The Journal of Rheumatology 2023;xx:xxxx
doi:10.3899/jrheum.220645
First Release February 1 2023

The Journal of Rheumatology

Treatment Response to Tumor Necrosis Factor Inhibitors and Methotrexate Monotherapy in Adults With Juvenile Idiopathic Arthritis: Data From NOR-DMARD

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ABSTRACT. ***Objective.*** To compare the effectiveness of tumor necrosis factor inhibitors (TNFi) ± comedication and methotrexate (MTX) monotherapy between patients with adult juvenile idiopathic arthritis (JIA) and patients with rheumatoid arthritis (RA).

Methods. Adult patients with JIA and RA were identified from the Norwegian Antirheumatic Drug Register (NOR-DMARD) register. Disease activity measurements at baseline, 3, 6, and 12 months were compared between patients with JIA and RA starting (1) TNFi and (2) MTX monotherapy, using age- and gender-weighted analyses. We calculated differences between JIA and RA in mean changes in Disease Activity Score in 28 joints (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI), among other disease activity measures. DAS28, CDAI, SDAI, and American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) remission rates at 3, 6, and 12 months, as well as 6- and 12-month Lund Efficacy Index (LUNDEX)-corrected rates, were calculated.

Results. We identified 478 patients with JIA (TNFi/MTX monotherapy, n = 358/120) and 4637 patients with RA (TNFi/MTX monotherapy, n = 2292/2345). Patients with JIA had lower baseline disease activity compared to patients with RA across treatment groups. After baseline disease activity adjustment, there were no significant differences in disease activity change from baseline to 3, 6, and 12-months of follow-up between patients with JIA and RA for either treatment group. Twelve-month remission rates were similar between groups based on DAS28 (TNFi: JIA 55.2%, RA 49.5%; MTX monotherapy: JIA 45.3%, RA 41.2%) and ACR/EULAR remission criteria (TNFi: JIA 20.4%, RA 20%; MTX monotherapy: JIA 17%, RA 12.7%). Median drug survival (yrs) was similar for JIA and RA in both treatment groups (TNFi: JIA 1.2, RA 1.4; MTX monotherapy: JIA 1.3, RA 1.6).

Conclusion. TNFi and MTX monotherapy are effective in adult JIA, with similar effectiveness to that shown in RA.

Key Indexing Terms: juvenile idiopathic arthritis, methotrexate monotherapy, rheumatoid arthritis, tumor necrosis factor inhibitors

This work was supported by the Faculty of Medicine, University of Oslo, Oslo, Norway.

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GB is on the speaker's bureau for AbbVie and has been a consultant of UCB, Pfizer, and Novartis. PM has been a consultant of Galapago. TKK is on the speaker's bureau and has received fees for speaking from Amgen, Celltrion, Egis, Evapharma, Ewopharma, Hikma, Oktal, Sandoz, and Sanofi; has received fees for consulting from AbbVie, Amgen, Biogen, Celltrion, Eli Lilly, Galapagos, Gliead, Mylan, Novartis, Pfizer, Sandoz, and Sanofi; and received research funding to Diakonhjemmet Hospital from AbbVie, Amgen, BMS, Galapagos, MSD, Pfizer and UCB. ABA has received personal fees from AbbVie, Eli Lilly, Novartis, and Pfizer, outside the submitted work. The remaining authors declare no conflicts of interest relevant to this article.

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Accepted for publication November 3, 2022.

Juvenile idiopathic arthritis (JIA) is the common term for a group of chronic inflammatory arthritis conditions with disease onset before the age of 16 years.[1] Several long-term outcome studies show that about 50% of children diagnosed with JIA have active arthritis in adulthood.[2-7] Although the disease course is variable among patients, JIA can cause considerable pain and disability, affect health-related outcomes,[1,8] and have a negative effect on social and working life in adulthood.[9-12] Finding treatment strategies that improve both symptoms and health-related outcomes would therefore be of benefit for the patients with JIA and their contribution to society at large.

There is some variation in treatment strategies across the International League of Associations for Rheumatology (ILAR) subtypes of JIA.[13] In general, a modern treatment approach for JIA in children includes the following, in order: nonsteroidal antiinflammatory drugs (NSAIDs), intraarticular glucocorticoid steroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and/or biologic DMARDs (bDMARDs), with the latter confined to patients not responding to first-line treatment. Although the csDMARD methotrexate (MTX) is still the cornerstone treatment for JIA in most subtypes, use of bDMARDs has increased dramatically since the first approvals of this drug class for JIA 2 decades ago.[14-16]

A number of clinical trials have shown that tumor necrosis factor inhibitors (TNFi) are effective in children with JIA.[15] Despite the high proportion of patients with JIA with disease activity persisting into adulthood, the knowledge base on treatment effects in adult patients with JIA is limited, with only a few studies exploring the effect of biologics, including TNFi, in this patient group.[17-19] Although MTX has been studied thoroughly in children with JIA, as well as in adults with inflammatory joint diseases other than JIA, to our knowledge no study has specifically explored the effectiveness of MTX monotherapy in adult patients with JIA. For this study, our objectives were (1) to compare the effectiveness of TNFi and MTX monotherapy on disease activity measures and remission rates between adult patients with JIA and patients with rheumatoid arthritis (RA), and (2) to explore TNFi and MTX 5-year drug survival in JIA, compared to a RA cohort using age- and gender-weighted analyses.

METHODS

The Norwegian DMARD study. We used data from the Norwegian DMARD study (NOR-DMARD), an ongoing prospective, longitudinal observational study initiated in the year 2000 including 6 rheumatology centers, covering approximately one-third of the Norwegian population.[20-23] NOR-DMARD enrolls patients aged > 18 years diagnosed with an inflammatory joint disease starting or switching DMARD treatment. Both DMARD-naïve patients and patients previously treated with DMARDs are included. Since 2012, NOR-DMARD has only included patients starting treatment with bDMARDs.

When enrolled, patients are assessed at baseline and after 3, 6, and 12 months. After 12-months of follow-up, patients were assessed annually up to 2012; after 2012, all patients have been followed every 6 months. At each study visit, disease activity, comorbidities, and patient-reported outcomes (PROs) are reported. Assessments and data collection are performed by the treating physician or a study nurse.[21,22]

The study complies with the Declaration of Helsinki. All patients have given informed, written consent prior to inclusion. Ethical approval is provided by the East-Norwegian Regional Committee for Medical and Health Research Ethics (ethical approval number: 2011/1339). Data storage is approved by the Data Inspectorate.

