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Short running head: Adult JIA DMARD response

Full title of manuscript: 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: Compare effectiveness of tumor necrosis factor inhibitors (TNFi) ± comedication and methotrexate monotherapy (MTX mono) between adult juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA) patients.

Methods: Adult JIA and RA patients were identified from the NOR-DMARD register. Disease activity measurements at baseline, 3, 6 and 12 months were compared between JIA and RA patients starting (1) TNFi and (2) MTX monotherapy, using age- and gender-weighted analyses. We calculated differences between JIA and RA in mean changes in DAS28, CDAI and SDAI, among other disease activity measures. DAS28, CDAI, SDAI and ACR/EULAR remission rates at 3, 6 and 12 months, as well as 6- and 12-month LUNDEX-corrected rates, were calculated.

Results: We identified 478 JIA patients (TNFi/MTX mono N=358/120) and 4637 RA patients (N=2292/2345). JIA patients had lower baseline disease activity compared to RA patients 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 follow-up between JIA and RA patients for either treatment group. 12-month remission rates were similar between groups based on DAS28 (TNFi: JIA 55.2%, RA 49.5%. MTX mono: JIA 45.3%, RA 41.2%) and ACR/EULAR remission criteria (TNF: JIA 20.4%, RA 20.0%. MTX mono: JIA 17.0%, RA 12.7%). Median drug survival (years) was similar for JIA and RA in both treatment groups (TNFi: JIA 1.2, RA 1.4; MTX mono: JIA 1.3, RA 1.6)

Conclusion: TNFi and MTX mono are effective in adult JIA, with similar effectiveness as in RA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the common term for a group of chronic inflammatory arthritis conditions with disease onset before the age of 16.[1] Several long-term outcome studies show that about 50% of children diagnosed with JIA have active arthritis in adulthood.[2-7] While the disease course is variable among patients, JIA can cause considerable pain and disability, affect health-related outcomes,[1,8] and have a negative impact 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, in the following order: nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoid steroids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and/or biologic DMARDs (bDMARDs), with the latter confined to patients not responding to first-line treatment. While the csDMARD methotrexate (MTX) still is the cornerstone treatment for JIA in most subtypes, use of bDMARDs has increased dramatically since the first approvals of this drug class for JIA two 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 JIA patients with disease activity persisting into adulthood, the knowledge base on treatment effects in adult JIA patients 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, no study has to our knowledge specifically explored effectiveness of MTX monotherapy in adult JIA patients. 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 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 disease-modifying anti-rheumatic drug study

We used data from the Norwegian disease-modifying anti-rheumatic drug study (NOR-DMARD), an ongoing prospective, longitudinal observational study initiated in year 2000 including six rheumatology centers, covering about 1/3 of the Norwegian population.[20-23] NOR-DMARD enrolls patients over 18 years of age 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 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-recorded outcomes are reported. Assessments and data collection is 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 (≥ 18 years of age) registered with (1) a clinical diagnosis of JIA (ICD10 M08 or M09), or (2) a clinical diagnosis of RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS) or undifferentiated arthritis, who received the diagnosis before the age of 16 years. If 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 re-included every time they switch treatment. In case of multiple inclusions for one patient, only the first treatment course within each treatment group was included in our analyses, i.e. 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 of 28 joints (SJC-28 and TJC-28), **(3) calculated composite scores:** disease activity score 28 (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 analogue scale (VAS) assessment of global disease activity (PHGA),[28] and **(5) patient-reported outcomes (PROMs):** modified health assessment questionnaire (MHAQ),[29] EuroQol-5 Dimension questionnaire (EQ5D)[30] and 0-100 mm VAS for pain, fatigue and patients global assessment

(PGA).[31]. To define remission, we used the established cut-offs DAS28 < 2.6,[32] SDAI ≤ 3.3,[33] CDAI ≤ 2.8,[34] and the joint American college of rheumatology and the European Alliance of Associations for Rheumatology remission criteria (ACR/EULAR remission).[35]

STATISTICAL ANALYSIS

Significance levels were set at $p<0.05$ in all analyses. Statistical analyses were performed using StataSE 16 (64-bit) for Windows.

