Trials Organisation, and the Pediatric Rheumatology Collaborative Study Group

**Objective.** To evaluate safety and effectiveness of adalimumab (ADA) in polyarticular-course juvenile idiopathic arthritis (JIA) in the STRIVE registry.

**Methods.** STRIVE enrolled patients with polyarticular-course JIA into 2 arms based on treatment with methotrexate (MTX) alone or ADA with/without MTX (ADA ± MTX). Adverse events (AEs) per 100 patient-years of observation time were analyzed by registry arm. Patients who entered the registry within 4 weeks of starting MTX or ADA ± MTX, defined as new users, were evaluated for change in disease activity assessed by the 27-joint Juvenile Arthritis Disease Activity Score with the C-reactive protein level (JADAS-$27_{CRP}$).

**Results.** At the 7-year cutoff date (June 1, 2016), data from 838 patients were available (MTX arm n = 301, ADA ± MTX arm n = 537). The most common AEs were nausea (10.3%), sinusitis (4.7%), and vomiting (4.3%) in the MTX arm and arthritis (3.9%), upper respiratory tract infection (3.5%), sinusitis, tonsillitis, and injection site pain (3.0% each) in the ADA ± MTX arm. Rates of serious infection were 1.5 events/100 patient-years in the MTX arm and 2.0 events/100 patient-years in the ADA ± MTX arm. AE and serious AE rates were similar in patients receiving ADA with versus without MTX. No deaths or malignancies were reported. New users in the ADA ± MTX arm showed a trend toward lower mean JADAS-$27_{CRP}$ compared with new users in the MTX arm in the first year of STRIVE.

**Conclusion.** The STRIVE registry 7-year interim results support the idea that ADA ± MTX is well tolerated by most children. Registry median ADA exposure was 2.47 (interquartile range 1.0–3.6) years, with 42% of patients continuing ADA at the 7-year cutoff date.

## INTRODUCTION

Juvenile idiopathic arthritis (JIA) can cause significant disability and often persists into adulthood (1,2). In European and North American populations, the reported incidence and prevalence of JIA ranges from 2 to 20 and from 16 to 150 per 100,000, respectively (1,3). The International League of Associations for Rheumatology classification describes 7 JIA categories, which consider the number of affected joints, serologic status, and systemic manifestations, among other factors (4). For clinical trials, the term polyarticular-course JIA was coined to describe children with JIA who have a history of ≥5 active joints with arthritis. These

Clinicaltrials.gov identifier: NCT00783510.
The STRIVE Registry is sponsored by AbbVie.

[1]Hermine I. Brunner, MD, Elizabeth Chalom, MD, Daniel J. Lovell, MD: Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [2]Kabita Nanda, MD: University of Washington School of Medicine and Seattle Children's Hospital, Seattle; [3]Mary Toth, MD: Nemours Children's Hospital, Orlando, Florida; [4]Ivan Foeldvari, MD: Hamburg Centre for Pediatric and Adolescence Rheumatology, Hamburg, Germany; [5]John Bohnsack, MD: University of Utah, Salt Lake City; [6]Diana Milojevic, MD: Johns Hopkins All Children's Hospital, St. Petersburg, Florida; [7]C. Egla Rabinovich, MD: Duke University Medical Center, Durham, North Carolina; [8]Daniel J. Kingsbury, MD: Randall Children's Hospital at Legacy Emanuel, Portland, Oregon; [9]Katherine Marzan, MD: Children's Hospital Los Angeles, Los Angeles, California; [10]Gerd Horneff, MD: Asklepios Klinik Sankt Augustin, Sankt Augustin, and University Hospital of Cologne, Cologne, Germany; [11]Rolf-Michael Kuester, MD: Orthopaediezentrum Altona, Hamburg, Germany; [12]Jason A. Dare, MD: Arkansas Children's Hospital, Little Rock, Arkansas; [13]Maria Trachana, MD: Hippokration General Hospital, Thessaloniki University School of Medicine, Thessaloniki, Greece; [14]Lawrence K. Jung, MD: Children's National Medical Center, Washington, DC; [15]Judyann Olson, MD: Medical College of Wisconsin, Milwaukee; [16]Kirsten Minden, MD: Charite University Medicine Berlin and German Rheumatism Research Center, Berlin, Germany; [17]Pierre Quartier, MD: Université Paris-Descartes, Institut IMAGINE and Centre de Référence RAISE, Hôpital Necker-Enfants

**SIGNIFICANCE & INNOVATIONS**

- Routine clinical care with methotrexate or adalimumab with or without methotrexate is well tolerated in children with polyarticular-course juvenile idiopathic arthritis.
- No deaths, malignancies, active tuberculosis, demyelinating disorders, or congestive heart failure were reported during 1,855.5 patient-years of observation time in the adalimumab arm.
- Serious adverse event rates were low in all patients with polyarticular-course juvenile idiopathic arthritis who received methotrexate alone or received adalimumab with or without concurrent methotrexate.
- More patients receiving methotrexate alone discontinued the study drug due to the need for additional therapy (33%) compared with those who received adalimumab with or without methotrexate (4%).

patients commonly have a more refractory disease course, rendering them at increased risk for joint damage, poor functional outcomes, and low health-related quality of life (5).

Children with polyarticular-course JIA are often treated with synthetic or biologic disease-modifying antirheumatic drugs (DMARDs) or with a combination of both. Methotrexate (MTX) is the most commonly used synthetic DMARD. However, in at least 40% of patients with JIA, MTX therapy will not result in adequate disease control (6–8). Children with inadequate response or intolerance to MTX require treatment with biologic DMARDs, such as inhibitors of tumor necrosis factor (TNF) or other proinflammatory pathways (9–14). Adalimumab (ADA) is a fully human anti-TNF antibody that is approved in many countries for treatment of moderate-to-severe polyarticular JIA in patients ≥2 years old (10,15–17). The STRIVE registry was established as a postmarketing surveillance effort for patients with polyarticular-course JIA exposed to ADA. Here we present the 7-year interim safety and effectiveness results for the STRIVE registry polyarticular-course JIA cohort treated with ADA with or without MTX, using patients in the MTX arm as the control population.

## PATIENTS AND METHODS

**Study design.** STRIVE is a 10-year, ongoing, multicenter, noninterventional, observational registry of children with active polyarticular-course JIA treated with MTX or ADA ± MTX. Patients were enrolled in 16 countries at 92 centers of the Paediatric Rheumatology International Trials Organisation (18) and the Pediatric Rheumatology Collaborative Study Group (19). Children entered the MTX arm (i.e., patients treated with MTX alone or in combination with other synthetic DMARDs according to the local product labeling) or the ADA ± MTX arm (i.e., patients treated with ADA alone [ADA – MTX] or ADA in combination with MTX [ADA + MTX]). The initial decision to prescribe ADA and/or MTX was made by the treating physician before registry participation. Until enrollment closed, patients receiving MTX who were nonresponders to or intolerant of MTX treatment could switch from the MTX arm to the ADA ± MTX arm if the treating physician decided to initiate ADA therapy as part of standard of clinical care. After enrollment closure,

Malades, Assistance Publique-Hôpitaux de Paris, Paris, France; [18]Mareike Bereswill, MSc, Jasmina Kalabic, MD, Hartmut Kupper, MD: AbbVie Deutschland GmbH and Co. KG, Ludwigshafen, Germany; [19]Alberto Martini, MD, Nicolino Ruperto, MD: Istituto Giannina Gaslini Clinica Pediatrica e Reumatologia–PRINTO, Genova, Italy.