Patient selection. Patients included in this study were adult patients (age ≥ 18 yrs) registered with (1) a clinical diagnosis of JIA (International Classification of Diseases, 10th Revision, M08 or M09) or (2) a clinical diagnosis of RA, psoriatic arthritis, ankylosing spondylitis, or undifferentiated arthritis, who received the diagnosis before the age of 16 years. If the diagnosis was undifferentiated arthritis, the disease duration had to be of at least 6 weeks at treatment start. Adults diagnosed with RA were included for comparative analyses. Only patients starting treatment with MTX monotherapy or TNFi with or without comedication with csDMARDs were included in the analyses.

In NOR-DMARD, patients are reincluded every time they switch treatment. In case of multiple inclusions for 1 patient, only the first treatment course within each treatment group was included in our analyses (ie, the first MTX monotherapy treatment course and the first TNFi treatment course).

Assessments. We included data from the baseline, 3-, 6-, and 12-month NOR-DMARD visits. Analyses of drug survival were based on 5-year follow-up data. Disease activity measurements included in the analyses were (1) laboratory tests: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); (2) joint counts: swollen and tender joint count in 28 joints (SJC28 and TJC28); (3) calculated composite scores: Disease Activity Score in 28 joints (DAS28) with CRP,[24,25] Simplified Disease Activity Index (SDAI),[26] and Clinical Disease Activity Index (CDAI)[27]; (4) investigator-reported outcomes: 0-100 mm visual analog scale (VAS) assessment of global disease activity (physician global assessment [PGA])[28]; and (5) PRO measures: modified Health Assessment Questionnaire (MHAQ),[29] EuroQol-5 Dimension questionnaire (EQ-5D),[30] and 0 mm to 100 mm VAS for pain, fatigue, and patient global assessment (PtGA).[31] To define remission, we used the established cut-offs of DAS28 < 2.6,[32] SDAI ≤ 3.3,[33] and CDAI ≤ 2.8,[34] and the joint American College of Rheumatology and the European Alliance of Associations for Rheumatology (ACR/EULAR) remission criteria.[35]

Statistical analysis. Significance levels were set at $P < 0.05$ in all analyses. Statistical analyses were performed using Stata/SE 16 (64-bit) for Windows (StataCorp).

Data are presented with mean (SD) for continuous variables, and frequencies with percentages for categorical variables.

- *Age- and gender-weighted comparison.* Mean changes in disease activity and absolute remission rates were estimated at 3-, 6-, and 12-months of follow-up and compared between patients with JIA and the RA cohort, using linear and logistic regression for continuous and categorical variables, respectively, with weights based on age and gender. The same method was used for comparing patient characteristics, however, nonweighted analyses of group differences in age and gender were performed using the independent samples *t* test.

The weighting method has previously been used in a similar cohort[17] and is based on the JIA to RA ratio in gender and 5-year age intervals. JIA observations were given the weight of 1, whereas RA observations were weighted according to the number of patients with JIA in the relevant age and gender group divided by the number of patients with RA in the same age and gender group. For example, in the group starting treatment with TNFi there were 134 female patients with JIA and 330 female patients with RA aged 30 to 35 years at inclusion. Consequently, each female patient with RA aged 30 to 35 years received a weight of 134/330. Hence, some observations have a greater effect on the results, but all included patients have contributed data to the analyses.

- *Adjustments for baseline disease activity.* We adjusted for baseline disease activity when analyzing group differences in changes of disease activity by doing bivariate regression analyses, including both the baseline value and

the mean change of a given variable in the regression model. The process was repeated for all disease activity measures. Due to multiple differences between groups, we only adjusted for baseline disease activity to avoid introducing overadjustment bias and complicate interpretation. Weighted analyses are presented with the JIA-RA difference (95% CI) for continuous variables and the JIA odds ratio (95% CI) for categorical variables. Absolute remission rate analyses were not adjusted for baseline disease activity.

· *Drug survival.* Five-year TNFi and MTX drug survival in patients with JIA and RA was assessed by using age- and gender-weighted Kaplan-Meier analyses.[36] Discontinuations for reasons other than remission and pregnancy were considered relevant events and time until event was defined as time between initiation date and discontinuation date; alternatively, the last recorded visit date if the discontinuation date was missing. Patients discontinuing treatment because of remission or pregnancy were censored, as well as patients with an observation period exceeding 5 years. Differences in drug survival between JIA and RA were assessed by a weighted log-rank test and summarized by 5-year median drug survival.

· *Lund Efficacy Index.* In the treatment response analyses, only patients adhering to treatment were included. This can introduce selection bias in at least 2 ways: (1) patients not responding to treatment might discontinue medication, and (2) mainly patients adhering to treatment experience its clinical effects. To account for differences in retention to therapy, we calculated Lund Efficacy Index (LUNDEX) values for the disease activity categories "high/moderate/low disease activity" and "remission" based on validated DAS28, CDAI, and SDAI disease activity state cut-off values.[33,34] Values were calculated by the LUNDEX value formula: (fraction of starters still in the study at the beginning of the relevant time interval) × (fraction responding at visit during that time interval).[37] Only 6- and 12-month LUNDEX values were assessed due to low withdrawal rates before 3 months. Visits at study day 137 to 227 and study day 319 to 455 were defined as 6- and 12-month visits, respectively. Estimated survival rates from the Kaplan-Meier analyses were used to calculate LUNDEX values.

· *Sensitivity analysis.* To assess treatment response in biologic-naïve patients with JIA, a sensitivity analysis was performed, exploring remission rates and 5-year drug survival in biologic-naïve JIA vs RA using age- and gender-weighted analyses. Statistical methods were similar to those in the primary analyses.

· *Treatment response in seropositive vs seronegative JIA.* DAS28 response and ACR/EULAR remission rates after 3, 6, and 12 months, as well as 5-year drug survival, were compared between patients with seropositive and seronegative JIA. Seropositivity was defined as being rheumatoid factor negative and/or anticyclic citrullinated peptide antibody positive. Statistical methods were similar to those in the primary analyses.

RESULTS

TNFi ± comedication.

· *Baseline demographics and disease activity.* Three hundred fifty-eight patients with JIA and 2292 patients with RA starting treatment with TNFi ± comedication were identified from the register. Mean age and gender distribution differed significantly between JIA and RA. Age- and gender-weighted analyses showed significant differences between JIA and RA in diagnosis duration and previous use of bDMARDs (Table 1). Based on age- and gender-weighted analyses, JIA had significantly lower baseline SJC28, TJC28, DAS28, SDAI, and CDAI compared to RA (Table 2), and significantly greater baseline scores in VAS fatigue, VAS joint pain, and PtGA (Supplementary Table S1, available with the online version of this article).