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 follow-up and compared between JIA patients 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, non-weighted 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 while RA observations were weighted according to the number of JIA patients in the relevant age and gender group divided by the number of RA patients the same in age and gender group. For example, in the group starting treatment with TNFi there were 134 female JIA patients and 330 female RA patients aged 30-35

years at inclusion. Consequently, each female RA patient aged 30-35 years received a weight of 134/330. Hence, some observations have greater impact 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 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 JIA and RA patients 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 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 five-year median drug survival.

LUNDEX

In the treatment response analyses, only patients adhering to treatment were included. This can introduce selection bias in at least two 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 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] x [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 JIA patients, 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 as 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 seropositive and seronegative JIA patients. Seropositivity was defined as being RF- and/or anti-CCP positive. Statistical methods were similar as in the primary analyses.

RESULTS

TNFi ± comedication

Baseline demographics and -disease activity

358 JIA patients and 2292 RA patients 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 SJC-28, TJC-28, DAS28, SDAI and CDAI compared to RA (**table 2**), and significantly greater baseline score in VAS fatigue, VAS joint pain and PGA (**table S1**).

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 EQ5D are presented in the data supplement (**table S1**).

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 JIA patients than in RA patients. 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 JIA and RA patients at 6- and 12-month follow-ups (**figure S1a**).

Drug survival

Median drug survival was 1.2 years for JIA patients and 1.4 years for RA patients. 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 3a.**

Sensitivity analysis

Biologic-naïve JIA and RA patients had similar remission rates (**figure S2a**)**.** LUNDEX-corrected remission rates did not show any substantial differences between JIA and RA at 6- and 12-month follow-up (**figure S2b**). 5-year treatment survival was similar between JIA (1.5 years) and RA (1.5 years) (**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. ACREULAR remission was significantly higher in seronegative JIA (**table S2**).

MTX monotherapy

Baseline demographics and disease activity

We included 120 JIA patients and 2345 RA patients starting treatment with MTX monotherapy. JIA patients had significantly lower baseline scores for ESR, SJC-28, TJC-28, DAS28 and SDAI than RA patients (**table 2**). Like the TNFi treatment group, mean age and gender distribution differed significantly between JIA and RA patients, and age- and gender-weighted analyses showed significant differences between JIA and RA patients 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 (**table S1**), and a significantly greater improvement in PHGA after 3 and 12 months in JIA compared to RA (**table S1**). The other disease activity measures were not significantly different. Treatment response on VAS pain, VAS fatigue, MHAQ and EQ5D is presented in the data supplementary (**table S1**).

Remission rates

JIA and RA patients treated with MTX monotherapy did not have significant differences in absolute or LUNDEX-corrected remission rates at any timepoints (**figure 2** and **figure S1b**).

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 3b**.

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 (**table S2**).

DISCUSSION

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

We found that both TNFi ± comedication and MTX monotherapy are effective in treating disease activity in adult JIA patients, with similar treatment effects as in adult RA patients. Weighted Kaplan-Meier survival analyses showed equal drug survival of TNFi and MTX in JIA and RA. As expected, the adult JIA patient had a 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 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 JIA patients 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 JIA patients from the same source population, using data from a real-life observational cohort. While 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 JIA patients to support its use in this patient group. Real-life observational studies provide information that complement 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 is the gold-standard in assessing treatment efficacy, and the need for RCTs evaluating efficacy of TNFi and MTX in adult JIA patients is currently unmet.