Dr. Brunner has received speaking and/or consulting fees from AbbVie, AstraZeneca, Centocor, Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, Regeneron, Hoffman La-Roche, Novartis, Takeda, UCB, and Genentech (less than $10,000 each). Dr. Nanda has received consulting fees from Novartis (less than $10,000). Dr. Foeldvari has received consulting fees from AbbVie (less than $10,000). Dr. Bohnsack has received consulting fees from Novartis and Regeneron (less than $10,000 each). Dr. Milojevic has received consulting fees from Genentech and Novartis (less than $10,000 each). Dr. Rabinovich has received consulting fees from AbbVie (less than $10,000) and has received research support from AbbVie, Hoffmann-La Roche, Janssen Research and Development, Sobi, and UCB. Dr. Kingsbury has received research support from AbbVie. Dr. Marzan has received research grants from AbbVie and Novartis. Dr. Chalom has received speaking fees from AbbVie (less than $10,000). Dr. Horneff has received speaking fees from AbbVie, Bristol Myers Squibb, Novartis, Sobi, Pfizer, and Roche (less than $10,000 each) and research grants from AbbVie, Pfizer, MSD, Novartis, and Roche. Dr. Kuester has received registry support from AbbVie and Wyeth/Pfizer. Dr. Dare has received research support from AbbVie, AstraZeneca, Bristol Myers Squibb, Horizon Pharma, Medac, Pfizer, Roche, and UCB. Dr. Trachana received speaking fees from Novartis, Pfizer, Roche, and Vianex (less than $10,000 each) and research grants from AbbVie, Pfizer, and Novartis. Dr. Jung has received consulting fees from Novartis and Bristol Myers Squibb (less than $10,000 each) and research support from AbbVie, Bristol Myers Squibb, and UCB Biosciences. Dr. Olson has received research support from AbbVie, Bristol Myers Squibb, CARRA, and Sobi. Dr. Minden has received consulting and/or speaking fees from AbbVie, Chugai, and Sanofi (less than $10,000 each) and research grants from AbbVie, Novartis, Pfizer, and Roche/Chugai. Dr. Quartier has received consulting and/or speaking fees from AbbVie, Bristol Myers Squibb, Eli Lilly and Company, Novartis, Novimmune, Pfizer, Roche, Sobi, and MedImmune (less than $10,000 each), has received research support from AbbVie, Bristol Myers Squibb, Novartis, Pfizer, Roche, and Sanofi, and is part of a data safety monitoring board for Sanofi. Ms Bereswill, Dr. Kalabic, and Dr. Kupper are full-time employees of AbbVie and hold stock or stock options. Dr. Lovell has received speaking fees from Genentech and Bristol Meyers Squibb (less than $10,000 each) and consulting fees from AbbVie, AstraZeneca, Bristol Myers Squibb, Centocor, Genentech, Hoffman La-Roche, Novartis, Pfizer, Regeneron, UBC, and Xoma (less than $10,000 each; paid to the Cincinnati Children's Hospital Medical Center), and has served on a data and safety monitoring board for Forest Research. Dr. Martini has received consulting fees from Janssen, Novartis, and Pfizer (less than $10,000 each), has served as a consultant on behalf of the Istituto Giannina Gaslini for AbbVie, Boehringer Ingelheim, Novartis, and R-Pharm, and has received contributions from Bristol Myers Squibb, Hoffman-La Roche, Janssen, Novartis, Pfizer, and Sobi for the coordination activity of the PRINTO network. Dr. Ruperto has received consulting and/or speaking fees from Ablynx, AbbVie, AstraZeneca-MedImmune, Biogen, Boehringer, Bristol Myers Squibb, Eli Lilly and Company, EMD Serono, GlaxoSmithKline, Hoffmann-La Roche, Janssen, Merck, Novartis, Pfizer, R-Pharma, SanofiServier, Sinergie, Sobi, and Takeda (less than $10,000 each). No other disclosures relevant to this article were reported.

Address correspondence to Hermine I. Brunner, MD, Professor of Pediatrics, Director, Division of Rheumatology, Scientific Director, Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Division of Rheumatology, 3333 Burnet Avenue, Cincinnati, OH 45229. Email: hermine.brunner@cchmc.org.

Submitted for publication March 26, 2019; accepted in revised form August 13, 2019.

patients in the MTX arm who newly required biologic DMARDs were considered to be taking an off-registry drug. All children were encouraged to continue registry participation to gather further observational safety information after discontinuation of the registry drug. All reasons for discontinuation were collected (multiple reasons were possible). Registry data were collected at enrollment, at months 1, 3, and 6, every 6 months through year 5, and annually for years 6 to 10 of individual registry follow-up.

The STRIVE registry is part of a postmarketing commitment from AbbVie to the US Food and Drug Administration and the European Medicines Agency. The registry is conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The registry protocol and informed consent/patient authorization were approved by an institutional review board and/or independent ethics committee, as applicable according to local law. Before any study procedures were performed, a parent or legal guardian provided written informed consent, and written informed assent was obtained from children age ≥9 years according to local standards.

**Patients.** Eligible patients were ages 2 to 17 years at enrollment and had a history of moderately to severely active JIA (i.e., arthritis affecting ≥5 joints). For enrollment into the ADA ± MTX arm, patients had to have commenced ADA therapy within 24 months of registry entry and continuously received ADA (≤70 consecutive days off the drug) according to the locally approved product label, or participated in the clinical studies DE038 (10) or M10-444 (15) from AbbVie Inc. (North Chicago, Illinois) and continued to receive ADA ± MTX. For enrollment into the MTX arm, patients had to have started MTX within 24 months of registry entry either as monotherapy or in combination with DMARDs, according to the locally approved product label. Patients who had prior treatment with any investigational agent or biologic DMARD were ineligible for the MTX arm. Background therapy with nonsteroidal antiinflammatory drugs (NSAIDs), folic acid, or folinic acid was permitted but not required.

Patients prescribed ADA and/or MTX were not enrolled if they were using regimens not in accordance with the local ADA or MTX product labels or if they were treated concurrently with biologic DMARDs other than ADA (for detailed eligibility criteria, see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24044/abstract).

**Study objectives.** The primary objective of this registry was to evaluate the long-term safety of ADA ± MTX. Evaluating effectiveness of treatment with ADA ± MTX was the secondary objective, with the MTX arm serving as a reference. The registry was not designed for a formal statistical comparison of the registry arms.

**Safety.** Serious adverse events (SAEs), events of special interest (e.g., infections, allergic reactions, malignancies, demyelinating disorder, and congestive heart failure; see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24044/abstract), and pregnancies were recorded for the initial 5 years of registry participation. Starting from year 6, only SAEs, a subset of events of special interest (congestive heart failure, malignancies), AEs possibly related or leading to discontinuation of registry treatment, and pregnancies were recorded. Exceptions were registry patients between the ages of 2 to 4 years at enrollment, for whom SAEs, all events of special interest, and pregnancies were collected for 10 years following registry entry.

SAEs, including serious infections, were defined as AEs that met any of the following criteria: death, life threatening (i.e., could result in immediate fatality without medical intervention), hospitalization, prolongation of hospitalization, congenital anomaly, persistent or significant disability, any important medical event requiring medical or surgical intervention to prevent serious outcome, or spontaneous or elective abortion. AEs and SAEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA, version 18.1, https://www.meddra.org/) and were defined according to the International Conference on Harmonisation guidelines (20).