· *Treatment response.* After adjusting for baseline disease activity there were no significant differences in change of any of the disease activity measurement scores after 3, 6, and 12 months between JIA and RA (Table 2). Change in VAS pain, VAS fatigue, MHAQ, and EQ-5D are presented in the data supplement (Supplementary Table S1, available with the online version of this article).

· *Remission rates.* In patients treated with TNFi ± comedication, age- and gender-weighted regression analyses showed that the 3-month DAS28 remission rate was significantly greater in patients with JIA than in patients with RA. These differences were not present after 6 and 12 months. SDAI, CDAI, and ACR/EULAR remission rates did not differ significantly between groups at any timepoint except from 12-month ACR/EULAR remission being significantly lower in JIA after weighting for age and gender (Figure 1). LUNDEX-corrected remission rates did not show any substantial differences between patients with JIA and RA at 6- and 12-month follow-ups (Supplementary Figure S1A, available with online version of this article).

· *Drug survival.* Median drug survival was 1.2 years for patients with JIA and 1.4 years for patients with RA. Age- and gender-weighted log-rank tests showed no significant difference in drug survival between the groups ($P = 0.68$). Weighted Kaplan-Meier survival estimates for JIA and RA are shown in Figure 2A.

· *Sensitivity analysis.* Biologic-naïve patients with JIA and RA had similar remission rates (Supplementary Figure S2A, available with the online version of this article). LUNDEX-corrected remission rates did not show any substantial differences between JIA and RA at 6- and 12-month follow-ups (Supplementary Figure S2B). Five-year treatment survival was similar between JIA (1.5 years) and RA (1.5 years; Supplementary Figure S2C).

· *Seropositive vs seronegative JIA.* Seropositive JIA had significantly higher DAS28 baseline disease activity but similar responses as seronegative JIA after 3, 6, and 12 months. ACR/EULAR remission was significantly higher in seronegative JIA (Supplementary Table S2, available with the online version of this article).

MTX monotherapy.

· *Baseline demographics and disease activity.* We included 120 patients with JIA and 2345 patients with RA starting treatment with MTX monotherapy. Patients with JIA had significantly lower baseline scores for ESR, SJC28, TJC28, DAS28, and SDAI than patients with RA (Table 2). Like the TNFi treatment group, mean age and gender distribution differed significantly between patients with JIA and RA, and age- and gender-weighted analyses showed significant differences between patients with JIA and RA in diagnosis duration and previous use of bDMARDs.

· *Treatment response.* Weighted analyses adjusted for baseline disease activity showed significantly less improvement in ESR after 3 months (Table 2) and MHAQ after 6 months (Supplementary Table S1, available with the online version of this article), and a significantly greater improvement in PGA after 3 and 12 months in JIA compared to RA (Supplementary Table S1). The other disease activity measures were not significantly different.

Table 1. Baseline characteristics with age- and gender-weighted comparison of adult patients with JIA and with RA starting TNFi ± comedication and MTX monotherapy.

	TNFi ± Comedication			MTX Monotherapy		
	JIA n = 358	RA n = 2292	*P**	JIA n = 120	RA n = 2345	*P**
Age, yrs, mean (SD)[a]	33.1 (11.2) n = 358	53.1 (13.9) n = 2288	**< 0.001**	35.7 (12.6) n = 119	56.4 (13.6) n = 2342	**< 0.001**
Female gender, n (%)[a]	249 (69.9) n = 356	1657 (72.5) n = 2286	0.43	98 (82.4) n = 119	1643 (70.2) n = 2340	**< 0.005**
Diagnosis duration, yrs, mean (SD)	23.6 (12.0) n = 241	9.4 (9.3) n = 1905	**< 0.001**	24.5 (12.7) n = 113	4.7 (8.4) n = 2303	**< 0.001**
Anti-CCP positive, n (%)	26 (20.2) n = 129	656 (73) n = 899	**< 0.001**	5 (10.2) n = 49	668 (66.8) n = 1000	**< 0.001**
RF positive, n (%)	46 (22.3) n = 206	1070 (75.3) n = 1422	**< 0.001**	24 (21.4) n = 112	1445 (62.9) n = 2296	**< 0.001**
ICD-10 diagnosis						
JIA	266 (74.3)	–	–	91 (76.5)	–	–
RA	26 (7.3)	–	–	10 (8.4)	–	–
PsA	20 (5.6)	–	–	10 (8.4)	–	–
AS	38 (10.6)	–	–	4 (3.4)	–	–
Other	8	–	–	4 (3.4)	–	–
Previous use of bDMARDs, n (%)	133 (37.6) n = 354	457 (20.1) n = 2269	**< 0.001**	8 (6.7) n = 119	69 (3) n = 2342	**0.01**
No. of previous bDMARDs, mean (SD)	0.6 (1.0) n = 354	0.3 (0.7) n = 2269	**< 0.001**	0.11 (0.4) n = 120	0.05 (0.3) n = 2345	0.13
Previous use of MTX, n (%)	271 (76.6) n = 354	1922 (84.9) n = 2265	**0.03**	44 (37) n = 119	363 (15.5) n = 2342	**< 0.001**
Concomitant use of csDMARDs, n (%)	209 (58.4) n = 358	1697 (74.2) n = 2288	0.06	–	–	–
TNFi, n (%)	n = 358	n = 2292	–	–	–	–
ADA	85 (23.7)	510 (22.3)	0.96	–	–	–
CZP	53 (14.8)	349 (15.2)	0.98	–	–	–
ETN	139 (38.8)	899 (39.2)	0.64	–	–	–
GOL	18 (5)	80 (3.5)	0.59	–	–	–
IFX	63 (17.6)	454 (19.8)	0.85	–	–	–

* Age- and gender-weighted group difference calculated by linear (for continuous variables) and logistic (for categorial variables) regression. Significance level is $P < 0.05$. Significant P values are in bold. [a] Unweighted analyses using the independent samples t test. Comedication includes csDMARDs (eg, MTX). ADA: adalimumab; anti-CPP: anticyclic citrullinated peptide; AS: ankylosing spondylitis; bDMARD: biological disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; ICD-10: International Classification of Diseases, 10th revision; IFX: infliximab; JIA: juvenile idiopathic arthritis; MTX: methotrexate; PsA: psoriatic arthritis; RA: rheumatoid arthritis; RF: rheumatoid factor; TNFi: tumor necrosis factor inhibitor.

Treatment response on VAS pain, VAS fatigue, MHAQ, and EQ-5D is presented in Supplementary Table S1.