In patients starting TNFi treatment, our study reports significantly higher 3-month DAS28 remission rates in JIA vs. RA, potentially due to 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 JIA patients were previously explored in two studies using data from the British Society for Rheumatology Biologics Register (BSRBR).[19,17] The most recent of these two studies explored the effectiveness of TNFi in adult JIA patients compared to adult RA patients and reported 1-year DAS28 remission rates of 27% for adult JIA patients and 26% for RA patients. McErlane et al. reported similar DAS28 remission rates (28%) in adult JIA patients 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 JIA patients in BSRBR (6.2-6.3)[17,19] than in NOR-DMARD (3.7). Another potential explanation is easier access to bDMARDs in Norway for many years and introduction to modern treatment strategies with tight control and treat to target in more recent years. However, 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 JIA and RA patients 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 SJC (**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. 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. Furthermore, neither JADAS/JADAS10 nor the remission rate measures used in our

study are validated for adult JIA patients, illustrating the need for studies aiming to validate the use of single and composite disease activity measures in adult JIA patients.

Median treatment duration was found to be higher in both Reuma.pt and BSRBR than the mean drug survival of TNFi in JIA patients 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 of 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. 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. 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, while we also included patients previously treated with bDMARDs.

In RA patients 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 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 TNFi-combo (4.1 years) and TNFi-mono, (3.0 years) in biologic-naïve RA patients 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 JIA vs. RA patients.

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

NOR-DMARD included patients treated with MTX from 2000 to 2012, whereas patients treated with bDMARDs were included from 2000 and onwards. Therefore, our results represent 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 JIA patients, measures developed for RA-patients was used. JIA-specific measures such as 71 active joint count including limited range of motion was unavailable. The fact that JIA is a heterogenous disease, and that disease manifestations differ considerably between ILAR subtypes also complicates the use of measures not validated for JIA patients. 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 captured 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 seropositive compared to seronegative JIA starting TNFi highlights the limitations to this approach.

Observational studies recruiting JIA patients during childhood with long-term follow-up into adulthood are highly needed to obtain a better understanding of long-term treatment effectiveness in JIA patients, and treatment effectiveness in adulthood compared to childhood. Such study design would possibly eliminate biases occurring with transferal from pediatric to adult services,[46] as well as being more representative to JIA patients 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 JIA patients and RA patients.

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Figure and table legends

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

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

Figure 1: Remission rates after 3, 6 and 12 months in adult JIA and RA patients treated with TNFi ± comedication

Figure 2: Remission rates after 3, 6 and 12 months in adult JIA and RA patients treated with MTX monotherapy

Figure 3a: Five-year age- and gender-weighted drug survival of TNF ± comedication in JIA and RA

Figure 3b: Five-year age- and gender-weighted drug survival of MTX monotherapy in JIA and RA

Figure S1a: TNFi ± comedication 6 - and 12 -month disease activity rates – LUNDEX values

Figure S1b: MTX monotherapy 6 - and 12 -month disease activity rates – LUNDEX values

Table S1: Disease activity measures at baseline and change after 3, 6 and 12 months with age- and gender weighted comparison of adult JIA and RA patients starting TNFi ± comedication and MTX monotherapy

Figure S2a: Sensitivity analysis. Remission rates after 3, 6 and 12 months in adult biologic-naïve JIA and RA patients treated with TNFi ± comedication for the first time

Figure S2b: Sensitivity analysis. 6- and 12-month disease activity rates in adult biologic-naïve JIA and RA patients treated with TNFi ± comedication for the first time – LUNDEX values

Figure S2c: Sensitivity analysis. Five-year age- and gender-weighted treatment survival in adult biologic-naïve JIA and RA patients treated with TNF ± comedication for the first time

Table S2: DAS28 and ACR/EULAR remission rates at baseline and after 3, 6 and 12 months in seropositive vs. seronegative JIA patients starting treatment with TNFi ± comedication or MTX monotherapy

Figure S3a: Five-year drug survival of TNF ± comedication in seropositive and seronegative JIA patients

Figure S3b: Five-year drug survival of MTX mono in seropositive and seronegative JIA patients