**Disease-specific data.** Disease characteristics were collected at baseline and at regular intervals through year 5. C-reactive protein (CRP) levels were recorded only when obtained as part of routine clinical care. Physical function was assessed using the Childhood Health Assessment Questionnaire disability index (range 0 [no disability] to 3 [major disability]) (21). Physician global assessment of patient disease activity, parent global assessment of patient disease activity, and parent assessment of patient pain were measured on a visual analog scale from 0 (inactive disease/very good condition/no pain) to 100 (very active disease/very bad condition/very severe pain) (22–24). The number of joints with limited range of motion and joints with active arthritis (i.e., joints with swelling, pain, or tenderness plus limited range of motion) were also recorded. Disease activity was measured using the 27-joint Juvenile Arthritis Disease Activity Score with the CRP level (JADAS-$27_{CRP}$; range 0–57) (25).

**JIA-associated uveitis.** Information about the course of JIA-associated uveitis was collected during the initial 5 years of registry participation. Thereafter, only AEs pertaining to uveitis were collected. For patients with JIA-associated uveitis, the treating rheumatologist was requested to report uveitis status from the ophthalmology examination performed according to the local clinical practice.

**Data analysis.** The all-treated population, comprising all registry patients who received ≥1 dose of ADA or MTX was used for analyses of patient disposition, baseline characteristics, registry drug-exposure duration, observation time, uveitis data, and safety. Baseline values for patient characteristics were defined as the last nonmissing value on or before registry enrollment or baseline

values from the previous study for patients who rolled over from an ADA clinical trial. Registry drug-exposure duration for the MTX arm was calculated from the date of first through the last MTX dose in the registry or up to the date of first ADA dose for patients who switched from the MTX arm to the ADA ± MTX arm. For the ADA ± MTX arm, registry drug-exposure duration was calculated from the date of the first day through 14 days after the last ADA dose in the registry, excluding treatment interruptions (i.e., intervals of >70 days during which a patient did not receive ADA injections). The duration of treatment interruption was calculated from day 71 after the previous ADA dose until the date of the subsequent ADA dose. Observation time was defined as the interval between registry enrollment and the last contact in the registry.

AEs were included if they occurred while a patient was observed in the registry, even after ADA and/or MTX may have been discontinued (registry observational AEs). The number of patients who experienced AEs was recorded, and AE incidence rates were calculated (i.e., the number of AEs per 100 patient-years of observation time in the registry). AE frequency was also analyzed with respect to patient age at registry entry (≤8 years or >8 years).

Effectiveness assessment was limited to a subset of registry patients who started MTX or ADA ± MTX within 4 weeks of enrollment into the registry (new users). Because the rate at which treatment-related outcomes, such as disease control, may vary with time, the new user analysis was used to synchronize the beginning of study follow-up with the start of treatment (26). This approach allowed for differences in JIA improvement with the registry drugs to be captured. New users belonged to 1 of 3 subgroups: patients who started the registry in the MTX arm without concomitant biologics (MTX new users) and patients who started the registry in the ADA ± MTX arm and received ADA with or without MTX (ADA + MTX new users, ADA – MTX new users). Effectiveness of registry drugs in new users was measured by change in JIA activity using the JADAS-$27_{CRP}$ for up to year 5 of individual registry follow-up. Missing data were imputed using the

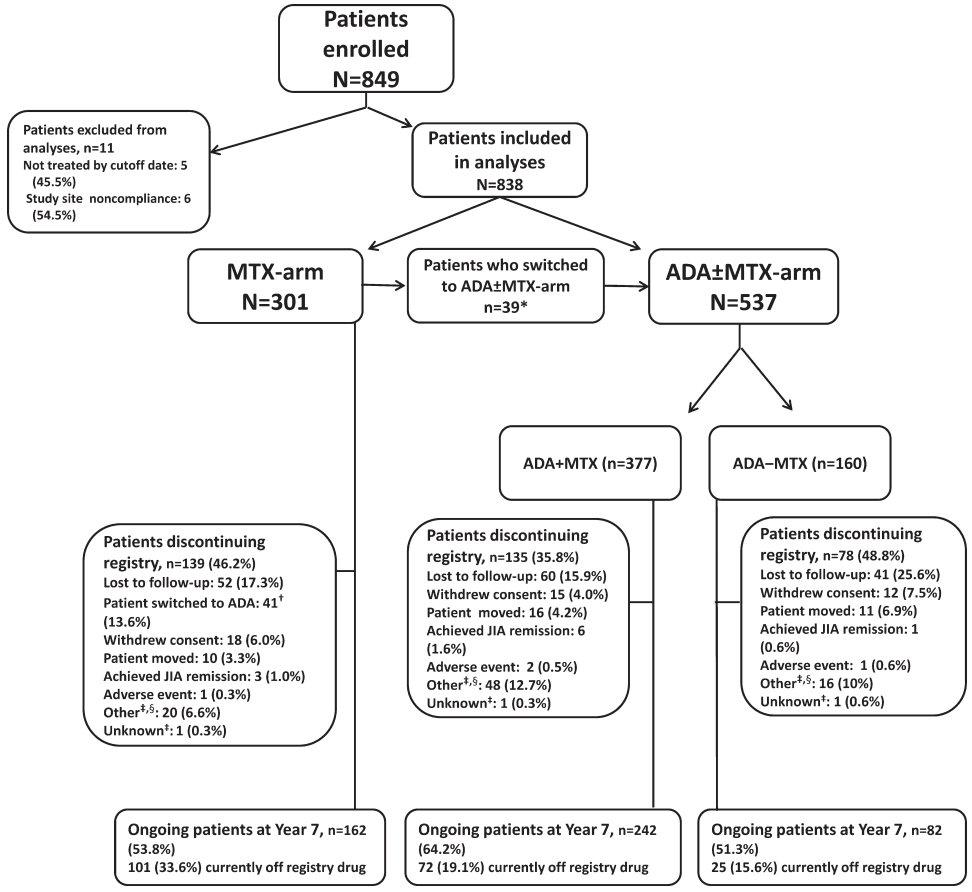


**Figure 1.** Seven-year interim patient disposition in all-treated population. ADA = adalimumab; JIA = juvenile idiopathic arthritis; MTX = methotrexate; * = these 39 patients are also included in the 537 patients in the ADA ± MTX arm; † = of the 41 patients, 39 were included in the 537 patients in the ADA ± MTX arm, the remaining 2 patients reported that they would switch to adalimumab but never received a dose of adalimumab; ‡ = if patient and family did not want to continue the registry owing to reasons other than the available options, the reasons were collected under Other; if patient discontinued registry but no reason for discontinuation was available in the database, the reasons were collected under Unknown; § = other reasons for registry discontinuation included lack of treatment effectiveness, protocol deviation, noncompliance, remission, partial remission, and flare of JIA disease. The sum of counts for each reason may exceed the total number of discontinuations because each reason given for discontinuation was counted for patients who discontinued from the registry.

last observation carried forward up to the time at which initial treatment was changed or stopped. Patient data were censored at the time of changing or stopping of initial therapy, and the duration of new user therapy was analyzed using the Kaplan-Meier method. For uveitis analyses, episodes of active JIA-associated uveitis were assessed per registry arm, irrespective of the presence of a diagnosis of JIA-associated uveitis before registry entry.