- *Remission rates.* Patients with JIA and RA treated with MTX monotherapy did not have significant differences in absolute or LUNDEX-corrected remission rates at any timepoints (Figure 3; Supplementary Figure S1B, available with the online version of this article).
- *Drug survival.* Median drug survival was 1.3 years in JIA and 1.6 years in RA. Weighted log-rank tests showed no significant group differences in drug survival. Weighted Kaplan-Meier survival estimates are shown in Figure 2B.
- *Seropositive vs seronegative JIA.* Seropositivity did not affect baseline DAS28 score and ACR/EULAR remission rates. Except from DAS28 at 3 months, which was significantly more improved in seropositive JIA, results across both measures were equal between groups (Supplementary Table S2, available with the online version of this article).

DISCUSSION

The current study is among the largest exploring treatment effects of TNFi and the first, that we know of, to explore MTX monotherapy in adult patients with JIA.

We found that both TNFi ± comedication and MTX monotherapy are effective in treating disease activity in adult patients with JIA, with similar treatment effects to those in adult patients with RA. Weighted Kaplan-Meier survival analyses showed equal drug survival of TNFi and MTX in JIA and RA. As expected, adult patients with JIA had significantly longer disease duration than patients with RA when included in the study. Long-standing arthritis often leads to joint damage, which in turn can cause pain that is difficult to treat medically, hence

Table 2. Disease activity measures at baseline and change after 3, 6, and 12 months with age- and gender-weighted comparison of adult patients with JIA and RA starting TNFi ± comedication and MTX monotherapy.

	TNFi ± Comedication			MTX Monotherapy		
	JIA[a] n = 358	RA[a] n = 2292	Group Difference, JIA – RA[b]	JIA[a] n = 120	RA[a] n = 2345	Group Difference, JIA – RA[b]
ESR, mm/h						
Baseline	19.3 (18.7)	26.3 (22.2)	−1.5 (−4.3 to 1.3)	20.0 (17.6)	28.3 (22.0)	
	n = 308	n = 2014		n = 108	n = 2157	**−4.3 (−8.2 to −0.5)**
3-month change	−7.1 (15.1)	−7.7 (16.7)	−2.1 (−4.2 to 0.1)	−2.9 (14.8)	−9.0 (18.4)	
	n = 195	n = 1375		n = 75	n = 1586	**3.0 (0.0 to 6.1)**
6-month change	−5.7 (17.2)	−9.2 (18.8)	1.2 (−1.6 to 4.0)	−2.0 (16.2)	−10.7 (19.5)	
	n = 141	n = 1001		n = 59	n = 1232	3.0 (−1.2 to 7.3)
12-month change	−6.7 (16.0)	−9.1 (18.7)	−0.9 (−3.4 to 1.5)	−4.6 (14.3)	−11.4 (19.6)	
	n = 107	n = 804		n = 47	n = 1029	2.9 (−0.6 to 6.4)
CRP, mg/L						
Baseline	18.7 (14.2)	18.5 (25.2)	−1.5 (−4.5 to 1.5)	14.5 (16.8)	21.6 (26.8)	
	n = 343	n = 2176		n = 111	n = 2241	−2.3 (−6.0 to 1.3)
3-month change	−6.3 (16.3)	−9.1 (23.0)	−1.4 (−3.4 to 0.6)	−5.6 (15.2)	−9.6 (26.0)	
	n = 223	n = 1559		n = 82	n = 1684	−1.1 (−3.8 to 1.5)
6-month change	−6.9 (17.1)	−9.8 (24.6)	−0.5 (−3.1 to 2.0)	−3.9 (16.2)	−10.5 (25.9)	
	n = 167	n = 1147		n = 64	n = 1337	1.0 (−2.1 to 4.0)
12-month change	−5.9 (18.7)	−10.5 (23.7)	0.7 (−2.0 to 3.5)	−4.6 (15.3)	−12.2 (25.6)	
	n = 140	n = 920		n = 50	n = 1094	2.5 (−0.4 to 5.4)
SJC28						
Baseline	2.8 (3.8)	6.0 (5.5)	**−1.9 (−2.5 to −1.3)**	3.6 (4.6)	6.9 (5.7)	
	n = 341	n = 2208		n = 118	n = 2332	**−2.3 (−3.3 to −1.3)**
3-month change	−1.7 (3.6)	−3.3 (4.9)	0.2 (−0.7 to 0.3)	−1.6 (3.3)	−3.3 (5.4)	
	n = 238	n = 1638		n = 98	n = 1887	−0.3 (−1.0 to 0.3)
6-month change	−1.9 (3.4)	−3.8 (5.0)	−0.1 (−0.6 to 0.4)	−1.6 (3.1)	−4.0 (5.5)	
	n = 191	n = 1225		n = 71	n = 1508	−0.1 (−0.8 to 0.7)
12-month change	−1.8 (3.8)	−4.3 (5.0)	0.4 (−0.2 to 1.1)	−2.7 (4.7)	−4.7 (5.8)	
	n = 146	n = 966		n = 59	n = 1277	−0.3 (−0.9 to 0.3)
TJC28						
Baseline	4.5 (5.8)	7.2 (6.7)	**−1.6 (−2.4 to −0.8)**	4.5 (4.9)	7.9 (7.0)	
	n = 342	n = 2205		n = 118	n = 2322	**−3.0 (−4.1 to −1.9)**
3-month change	−2.2 (4.4)	−3.5 (6.2)	0.1 (−0.5 to 0.6)	−0.8 (4.1)	−3.2 (7.3)	
	n = 238	n = 1635		n = 98	n = 1876	−0.1 (−1.1 to 0.9)
6-month change	−2.5 (4.4)	−4.0 (6.4)	0.0 (−0.7 to 0.7)	−1.4 (3.6)	−3.8 (6.8)	
	n = 192	n = 1222		n = 71	n = 1501	0.3 (−0.8 to 1.4)
12-month change	−2.3 (4.6)	−4.3 (6.2)	0.5 (−0.3 to 1.2)	−2.0 (4.8)	−4.5 (6.9)	
	n = 147	n = 961		n = 59	n = 1273	0.4 (−0.6 to 1.3)
DAS28 (with CRP)						
Baseline	3.7 (1.3)	4.4 (1.4)	**−0.4 (−0.6 to −0.2)**	3.9 (1.1)	4.6 (1.2)	
	n = 328	n = 2108		n = 110	n = 2223	**−0.5 (−0.7 to −0.2)**
3-month change	−1.0 (1.1)	−1.2 (1.3)	−0.1 (−0.3 to 0.1)	−0.6 (1.1)	−1.1 (1.4)	
	n = 213	n = 1488		n = 81	n = 1659	0.0 (−0.2 to 0.3)
6-month change	−1.0 (1.1)	−1.4 (1.4)	0.1 (−0.1 to 0.3)	−0.7 (1.2)	−1.2 (1.4)	
	n = 157	n = 1104		n = 64	1317	0.2 (−0.1 to 0.5)
12-month change	−1.0 (1.2)	−1.5 (1.3)	0.3 (0.0 to 0.5)	−0.8 (1.3)	−1.5 (1.5)	
	n = 132	n = 879		n = 50	n = 1075	0.3 (−0.0 to 0.6)
SDAI						
Baseline	17.9 (11.0)	24.6 (14.6)	**−3.3 (−5.1 to −1.5)**	17.9 (11.0)	25.9 (13.6)	
	n = 292	n = 1928		n = 108	n = 2152	**−5.9 (−8.4 to −3.4)**
3-month change	−8.2 (10.1)	−11.7 (13.0)	−0.1 (−1.7 to 1.5)	−5.7 (9.3)	−10.4 (13.9)	
	n = 185	n = 1311		n = 79	n = 1559	−0.0 (−2.2 to 2.2)
6-month change	−8.4 (8.8)	−13.2 (13.4)	1.7 (−0.2 to 3.5)	−5.6 (8.3)	−12.3 (14.2)	
	n = 139	n = 982		n = 61	n = 1240	1.9 (−0.5 to 4.2)
12-month change	−8.6 (9.8)	−14.4 (13.1)	2.5 (0.6 to 4.4)	−8.7 (11.6)	−14.1 (14.6)	
	n = 119	n = 775		n = 48	n = 1015	0.9 (−1.4 to 3.3)