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

	TNFi ± comedication			**MTX monotherapy**		
	JIA N=358	**RA N=2,292**	**P-value***	**JIA N=120**	**RA N=2,345**	**P-value***
Age, years, mean (SD)**	33.1 (11.2) N=358	53.1 (13.9) N=2,288	<0.001	35.7 (12.6) N=119	56.4 (13.6) N=2,342	<0.001
Female gender, n (%)**	249 (69.9) N=356	1,657 (72.5) N=2,286	0.43	98 (82.4) N=119	1,643 (70.2) N=2,340	<0.005
Diagnosis duration, years, mean (SD)	23.6 (12.0) N=241	9.4 (9.3) N=1,905	**<0.001**	24.5 (12.7) N=113	4.7 (8.4) N=2,303	**<0.001**
Anti-CCP positive, n (%)	26 (20.2) N=129	656 (73.0) N=899	**<0.001**	5 (10.2) N=49	668 (66.8) N=1,000	**<0.001**
Rheumatoid factor positive, n (%)	46 (22.3) N=206	1,070 (75.3) N=1,422	**<0.001**	24 (21.4) N=112	1,445 (62.9) N=2,296	**<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=2,269	**<0.001**	8 (6.7) N=119	69 (3.0) N=2,342	**0.013**
No. of previous bDMARDs, mean (SD)	0.6 (1.0) N=354	0.3 (0.7) N=2,269	**<0.001**	0.11 (0.4) N=120	0.05 (0.3) N=2,345	0.13
Previous use of MTX, n (%)	271 (76.6)	1,922 (84.9)	**0.03**	44 (37.0) N=119	363 (15.5) N=2,342	**<0.001**

	N=354	N=2,265				
Concomitant use of csDMARDs, n (%)	209 (58.4) N=358	1,697 (74.2) N=2,288	0.06	-	-	-
TNFi, n (%)	N=358	N=2,292	-	-	-	-
Adalimumab	85 (23.7)	510 (22.3)	0.96	-	-	-
Certolizumab	53 (14.8)	349 (15.2)	0.98	-	-	-
Etanercept	139 (38.8)	899 (39.2)	0.64	-	-	-
Golimumab	18 (5.0)	80 (3.5)	0.59	-	-	-
Infliximab	63 (17.6)	454 (19.8)	0.85	-	-	-

* Age – and gender weighted group difference calculated by linear (continuous variables) and logistic (categorial variables), significance level: p<0.05. **Significant p-values are in bold.**

**Unweighted analyses using the independent samples t-test.

JIA, juvenile idiopathic arthritis; **RA**, rheumatoid arthritis; **TNFi**, tumor necrosis factor inhibitors; **comedication,** csDMARDs, e.g. methotrexate**; MTX**, methotrexate; **Anti-CCP**, anti-cyclic citrullinated peptide; **ICD-10**, International Classification of Diseases, tenth revision; **PsA**, psoriatic arthritis; **AS**, ankylosing spondylitis, **bDMARD**, biological disease-modifying anti-rheumatic drug; **csDMARD**, conventional synthetic disease-modifying anti-rheumatic drug.