## RESULTS

**Patient disposition.** Enrollment into the registry started in June 2008 and was completed in January 2014. This 7-year interim analysis includes data collected up to June 1, 2016, in 838 patients. Eleven enrolled patients were excluded from analyses because they never began treatment with the registry drug or because proper execution of informed consents/assents could not be confirmed (Figure 1). Overall, 301 patients were included in the MTX arm and 537 in the ADA ± MTX arm (ADA – MTX n = 160, ADA + MTX n = 377). Twenty-five patients previously treated in the ADA studies DE038 (n = 13) and M10-444 (n = 12) were enrolled in the ADA ± MTX arm. Cumulative observation times in this interim analysis were 1,170.3 patient-years for the MTX arm and 1,855.5 patient-years for the ADA ± MTX arm (ADA – MTX 517.0 patient-years, ADA + MTX 1,338.5 patient-years). The median of observation time during the registry was 4.49 (interquartile range [IQR] 1.8–5.8) years for the MTX arm and 3.45 (IQR 2.4–4.7) years for the ADA ± MTX arm (ADA – MTX 3.08 [IQR 1.6–4.5] years, ADA + MTX 3.55 [IQR 2.6–4.8] years). The median duration of registry drug exposure in the registry was 1.40 (IQR 0.4–3.2) years for the MTX arm and 2.47 (IQR 1.0–3.6) years for the ADA ± MTX arm (ADA – MTX 2.18 [IQR 0.8–3.3] years, ADA + MTX 2.55 [IQR 1.0–3.7] years).

In the MTX arm, 240 patients (79.7%) prematurely discontinued either from the registry (n = 139 [46.2%]; 39 patients switched to the ADA ± MTX arm) or discontinued MTX but remained in the registry (n = 101 [33.6%]) (Figure 1). In the ADA ± MTX arm, 310 patients (57.7%) prematurely discontinued either from the registry (n = 213 [39.7%]; ADA – MTX n = 78 [48.8%], ADA + MTX n = 135 [35.8%]) or discontinued ADA ± MTX but remained in the registry (n = 97 [18.1%]; ADA – MTX n = 25 [15.6%], ADA + MTX n = 72 [19.1%]). The main reasons for registry discontinuation were lost to follow-up (MTX arm n = 52 [17.3%], ADA ± MTX arm n = 101 [18.8%]) or withdrawal of consent (MTX arm n = 18 [6.0%], ADA ± MTX arm n = 27 [5.0%]) (Figure 1). Only 1 patient in the MTX arm (0.3%) and 3 patients in the ADA ± MTX arm (0.6%) discontinued the registry owing to an AE.

The reasons (≥5% frequency) cited for registry drug discontinuation in the MTX arm were a need for additional therapy (n = 98 [32.6%]), other reasons (n = 40 [13.3%]), lack of effectiveness (n = 35 [11.6%]), AEs (n = 28 [9.3%]), achieved JIA remission (n = 26 [8.6%]), and intolerance (n = 18 [6.0%]). The main reasons for registry drug discontinuation in the ADA ± MTX arm were lack of effectiveness (n = 96 [17.9%]; ADA – MTX n = 31 [19.4%], ADA + MTX n = 65 [17.2%]), other reasons (n = 39 [7.3%]; ADA – MTX n = 9 [5.6%], ADA + MTX n = 30 [8.0%]), lost to follow-up (n = 30 [5.6%]; ADA – MTX n = 12 [7.5%], ADA + MTX n = 18 [4.8%]), AEs (n = 29 [5.4%]; ADA – MTX n = 8 [5.0%], ADA + MTX n = 21 [5.6%]), and achieved JIA remission (n = 27 [5.0%]; ADA – MTX n = 6 [3.8%], ADA + MTX n = 21 [5.6%]). Of note, 20 patients (3.7%)

**Table 1.** Baseline patient demographics, all-treated population*

| Demographic | MTX arm (n = 301) | ADA ± MTX arm | | |
|---|---|---|---|---|
| | | ADA ± MTX (n = 537) | ADA – MTX (n = 160) | ADA + MTX (n = 377) |
| Age, mean ± SD years | 9.5 ± 4.1 | 12.2 ± 4.0 | 13.0 ± 3.7 | 11.8 ± 4.1 |
| <4 | 20 (7) | 2 (<1) | 1 (1) | 1 (<1) |
| 4–8 | 111 (37) | 114 (21) | 23 (14) | 91 (24) |
| >8† | 170 (56) | 421 (78) | 136 (85) | 285 (76) |
| Female | 229 (76) | 377 (70) | 116 (73) | 261 (69) |
| White‡ | 267 (90) | 477 (90) | 147 (92) | 330 (89) |
| Previous JIA therapy use | | | | |
| NSAIDs | 247 (82) | 389 (72) | 117 (73) | 272 (72) |
| Systemic corticosteroids | 117 (39) | 212 (39) | 60 (38) | 152 (40) |
| Synthetic DMARDs | 23 (8) | 480 (89) | 120 (75) | 360 (95) |
| Biologic DMARDs | 2 (1)§ | 164 (31) | 59 (37) | 105 (28) |
| Concomitant JIA therapy use | | | | |
| NSAIDs | 229 (76) | 301 (56) | 74 (46) | 227 (60) |
| Systemic corticosteroids | 122 (41) | 158 (29) | 38 (24) | 120 (32) |

* Values are the number (%) unless indicated otherwise. ADA = adalimumab; MTX = methotrexate; JIA = juvenile idiopathic arthritis; NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease modifying antirheumatic drugs.
† 10 patients age ≥18 years in the ADA ± MTX arm were protocol deviations that are included in the analyses.
‡ Missing data (no. of patients): MTX 4, ADA ± MTX 7, ADA – MTX 1, ADA + MTX 6.
§ Both of the patients in the MTX arm were considered protocol deviations.

discontinued because of a need for additional therapy in the ADA ± MTX arm (ADA – MTX 8 of 160 [5.0%], ADA + MTX 12 of 377 [3.2%]).

**Baseline demographics and disease characteristics.** The majority of patients were female and white (Table 1). In the ADA ± MTX arm, 164 patients (30.5%) (ADA – MTX n = 59 [36.9%], ADA + MTX n = 105 [27.9%]) had previously received ≥1 biologic DMARD, mostly etanercept (93.3%); in the MTX arm, 2 patients (0.7%) had previously received etanercept (protocol violations). Concomitant NSAID and systemic corticosteroid use were more common in the MTX arm than in the ADA ± MTX arm (Table 1).

Patients in the 2 treatment arms had similar disease characteristics at baseline (Table 2). Most enrolled patients had polyarticular or extended oligoarticular JIA (79.7% in the MTX arm, 80.9% in the ADA ± MTX arm). At registry entry, disease duration was longer for the ADA ± MTX arm, irrespective of concurrent MTX use, compared with the MTX arm. Similarly, more patients had JIA-associated uveitis in the ADA ± MTX arm compared with the MTX arm reported at registry entry.