Table 2. Continued.

	TNFi ± Comedication			MTX Monotherapy		
	JIA[a] n = 358	RA[a] n = 2292	Group Difference, JIA – RA[b]	JIA[a] n = 120	RA[a] n = 2345	Group Difference, JIA – RA[b]
CDAI						
Baseline	16.5 (10.5) n = 303	22.6 (13.5) n = 2009	**–3.0 (–4.6 to –1.3)**	16.3 (10.4) n = 116	23.6 (12.8) n = 2244	–5.6 (–7.9 to –3.3)
3-month change	–8.0 (9.8) n = 207	–10.7 (12.2) n = 1425	–0.3 (–1.7 to 1.2)	–4.7 (8.3) n = 96	–9.5 (13.1) n = 1755	0.4 (–1.5 to 2.3)
6-month change	–8.5 (8.8) n = 171	–12.1 (12.6) n = 1080	0.8 (–0.7 to 2.4)	–4.9 (7.7) n = 67	–11.1 (13.1) n = 1405	1.7 (–0.5 to 3.9)
12-month change	–8.1 (9.3) n = 131	–13.2 (12.3) n = 842	2.3 (0.5 to 3.9)	–8.1 (10.4) n = 56	–12.9 (13.6) n = 1196	0.6 (–1.4 to 2.6)
PtGA						
Baseline	52.9 (25.8) n = 344	51.0 (25.4) n = 2216	**4.4 (0.9 to 8.0)**	50.6 (24.4) n = 118	48.4 (24.2) n = 2294	4.5 (–0.6 to 9.5)
3-month change	–22.1 (26.3) n = 241	–17.6 (26.9) n = 1624	–1.8 (–5.3 to 1.8)	–11.5 (26.0) n = 99	–14.0 (26.3) n = 1826	3.9 (–0.9 to 8.7)
6-month change	–23.0 (24.9) n = 195	–19.5 (27.7) n = 1234	0.9 (–3.1 to 4.9)	–10.0 (24.6) n = 69	–13.8 (26.5) n = 1463	5.5 (–0.1 to 11.0)
12-month change	–21.9 (28.6) n = 154	–20.9 (27.6) n = 963	4.0 (–0.7 to 8.6)	–16.0 (25.4) n = 58	–14.5 (26.4) n = 1250	1.3 (–4.9 to 7.5)
PGA						
Baseline	35.7 (18.0) n = 322	39.4 (19.7) n = 2078	–0.8 (–3.5 to 1.9)	29.8 (16.7) n = 118	39.1 (18.4) n = 2304	–8.7 (–12.2 to –5.1)
3-month change	–35.6 (25.7) n = 229	–29.6 (26.2) n = 1579	–7.5 (–11.7 to –3.4)	–32.3 (24.8) n = 97	–25.8 (25.8) n = 1844	**–10.2 (–15.6 to –4.8)**
6-month change	–37.4 (24.3) n = 186	–31.8 (26.3) n = 1176	–6.3 (–10.7 to 1.9)	–26.9 (24.1) n = 69	–27.9 (25.5) n = 1476	–3.5 (–9.9 to 3.0)
12-month change	–35.3 (26.1) n = 148	–32.8 (26.4) n = 940	–4.8 (–10.0 to 0.4)	–34.1 (25.5) n = 57	–29.6 (24.8) n = 1254	**–9.9 (–16.8 to –3.1)**

[a] Units are mean (SD). [b] Adjusted difference between groups in change of disease activity from baseline to 3-, 6-, and 12-months of follow-up (JIA change minus RA change; JIA – RA [95% CI]). Significant values are in bold. Comedication includes csDMARDs (eg, MTX). CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; JIA: juvenile idiopathic arthritis; MTX: methotrexate; PGA: physician global assessment; PtGA: patient global assessment; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints; TNFi: tumor necrosis factor inhibitor.

potentially leading to a reduced treatment response. Our results did not, however, indicate inferior treatment responses in adult JIA, strengthening the hypothesis that both MTX and TNFi are efficient treatment options in adult patients with JIA with long-standing disease.

A unique feature of this study is that it investigates both the effects of TNFi and the effects of MTX monotherapy in adult patients with JIA from the same source population, using data from a real-life observational cohort. Although previous studies report TNFi as safe in both adults[17,18] and children[18,38-43] with JIA, there is a need for studies confirming the efficacy of TNFi treatment in adult patients with JIA to support its use in this patient group. Real-life observational studies provide information that complements results from randomized controlled trials (RCTs), as they usually have less strict inclusion and exclusion criteria, making them suitable for exploring real-life treatment effects and treatment survival across large patient groups with well-defined clinical diagnoses. Still, RCTs are the gold standard in assessing treatment efficacy, and the need for RCTs evaluating the efficacy of TNFi and MTX in adult patients with JIA is currently unmet.

In patients starting TNFi treatment, our study reports significantly higher 3-month DAS28 remission rates in JIA vs RA, potentially as a result of lower disease activity in adult JIA at baseline. At 6 months these differences are insignificant, and by 12 months, DAS28 remission rates are 55.2% and 49.5% in JIA and RA, respectively. Treatment effects of bDMARDs in adult patients with JIA were previously explored in 2 studies using data from the British Society for Rheumatology Biologics Register (BSRBR).[17,19] The most recent of these 2 studies explored the effectiveness of TNFi in adult patients with JIA compared to adult patients with RA and reported 1-year DAS28 remission rates of 27% for adult patients with JIA and 26% for patients with RA. McErlane et al reported similar DAS28 remission rates (28%) in adult patients with JIA receiving bDMARD treatment, with 94% starting TNFi treatment.[19] Our study reports considerably higher 1-year DAS28 remission rates, possibly explained by higher baseline DAS28 in adult patients with JIA in BSRBR (6.2-6.3)[17,19] than in NOR-DMARD (3.7). Another potential explanation is the easier access to bDMARDs in Norway for many years, and the introduction to modern treatment strategies with tight control and treat-to-target in more recent years. However,

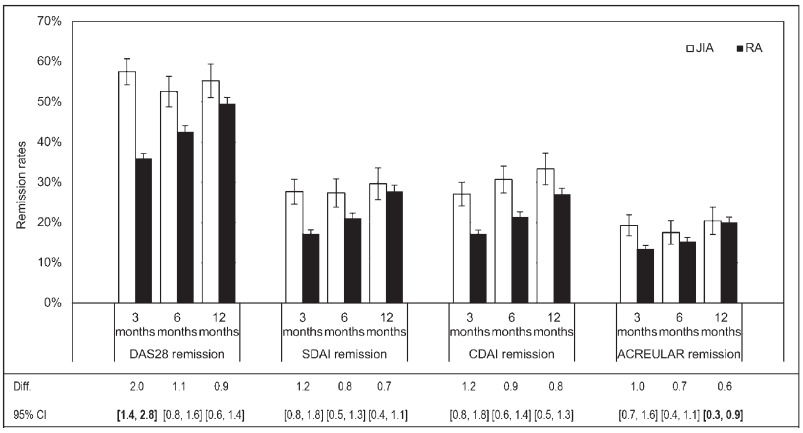

Figure 1. Remission rates after 3, 6, and 12 months in adult patients with JIA and patients with RA treated with TNFi ± comedication. Comedication includes csDMARDs (eg, MTX). Diff. is the age- and gender-weighted difference between patients with JIA and RA presented with JIA OR. The error bars represent standard error. ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; DAS28: Disease Activity Score in 28 joints; EULAR: European Alliance of Associations for Rheumatology; JIA: juvenile idiopathic arthritis; MTX: methotrexate; OR: odds ratio; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index; TNFi: tumor necrosis factor inhibitor.

the association between DAS28 remission rates and accessibility to bDMARDs and modern treatment strategies remains hypothetical. Still, our study highlights that 1-year DAS28 remission rates in patients with JIA and RA starting treatment with TNFi ± comedication are statistically comparable.

A study published in 2016 using data from the Portuguese national register (Reuma.pt) found TNFi to be safe and effective at 6 months and 1 year after treatment initiation in biologic-naïve children and adults with JIA.[18] Our findings of reduction in ESR and SJC28 (Table 2) were similar to the findings of Mourão et al.[18] Still, it is important to note that only 30.4% of the patients in the study from Portugal were adults, compared to 100% in our study. Mourão et al[18] measured remission rates using the delta Juvenile Disease Activity Score (JADAS) and the JADAS10, which was not used in our study, complicating a comparison of the remission rates. Further, neither JADAS/JADAS10 nor the remission rate measures used in our study are validated for adult patients with JIA, illustrating the need for studies aiming to validate the use of single and composite disease activity measures in adult patients with JIA.

Median treatment duration was found to be higher in both Reuma.pt and BSRBR than the mean drug survival of TNFi in patients with JIA in our study (5.8 years in Reuma.pt[18] and 6.1 years in BSRBR[17] vs 1.2 years in NOR-DMARD). Notably, Reuma.pt reports treatment survival for bDMARDs, and not exclusively for TNFi, but 90.3% of patients started treatment with TNFi. Possible explanations for the differences in treatment survival are differences in inclusion criteria. Mourão et al included both children and adults, with a mean age of 16.2 years at inclusion.[18] In the survival analyses, only patients with a follow-up period of at least 1 year were included. Both the study of Kearsley-Fleet et al[17] and our study only included adults, and all patients in the survival analyses, regardless of follow-up time. Both Kearsley-Fleet et al and Mourão et al included patients starting treatment with TNFi and bDMARDs for the first time, respectively,[17,18] whereas we also included patients previously treated with bDMARDs.

In patients with RA starting TNFi treatment, we found a median drug survival of 1.4 years, confirming the findings of a previous study published in 2018 using data from the pan-European Tocilizumab Collaboration of European Registries in RA (TOCERRA) register, which, like our study, included patients previously treated with bDMARDs.[44] In 2020, a study from the same register was published, reporting significantly higher median retention for combination TNFi (ie, TNFi with csDMARDs; 4.1 yrs) and TNFi monotherapy (3.0 yrs) in biologic-naïve patients with RA compared to both our study and the 2018 TOCERRA study.[45] This may illustrate that patients previously treated with bDMARDs might have more refractory disease and be more resistant to DMARD therapy. It is also reassuring that TNFi has comparable drug survival in patients with JIA vs RA.

Our study has several limitations. The NOR-DMARD register only includes patients starting or switching DMARD treatment in adulthood, indicating a selected group of patients with JIA with disease flares. Today, most patients with JIA are treated with TNFi or MTX as children. Some will continue their treatment regimen into adulthood, hence they are not included in our analyses. However, patients are included if they switch treatment regimen after the age of 18 years. Also, patients with systemic JIA are not included in the data material. Therefore, our results may not be representative to all adult patients with JIA in Norway.