**Safety results**. A total of 157 patients (52.2%) in the MTX arm and 244 patients (45.4%) in the ADA ± MTX arm (ADA – MTX n = 66 [41.3%], ADA + MTX n = 178 [47.2%]) reported ≥1 registry observational AE, corresponding to 43.2 events/100 patient-years in the MTX arm and 41.4 events/100 patient-years in the ADA ± MTX arm (Table 3). Registry observational AEs for patients in the ADA ± MTX arm who received prior biologic DMARDs are summarized in Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24044/abstract. SAEs related to registry treatment were rare but numerically higher with ADA use; 6 SAEs were observed in the MTX arm (0.5 events/100 patient-years) compared with 32 in the ADA ± MTX arm (1.7 events/100 patient-years; 9 with ADA – MTX [1.7 events/100 patient-years] and 23 with ADA + MTX [1.7 events/100 patient-years]). Serious infections were observed in 14 patients (4.7%) in the MTX

**Table 2.** Baseline disease characteristics, all-treated population*

| Characteristic | MTX arm (n = 301) | ADA ± MTX arm | | |
|---|---|---|---|---|
| | | ADA ± MTX (n = 537) | ADA – MTX (n = 160) | ADA + MTX (n = 377) |
| Disease duration, years | 1.3 ± 2.5 | 3.7 ± 3.9 | 4.5 ± 4.3 | 3.4 ± 3.7 |
| CRP, mg/dl† | 1.3 ± 3.9 | 1.5 ± 6.4 | 0.9 ± 1.9 | 1.7 ± 7.5 |
| C-HAQ disability index‡ | 0.6 ± 0.6 | 0.6 ± 0.6 | 0.6 ± 0.6 | 0.6 ± 0.6 |
| JADAS-$27_{CRP}$§ | 12.2 ± 8.2 | 11.7 ± 8.3 | 11.3 ± 8.7 | 11.8 ± 8.2 |
| Physician global assessment‡ | 31.1 ± 22.6 | 31.3 ± 24.0 | 30.5 ± 24.8 | 31.6 ± 23.6 |
| Parent global assessment‡ | 26.4 ± 23.8 | 28.8 ± 26.3 | 29.4 ± 25.4 | 28.5 ± 26.7 |
| Parent assessment of pain‡ | 28.8 ± 25.6 | 30.0 ± 27.1 | 30.0 ± 27.0 | 30.1 ± 27.2 |
| No. of joints with LROM‡ | 4.2 ± 5.8 | 4.6 ± 6.6 | 4.6 ± 6.6 | 4.6 ± 6.5 |
| No. of active joints‡ | 5.8 ± 6.5 | 5.2 ± 6.5 | 5.1 ± 7.3 | 5.3 ± 6.1 |
| Uveitis, no. (%) | 10 (3) | 42 (8) | 11 (7) | 31 (8) |
| JIA subtypes, no. (%)¶ | | | | |
| Systemic arthritis | 2 (1) | 12 (2) | 3 (2) | 9 (2) |
| Seronegative polyarthritis, RF– | 155 (51) | 230 (44) | 62 (40) | 168 (45) |
| Seropositive polyarthritis, RF+ | 29 (10) | 75 (14) | 19 (12) | 56 (15) |
| Persistent oligoarthritis# | 51 (17) | 39 (7) | 12 (8) | 27 (7) |
| Extended oligoarthritis | 22 (7) | 86 (16) | 31 (20) | 55 (15) |
| Enthesitis-related arthritis | 24 (8) | 50 (10) | 16 (10) | 34 (9) |
| Psoriatic arthritis# | 12 (4) | 24 (5) | 6 (4) | 18 (5) |
| Undifferentiated arthritis# | 6 (2) | 8 (2) | 5 (3) | 3 (1) |

* Values are the mean ± SD unless indicated otherwise. ADA = adalimumab; MTX = methotrexate; CRP = C-reactive protein; C-HAQ = Childhood Health Assessment Questionnaire; JADAS-$27_{CRP}$ = 27-joint Juvenile Arthritis Disease Activity Score with the C-reactive protein level; LROM = limited range of motion; JIA = juvenile idiopathic arthritis; RF = rheumatoid factor.

† CRP level: n = 212 for MTX, n = 379 for ADA ± MTX, n = 110 for ADA – MTX, n = 269 for ADA + MTX.

‡ Baseline values were defined as the last nonmissing value on or before registry enrollment or baseline values from the previous study for patients who rolled over from an adalimumab clinical trial. Missing data (no. of patients): C-HAQ: MTX 9, ADA ± MTX 27, ADA – MTX 7, ADA + MTX 20; physician global assessment (measured with visual analog scale [VAS] 0–100 mm): MTX 7, ADA ± MTX 22, ADA – MTX 7, ADA + MTX 15; parent global assessment (measured with VAS 0–100 mm): MTX 6, ADA ± MTX 20, ADA – MTX 13, ADA + MTX 17; parent assessment of pain (measured with VAS 0–100 mm): MTX 6, ADA ± MTX 20, ADA – MTX 13, ADA + MTX 17; no. of joints with LROM: MTX 6, ADA ± MTX 17, ADA – MTX 4, ADA + MTX 13; no. of active joints: MTX 5, ADA ± MTX 16, ADA – MTX 4, ADA + MTX 12.

§ Baseline values were defined as the last nonmissing value on or before registry enrollment or baseline values from the previous study for patients who rolled over from an adalimumab clinical trial. JADAS-$27_{CRP}$: n = 195 for MTX, n = 352 for ADA ± MTX, n = 99 for ADA – MTX, n = 253 for ADA + MTX.

¶ JIA subtypes: n = 524 for ADA ± MTX, n = 154 for ADA – MTX, n = 370 for ADA + MTX.

# Further diagnosis information in 67 patients showed polyarthritis or extended oligoarthritis (33 for ADA ± MTX, 34 for MTX).

**Table 3.** Incidence rates of registry observational adverse events, all-treated population*

| Events/100 patient-years | MTX arm (n = 301, PY = 1,170.3) | ADA ± MTX arm | | |
|---|---|---|---|---|
| | | ADA ± MTX (n = 537, PY = 1,855.5) | ADA – MTX (n = 160, PY = 517.0) | ADA + MTX (n = 377, PY = 1,338.5) |
| Any AE | 505 (43.2) | 769 (41.4) | 216 (41.8) | 553 (41.3) |
| Age ≤8 years | 222 (38.7) | 180 (42.2) | 42 (48.8) | 138 (40.5) |
| Age >8 years | 283 (47.4) | 589 (41.2) | 174 (40.4) | 415 (41.6) |
| AE at least possibly drug related | 197 (16.8) | 243 (13.1) | 66 (12.8) | 177 (13.2) |
| Age ≤8 years | 100 (17.4) | 70 (16.4) | 13 (15.1) | 57 (16.7) |
| Age >8 years | 97 (16.3) | 173 (12.1) | 53 (12.3) | 120 (12.0) |
| SAE | 52 (4.4) | 134 (7.2) | 39 (7.5) | 95 (7.1) |
| Age ≤8 years | 15 (2.6) | 21 (4.9) | 6 (7.0) | 15 (4.4) |
| Age >8 years | 37 (6.2) | 113 (7.9) | 33 (7.7) | 80 (8.0) |
| SAE at least possibly drug related | 6 (0.5) | 32 (1.7) | 9 (1.7) | 23 (1.7) |
| Age ≤8 years | 2 (0.3) | 5 (1.2) | 0 (0) | 5 (1.5) |
| Age >8 years | 4 (0.7) | 27 (1.9) | 9 (2.1) | 18 (1.8) |
| AE leading to discontinuation† | 36 (3.1) | 59 (3.2) | 19 (3.7) | 40 (3.0) |
| Age ≤8 years | 12 (2.1) | 1 (0.2) | 0 (0) | 1 (0.3) |
| Age >8 years | 24 (4.0) | 58 (4.1) | 19 (4.4) | 39 (3.9) |
| Infection | 179 (15.3) | 262 (14.1) | 75 (14.5) | 187 (14.0) |
| Age ≤8 years | 104 (18.1) | 74 (17.3) | 16 (18.6) | 58 (17.0) |
| Age >8 years | 75 (12.6) | 188 (13.2) | 59 (13.7) | 129 (12.9) |
| SAE of infection | 17 (1.5) | 38 (2.0) | 8 (1.5) | 30 (2.2) |
| Age ≤8 years | 5 (0.9) | 8 (1.9) | 0 (0) | 8 (2.3) |
| Age >8 years | 12 (2.0) | 30 (2.1) | 8 (1.9) | 22 (2.2) |