NOR-DMARD included patients treated with MTX from 2000 to 2012, whereas patients treated with bDMARDs were included from 2000 onward. Therefore, our results represent

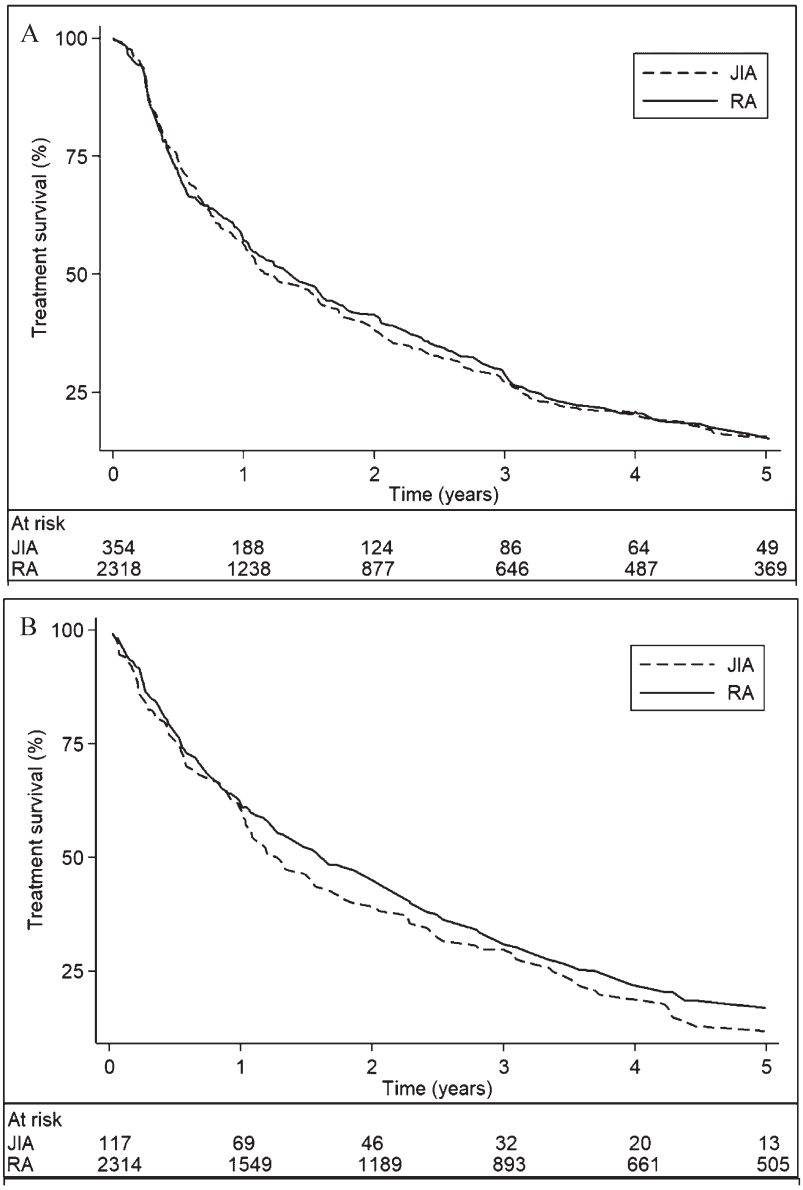

Figure 2. (A) Five-year age- and gender-weighted drug survival of TNFi ± comedication in JIA and RA. (B) Five-year age- and gender-weighted drug survival of MTX monotherapy in JIA and RA. "At risk" indicates the number of patients still on the drug. Comedication includes csDMARDs (eg, MTX). csDMARD: conventional synthetic disease-modifying antirheumatic drug; JIA: juvenile idiopathic arthritis; MTX: methotrexate; RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitors.

MTX data from at least a decade ago. Still, this should not affect our outcomes as we compare drug effectiveness in JIA vs RA and not MTX vs TNFi.

In lack of validated disease activity measures for adult patients with JIA, measures developed for patients with RA were used. JIA-specific measures such as active joint count in 71 joints including limited range of motion were unavailable. The fact that JIA is a heterogenous disease, and disease manifestations differ considerably between ILAR subtypes, also complicates the use of measures not validated for patients with JIA. It would be preferable to stratify the JIA population into ILAR subtypes, but this information was not available. Although RA differs from JIA in several ways, we considered it the most suitable control group as important features of the disease are identified by the available disease activity measures like DAS28 and CDAI. However, our finding of significantly higher disease activity (as measured by RA-specific measures) and correspondingly lower remission rates in patients with seropositive compared to seronegative JIA starting TNFi highlights the limitations to this approach.

Observational studies recruiting patients with JIA during childhood with long-term follow-up into adulthood are highly needed to obtain a better understanding of long-term treatment effectiveness in patients with JIA and treatment effectiveness in adulthood compared to childhood. Such study design would

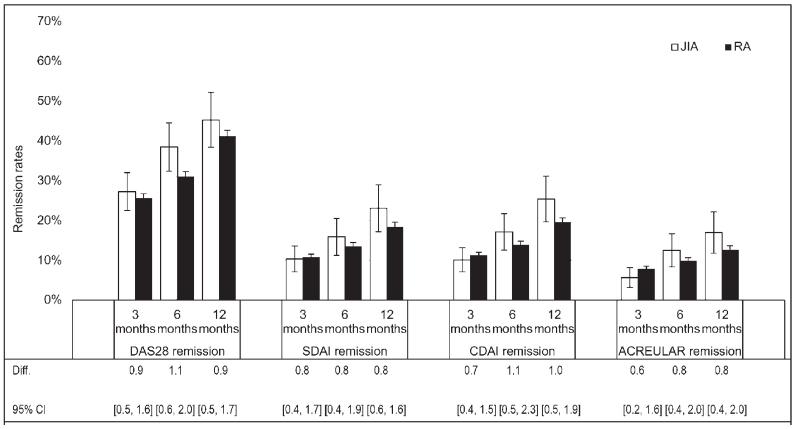

Figure 3. Remission rates after 3, 6, and 12 months in adult patients with JIA and patients with RA treated with MTX monotherapy. Diff. is the age- and gender-weighted difference between patients with JIA and RA presented with JIA OR. The error bars represent standard error. ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; EULAR: European Alliance of Associations for Rheumatology; JIA: juvenile idiopathic arthritis; MTX: methotrexate; OR: odds ratio; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index.

possibly eliminate biases occurring with transferal from pediatric to adult services,[46] as well as being more representative to patients with JIA in general.

In conclusion, these real-life data from the NOR-DMARD study showed that TNFi and MTX have similar effectiveness in reducing disease activity and inducing clinical remission in adult patients with JIA and patients with RA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet 2011;377:2138-49.
2. Feger DM, Longson N, Dodanwala H, Ostrov BE, Olsen NJ, June RR. Comparison of adults with polyarticular juvenile idiopathic arthritis to adults with rheumatoid arthritis: a cross-sectional analysis of clinical features and medication use. J Clin Rheumatol 2019;25:163-70.
3. Minden K, Niewerth M, Listing J, et al. Long-term outcome in patients with juvenile idiopathic arthritis. Arthritis Rheum 2002;46:2392-401.
4. Zak M, Pedersen FK. Juvenile chronic arthritis into adulthood: a long-term follow-up study. Rheumatology 2000;39:198-204.
5. Bertilsson L, Andersson-Gäre B, Fasth A, Petersson IF, Forsblad-D'elia H. Disease course, outcome, and predictors of outcome in a population-based juvenile chronic arthritis cohort followed for 17 years. J Rheumatol 2013;40:715-24.
6. Selvaag AM, Aulie HA, Lilleby V, Flatø B. Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. Ann Rheum Dis 2016;75:190-5.
7. Glerup M, Rypdal V, Arnstad ED, et al; Nordic Study Group of Pediatric Rheumatology. Long-term outcomes in juvenile idiopathic arthritis: eighteen years of follow-up in the population-based Nordic juvenile idiopathic arthritis cohort. Arthritis Care Res 2020; 72:507-16.
8. Giancane G, Muratore V, Marzetti V, et al. Disease activity and damage in juvenile idiopathic arthritis: methotrexate era versus biologic era. Arthritis Res Ther 2019;21:168.
9. Minden K. Adult outcomes of patients with juvenile idiopathic arthritis. Horm Res 2009;72:20-5.
10. Magni-Manzoni S, Pistorio A, Labò E, et al. A longitudinal analysis of physical functional disability over the course of juvenile idiopathic arthritis. Ann Rheum Dis 2008;67:1159-64.
11. Tollisen A, Selvaag AM, Aulie HA, et al. Physical functioning, pain, and health-related quality of life in adults with juvenile idiopathic arthritis: a longitudinal 30-year followup study. Arthritis Care Res 2018;70:741-9.
12. Rebane K, Ristolainen L, Relas H, et al. Disability and health-related quality of life are associated with restricted social participation in young adults with juvenile idiopathic arthritis. Scand J Rheumatol 2019;48:105-13.
13. Petty RE, Southwood TR, Manners P, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
14. Ringold S, Weiss PF, Colbert RA, et al; Juvenile Idiopathic Arthritis Research Committee of the Childhood Arthritis and Rheumatology Research Alliance. Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for new-onset polyarticular juvenile idiopathic arthritis. Arthritis Care Res 2014;66:1063-72.
15. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis: a revolution in care. Pediatr Rheumatol Online J 2014;12:13.
16. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis in the biologic age. Rheum Dis Clin North Am 2013;39:751-66.
17. Kearsley-Fleet L, McErlane F, Foster HE, et al. Effectiveness and safety of TNF inhibitors in adults with juvenile idiopathic arthritis. RMD Open 2016;2:e000273.
18. Mourão AF, Santos MJ, Melo Gomes JA, et al. Effectiveness and long-term retention of anti-tumour necrosis factor treatment in juvenile and adult patients with juvenile idiopathic arthritis: data from Reuma.pt. Rheumatology 2016;55:697-703.
19. McErlane F, Foster HE, Davies R, et al. Biologic treatment response among adults with juvenile idiopathic arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2013;52:1905-13.
20. Kvien TK, Heiberg, Lie E, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients

with inflammatory rheumatic diseases. Clin Exp Rheumatol 2005;23:S188-94.
21. Norvang V, Sexton J, Kristianslund EK, et al. Predicting achievement of the treatment targets at 6 months from 3-month response levels in rheumatoid arthritis: data from real-life follow-up in the NOR-DMARD study. RMD Open 2018;4:e000773.
22. Aga AB, Lie E, Uhlig T, et al. Time trends in disease activity, response and remission rates in rheumatoid arthritis during the past decade: results from the NOR-DMARD study 2000-2010. Ann Rheum Dis 2015;74:381-8.
23. Olsen IC, Haavardsholm EA, Moholt E, Kvien TK, Lie E. NOR-DMARD data management: implementation of data capture from electronic health records. Clin Exp Rheumatol 2014; 32:S158-62.
24. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
25. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009;68:954-60.
26. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology 2003;42:244-57.
27. Greenberg JD, Harrold LR, Bentley MJ, Kremer J, Reed G, Strand V. Evaluation of composite measures of treatment response without acute-phase reactants in patients with rheumatoid arthritis. Rheumatology 2009;48:686-90.
28. Harrington JT. The uses of disease activity scoring and the physician global assessment of disease activity for managing rheumatoid arthritis in rheumatology practice. J Rheumatol 2009;36:925-9.
29. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 1983;26:1346-53.
30. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
31. Nikiphorou E, Radner H, Chatzidionysiou K, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016;18:251.
32. van Riel PL, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis 2000;59 Suppl 1:i28-31.
33. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 2005;52:2625-36.
34. Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. Rheum Dis Clin North Am 2006;32:9-44.
35. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404-13.
36. Ghali WA, Quan H, Brant R, et al. Comparison of 2 methods for calculating adjusted survival curves from proportional hazards models. JAMA 2001;286:1494-7.
37. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. Arthritis Rheum 2006;54:600-6.
38. Armaroli G, Klein A, Ganser G, et al. Long-term safety and effectiveness of etanercept in JIA: an 18-year experience from the BiKeR registry. Arthritis Res Ther 2020;22:258.
39. Klotsche J, Niewerth M, Haas JP, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis 2016;75:855-61.
40. Tarkiainen M, Tynjälä P, Vähäsalo P, Lahdenne P. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. Rheumatology 2015;54:1170-6.
41. Prince FH, Twilt M, ten Cate R, 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.
42. Verazza S, Davì S, Consolaro A, et al; Italian Pediatric Rheumatology Study Group. Disease status, reasons for discontinuation and adverse events in 1038 Italian children with juvenile idiopathic arthritis treated with etanercept. Pediatr Rheumatol Online J 2016;14:68.
43. Brunner HI, Nanda K, Toth M, et al; Paediatric Rheumatology International Trials Organisation, Pediatric Rheumatology Collaborative Study Group. Safety and effectiveness of adalimumab in patients with polyarticular course of juvenile idiopathic arthritis: STRIVE registry seven-year interim results. Arthritis Care Res 2020;72:1420-30.
44. Lauper K, Nordström DC, Pavelka K, et al. Comparative effectiveness of tocilizumab versus TNF inhibitors as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis after the use of at least one biologic disease-modifying antirheumatic drug: analyses from the pan-European TOCERRA register collaboration. Ann Rheum Dis 2018;77:1276-82.
45. Lauper K, Mongin D, Iannone F, et al. Comparative effectiveness of TNF inhibitors and tocilizumab with and without conventional synthetic disease-modifying antirheumatic drugs in a pan-European observational cohort of bio-naïve patients with rheumatoid arthritis. Semin Arthritis Rheum 2020;50:17-24.
46. McDonagh JE. Transition of care from paediatric to adult rheumatology. Arch Dis Child 2007;92:802-7.