* Values are the number (%) of events per 100 patient-years of observation time during the registry. Registry observational adverse event (AE) is defined as having an onset on or after the first day in the registry through the last contact in the registry. ADA = adalimumab; MTX = methotrexate; PY = patient-years; SAE = serious AE.
† AE leading to discontinuation of registry or registry drug. Events with unknown relationship to study drugs were counted as related. AEs were coded using the Medical Dictionary for Regulatory Activities, version 18.1.

arm and 28 patients (5.2%) in the ADA ± MTX arm (ADA – MTX n = 6 [3.8%], ADA + MTX n = 22 [5.8%]), corresponding to 1.5 events/100 patient-years in the MTX arm and 2.0 events/100 patient-years in the ADA ± MTX arm (Table 3). Additional details on the most common types of serious infections are provided in Table 4. Overall, the incidence rates of AEs and SAEs were similar for patients ages ≤8 and >8 years (Table 3). However, infection rates, but not serious infection rates, were numerically higher for patients age ≤8 years versus >8 years in the MTX arm (18.1 versus 12.6 events/100 patient-years) and in the ADA – MTX (18.6 versus 13.7 events/100 patient-years) and ADA + MTX (17.0 versus 12.9 events/100 patient-years) subgroups. AEs occur-

**Table 4.** Incidence rates of most common registry observational serious adverse events of infections, all-treated population*

| AE preferred term | MTX arm (n = 301, PY = 1,170.3) | ADA ± MTX arm | | |
|---|---|---|---|---|
| | | ADA ± MTX (n = 537, PY = 1,855.5) | ADA – MTX (n = 301, PY = 517.0) | ADA + MTX (n = 377, PY = 1,338.5) |
| Pyelonephritis | 1 (<0.1) | 4 (0.2) | 1 (0.2) | 3 (0.2) |
| Tonsillitis | 5 (0.4) | 3 (0.2) | 0 | 3 (0.2) |
| Appendicitis | 1 (<0.1) | 3 (0.2) | 1 (0.2) | 2 (0.1) |
| Cellulitis | 0 | 3 (0.2) | 1 (0.2) | 2 (0.1) |
| Gastroenteritis | 0 | 2 (0.1) | 0 | 2 (0.1) |
| Herpes zoster | 1 (<0.1) | 2 (0.1) | 0 | 2 (0.1) |
| Impetigo | 0 | 2 (0.1) | 0 | 2 (0.1) |
| Pneumonia | 0 | 2 (0.1) | 0 | 2 (0.1) |
| Varicella | 2 (0.2) | 1 (<0.1) | 0 | 1 (<0.1) |

* Values are the number (%) of events per 100 patient-years of observation time during the registry, occurrence ≥0.1 events/100 patient-years (PY) in either treatment arm. Registry observational adverse events (AEs) are defined as having an onset on or after the first day in the registry through the last contact in the registry. Overall, 14 patients (4.7%) and 28 patients (5.2%), respectively, had 1 or more serious infections in the methotrexate (MTX) arm and the adalimumab (ADA) ± MTX arm (6 [3.8%] for ADA – MTX, 22 [5.8%] for ADA + MTX). AEs were coded using the Medical Dictionary for Regulatory Activities, version 18.1.

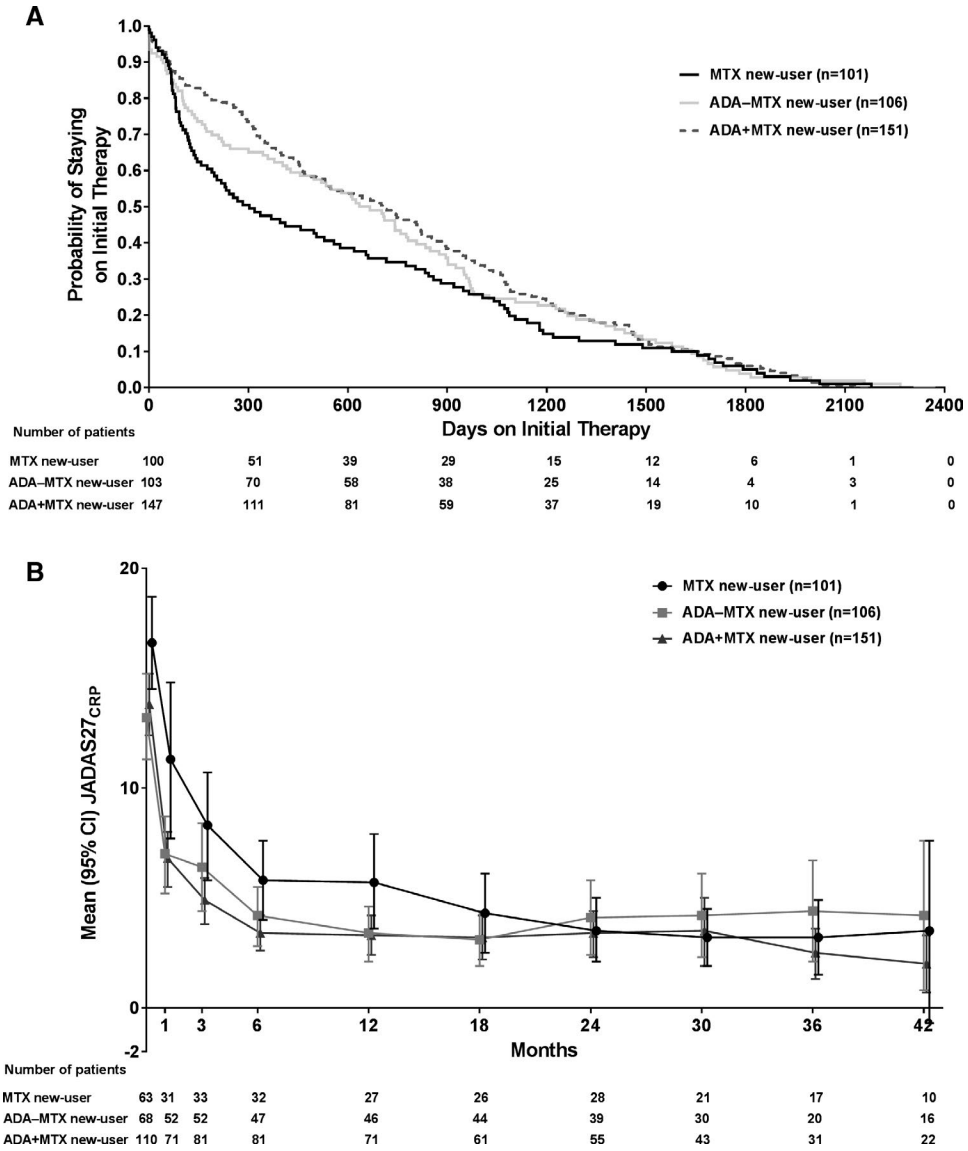


**Figure 2.** **A**, Kaplan-Meier plot of time to change or discontinuation of initial therapy in adalimumab (ADA) – methotrexate (MTX) new users, ADA + MTX new users, and MTX new users at registry enrollment. Change or discontinuation of initial therapy was defined as adding MTX or stopping ADA for ADA – MTX new users, stopping 1 or both drugs for ADA + MTX new users, or adding ADA or any other biologic or stopping MTX for MTX new users, whichever occurred first. **B**, Mean score for the 27-joint Juvenile Arthritis Disease Activity Score with the C-reactive protein level ($JADAS\text{-}27_{CRP}$) over time. The last observation was carried forward until initial therapy was stopped or changed for ADA – MTX new users, ADA + MTX new users, and MTX new users at registry enrollment, excluding $JADAS\text{-}27_{CRP}$ data as soon as initial therapy was stopped or changed. n = number of patients with nonmissing baseline and nonmissing value after imputation. Error bars represent 95% confidence interval (95% CI).

ring in >2% of patients were nausea, vomiting, infections, and abnormal liver function tests in the MTX arm, and worsening of arthritis, infections, and injection-site pain in the ADA ± MTX arm (see Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24044/abstract).

No cases of death, malignancy, active tuberculosis, oral candidiasis, demyelination, cerebrovascular event, or congestive heart failure were reported. Two patients in the ADA ± MTX arm had lupus-like reactions (ADA – MTX n = 1 [0.6%], ADA + MTX n = 1 [0.3%]). Worsening of or new onset of psoriasis was reported in 2 patients (0.7%) in the MTX arm and 8 patients (1.5%) in the ADA ± MTX arm (ADA – MTX n = 3 [1.9%], ADA + MTX n = 5 [1.3%]). Five pregnancies were reported in 4 patients, resulting in 2 live births, 2 abortions (1 spontaneous, 1 elective), and 1 unknown outcome (lost to follow-up).

**JIA-associated uveitis results.** A total of 22 patients (7.3%) in the MTX arm and 75 patients (14.0%) in the ADA ± MTX arm (ADA – MTX n = 21 of 160 [13.1%], ADA + MTX n = 54 of 377 [14.3%]) had ≥1 documented report of JIA-associated uveitis while in the registry. Of these patients, 10 of 22 (45.5%) in the

MTX arm and 42 of 75 (56.0%) in the ADA ± MTX arm (ADA – MTX n = 11 of 21 [52.4%], ADA + MTX n = 31 of 54 [57.4%]) had first documentation of uveitis at registry entry. For patients with JIA-associated uveitis, the first documented report in the registry was persisting or recurring uveitis in 6 of 21 patients (28.6%) in the MTX arm and 21 of 75 patients (28.0%) in the ADA ± MTX arm, and new onset or acute JIA-associated uveitis in 12 of 21 patients (57.1%) and 34 of 75 patients (45.3%) in the MTX and ADA ± MTX arms, respectively; detailed information about JIA-associated uveitis in 1 patient in the MTX arm was missing. A first uveitis episode was reported in each registry arm for 2 patients with uveitis who switched from the MTX arm to the ADA ± MTX arm.

**Effectiveness.** Effectiveness data were analyzed in 358 new users (43%: MTX new users n = 101, ADA ± MTX new users n = 257, ADA – MTX new users n = 106, ADA + MTX new users n = 151) (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24044/abstract). On average, ADA – MTX or ADA + MTX new users were older and had longer disease duration compared with MTX new users (see Supplementary Table 5, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24044/abstract). Other disease characteristics were similar in all new users at baseline, except mean JADAS-$27_{CRP}$ measurements, which were lower in ADA – MTX or ADA + MTX new users compared with MTX new users.

The probability of remaining on initial therapy was lower in patients who were MTX new users versus those who were ADA ± MTX new users (Figure 2A). Improvement in disease activity (JADAS-$27_{CRP}$) from baseline was achieved in all groups (Figure 2B). There was a numerical trend toward earlier improvement in the ADA – MTX and ADA + MTX new users compared with the MTX new users, resulting in lower mean disease activity in the first 12 months of registry follow-up in ADA – MTX and ADA + MTX new users.

## DISCUSSION

The STRIVE registry prospectively evaluated the safety and effectiveness of ADA ± MTX, with the MTX arm as a reference, in patients with moderate-to-severe polyarticular-course JIA. No new safety signals were observed with ADA treatment, and no deaths, malignancies, active tuberculosis, oral candidiasis, demyelination, cerebrovascular events, or congestive heart failure were reported in the STRIVE registry. More patients in the MTX arm reported the need for additional treatment as a reason for discontinuing the registry drug compared with those who received ADA ± MTX. Overall, the 7-year safety data from this registry support the known safety profile of ADA (27,28) and suggest that ADA is well tolerated in patients with active polyarticular-course JIA during long-term exposure.

Infections were the most frequently reported AEs, and most of these events were considered mild to moderate in severity. The rates of infections for the subgroups ADA – MTX (14.5 events/100 patient-years) and ADA + MTX (14.0 events/100 patient-years) were comparable to the rates of events reported for the ADA cohort in the BIKER registry (17.2–18.6 events/100 patient-years) (29,30) but higher than the rate observed in patients with JIA treated with etanercept (5.0 events/100 patient-years in the BIKER registry; 5.4 events/100 patient-years in the Dutch JIA registry) (31,32). Infections are more common in children, especially when young, than in adults, which could partially explain the high infection rate; in this study, the infection rate was higher among patients age ≤8 years versus >8 years, regardless of treatment. The frequency of infections was similar in patients in the ADA ± MTX arm who had previously been treated with a biologic DMARD compared with the incidence rates in all patients in the ADA ± MTX arm. However, the rate of serious infections was 1.5 events/100 patient-years in the MTX arm and 2.0 events/100 patient-years in the ADA ± MTX arm, which was higher than the rate of serious infections reported previously in JIA (29,30). Reasons for these differences may include differences in patient populations, in methodology in recording serious infections between registries, and in analysis methods for incidence rates of AEs (e.g., registry observational AEs were analyzed in STRIVE and treatment-emergent AEs were reported in other published studies). In addition, biologics plus concomitant steroids can lead to an increased risk of infection (33).

SAEs related to registry treatment were rare but numerically higher with ADA use, 6 in the MTX arm (0.5 events/100 patient-years) versus 32 in the ADA ± MTX arm (1.7 events/100 patient-years). These results are consistent with the safety data derived from the BIKER registry and are in alignment with the previously published long-term safety analysis on 23,458 patients in 71 ADA clinical trials and pediatric safety analysis on 577 patients in 7 ADA clinical trials (27–29).

STRIVE also collected uveitis data for patients seeing an ophthalmologist as applicable. However, the nonsystematic collection of uveitis data and the nonrandomized character of the registry limits the interpretation of these data and can only provide a descriptive summary of patients with uveitis as observed. Recently, double-blind, placebo-controlled trials demonstrated the efficacy of ADA in combination with MTX in JIA-associated uveitis (34,35). The incidence of injection-site pain was slightly higher in the ADA ± MTX versus MTX arm; of note, a citrate-free formulation of ADA with reduced injection-site pain became available after the data cut for this analysis (36).

The main objective of STRIVE was to assess the long-term safety of ADA ± MTX treatment. However, given the interest of clinicians in obtaining real-time estimates of the effectiveness of ADA with standard use, we attempted to derive estimates of the reduction of JIA activity using JADAS-$27_{CRP}$ measurements among treatment new users. Findings suggested that ADA

treatment might more rapidly improve JIA signs and symptoms compared with MTX alone in new users. JADAS-$27_{CRP}$ was analyzed in the new users because long periods of therapy with ADA and/or MTX before the start of the registry may have affected the overall effectiveness results. The JADAS-$27_{CRP}$ analysis included data up until patients changed/stopped their initial therapy, to exclude patients who may not have been receiving the registry drug at the time of effectiveness measurement but were still enrolled in the registry; this exclusion may have resulted in a selection bias because of treatment discontinuation for inadequate improvement.

The findings of this registry must be interpreted in the context of potential limitations. Because the registry reflects the standard of care, patients were not randomized and disease characteristics conceivably influenced medication choice (37). Moreover, because a registry is not a controlled setting, patients may have received concomitant therapy or added/switched to other biologic treatments. For this reason, the results in the different registry arms should not be directly compared. Additionally, some variables, such as CRP level and erythrocyte sedimentation rate, were available only if they were part of the physician's routine care. Lastly, not all events of special interest were collected throughout the full 10-year period (limited collection starting from year 6), and systematic uveitis assessments before and during the registry were not performed. Despite these limitations, the results of these interim data are consistent with results obtained from previous polyarticular-course JIA clinical studies with ADA and support the safety of ADA ± MTX in children with polyarticular-course JIA (10,15).

In conclusion, the 7-year interim results in this ongoing post-marketing registry show that ADA continues to be well tolerated in these patients with active polyarticular-course JIA. No new safety signals were observed, and the safety of ADA in this patient population was comparable to that observed in prior polyarticular-course JIA studies. The known safety profile of ADA remains unchanged.

## ACKNOWLEDGMENT

The authors thank Dr. Pavla Vavrincova for her contribution in acquisition of data.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Brunner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Brunner, Nanda, Milojevic, Rabinovich, Kingsbury, Marzan, Jung, Bereswill, Kalabic, Kupper, Lovell, Martini, Ruperto.

**Acquisition of data.** Brunner, Nanda, Toth, Foeldvari, Bohnsack, Milojevic, Rabinovich, Kingsbury, Marzan, Chalom, Horneff, Kuester, Dare, Trachana, Jung, Olson, Minden, Quartier, Bereswill, Kalabic, Kupper, Lovell, Martini, Ruperto.

**Analysis and interpretation of data.** Brunner, Milojevic, Quartier, Bereswill, Kalabic, Kupper, Martini, Ruperto.

## ROLE OF THE STUDY SPONSOR

AbbVie sponsors the STRIVE registry; AbbVie contributed to the design, and participated in collection, analysis, and interpretation of data, and in writing, reviewing, and approval of the final version. Publication of this article was contingent upon approval by AbbVie. Medical writing support was provided by Jessica L. Suboticki, PhD, Naina Barretto, PhD, and Gaurav Patki, PhD, of AbbVie, and by Maria Hovenden, PhD, and Janet E. Matsuura, PhD, of Complete Publication Solutions, LLC, and programming support was provided by Xiaolei Leahy, PhD, of AbbVie.

## REFERENCES

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369: 767–78.
2. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet 2011; 377:2138–49.
3. Giancane G, Consolaro A, Lanni S, Davi S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: diagnosis and treatment. Rheumatol Ther 2016;3:187–207.
4. 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.
5. Ringold S, Seidel KD, Koepsell TD, Wallace CA. Inactive disease in polyarticular juvenile idiopathic arthritis: current patterns and associations. Rheumatology (Oxford) 2009;48:972–7.
6. 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.
7. Woo P, Southwood TR, Prieur AM, Doré CJ, Grainger J, David J, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000;43:1849–57.
8. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, Feitosa 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.
9. Ramanan AV, Whitworth P, Baildam EM. Use of methotrexate in juvenile idiopathic arthritis. Arch Dis Child 2003;88:197–200.
10. 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.
11. 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.
12. Brunner HI, Ruperto N, Tzaribachev N, Horneff G, Chasnyk VG, Panaviene V, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis 2018;77:21–9.
13. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis 2015;74:1110–7.

14. 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.
15. Kingsbury DJ, Bader-Meunier B, Patel G, Arora V, Kalabic J, Kupper H. Safety, effectiveness, and pharmacokinetics of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to 4 years. Clin Rheumatol 2014;33:1433–41.
16. Humira (adalimumab). Summary of product characteristics, AbbVie Ltd, Maidenhead, UK, 2016.
17. Humira (adalimumab). Full prescribing information, AbbVie Inc., North Chicago, IL, 2016.
18. Ruperto N, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). Arch Dis Child 2011;96:596–601.
19. Brunner HI, Rider LG, Kingsbury DJ, Co D, Schneider R, Goldmuntz E, et al. Pediatric Rheumatology Collaborative Study Group: over four decades of pivotal clinical drug research in pediatric rheumatology. Pediatr Rheumatol Online J 2018;16:45.
20. International Conference on Harmonisation. Introductory Guide MedDRA Version 20.1. URL: https://www.meddra.org/sites/default/files/guidance/file/intguide_20_1_english_0.pdf.
21. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994;37:1761–9.
22. Ruperto N, Ravelli A, Pistorio A, Ferriani V, Calvo I, Ganser G, et al. The provisional Paediatric Rheumatology International Trials Organisation/American College of Rheumatology/European League Against Rheumatism disease activity core set for the evaluation of response to therapy in juvenile dermatomyositis: a prospective validation study. Arthritis Rheum 2008;59:4–13.
23. Rider LG, Feldman BM, Perez MD, Rennebohm RM, Lindsley CB, Zemel LS, et al. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies: I. physician, parent, and patient global assessments. Arthritis Rheum 1997;40:1976–83.
24. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202–9.
25. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009;61:658–66.
26. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915–20.
27. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis 2013;72:517–24.
28. Horneff G, Seyger MM, Arikan D, Kalabic J, Anderson JK, Lazar A, et al. Safety of adalimumab in pediatric patients with polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, psoriasis, and Crohn's disease. J Pediatr 2018;201:166–75.
29. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German Biologics JIA Registry. Arthritis Rheumatol 2014;66:2580–9.
30. Horneff G. Safety of biologic therapies for the treatment of juvenile idiopathic arthritis. Expert Opin Drug Saf 2015;14:1111–26.
31. Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis 2009;68:519–25.
32. 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.
33. Becker I, Horneff G. Risk of serious infection in juvenile idiopathic arthritis patients associated with tumor necrosis factor inhibitors and disease activity in the German Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken) 2017;69:552–60.
34. Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med 2017;376:1637–46.
35. Quartier P, Baptiste A, Despert V, Allain-Launay E, Kone-Paut I, Belot A, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. Ann Rheum Dis 2018;27:1003–11.
36. Nash P, Vanhoof J, Hall S, Arulmani U, Tarzynski-Potempa R, Unnebrink K, et al. Randomized crossover comparison of injection site pain with 40 mg/0.4 or 0.8 mL formulations of adalimumab in patients with rheumatoid arthritis. Rheumatol Ther 2016;3:257–70.
37. Delgado-Rodriguez M, Llorca J. Bias. J Epidemiol Community Health 2004;58:635–41.