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

	TNFi ± comedication			**MTX monotherapy**		
	JIA N=358	**RA N=2,292**	**Group difference, JIA-RA****	**JIA* N=120**	**RA* N=2,345**	**Group difference, JIA-RA****
ESR*, mm/h						
Baseline	19.3 (18.7) N=308	26.3 (22.2) N=2,014	-1.5 [-4.3, 1.3]	20.0 (17.6) N=108	28.3 (22.0) N=2,157	**-4.3 [-8.2, -0.5]**
3-month change	-7.1 (15.1) N=195	-7.7 (16.7) N=1,375	-2.1 [-4.2, 0.1]	-2.9 (14.8) N=75	-9.0 (18.4) N=1,586	**3.0 [0.0, 6.1]**
6-month change	-5.7 (17.2) N=141	-9.2 (18.8) N=1,001	1.2 [-1.6, 4.0]	-2.0 (16.2) N=59	-10.7 (19.5) N=1,232	3.0 [-1.2, 7.3]
12-month change	-6.7 (16.0) N=107	-9.1 (18.7) N=804	-0.9 [-3.4, 1.5]	-4.6 (14.3) N=47	-11.4 (19.6) N=1,029	2.9 [-0.6, 6.4]
CRP*, mg/L						
Baseline	18.7 (14.2) N=343	18.5 (25.2) N=2,176	-1.5 [-4.5, 1.5]	14.5 (16.8) N=111	21.6 (26.8) N=2,241	-2.3 [-6.0, 1.3]
3-month change	-6.3 (16.3) N=223	-9.1 (23.0) N=1,559	-1.4 [-3.4, 0.6]	-5.6 (15.2) N=82	-9.6 (26.0) N=1,684	-1.1 [-3.8, 1.5]
6-month change	-6.9 (17.1) N=167	-9.8 (24.6) N=1,147	-0.5 [-3.1, 2.0]	-3.9 (16.2) N=64	-10.5 (25.9) N=1,337	1.0 [-2.1, 4.0]
12-month change	-5.9 (18.7) N=140	-10.5 (23.7) N=920	0.7 [-2.0, 3.5]	-4.6 (15.3) N=50	-12.2 (25.6) N=1,094	2.5 [-0.4, 5.4]
SJC-28*						

Baseline	2.8 (3.8) N=341	6.0 (5.5) N=2,208	**-1.9 [-2.5, -1.3]**	3.6 (4.6) N=118	6.9 (5.7) N=2,332	**-2.3 [-3.3, -1.3]**
3-month change	-1.7 (3.6) N=238	-3.3 (4.9) N=1,638	0.2 [-0.7, 0.3]	-1.6 (3.3) N=98	-3.3 (5.4) N=1,887	-0.3 [-1.0, 0.3]
6-month change	-1.9 (3.4) N=191	-3.8 (5.0) N=1,225	-0.1 [-0.6, 0.4]	-1.6 (3.1) N=71	-4.0 (5.5) N=1,508	-0.1 [-0.8, 0.7]
12-month change	-1.8 (3.8) N=146	-4.3 (5.0) N=966	0.4 [-0.2, 1.1]	-2.7 (4.7) N=59	-4.7 (5.8) N=1,277	-0.3 [-0.9, 0.3]
TJC-28*						
Baseline	4.5 (5.8) N=342	7.2 (6.7) N=2,205	**-1.6 [-2.4, -0.8]**	4.5 (4.9) N=118	7.9 (7.0) N=2,322	**-3.0 [-4.1, -1.9]**
3-month change	-2.2 (4.4) N=238	-3.5 (6.2) N=1,635	0.1 [-0.5, 0.6]	-0.8 (4.1) N=98	-3.2 (7.3) N=1,876	-0.1 [-1.1, 0.9]
6-month change	-2.5 (4.4) N=192	-4.0 (6.4) N=1,222	0.0 [-0.7, 0.7]	-1.4 (3.6) N=71	-3.8 (6.8) N=1,501	0.3 [-0.8, 1.4]
12-month change	-2.3 (4.6) N=147	-4.3 (6.2) N=961	0.5 [-0.3, 1.2]	-2.0 (4.8) N=59	-4.5 (6.9) N=1,273	0.4 [-0.6, 1.3]
DAS28 (with CRP)*						
Baseline	3.7 (1.3) N=328	4.4 (1.4) N=2,108	**-0.4 [-0.6, -0.2]**	3.9 (1.1) N=110	4.6 (1.2) N=2,223	**-0.5 [-0.7, -0.2]**
3-month change	-1.0 (1.1) N=213	-1.2 (1.3) N=1,488	-0.1 [-0.3, 0.1]	-0.6 (1.1) N=81	-1.1 (1.4) N=1,659	0.0 [-0.2, 0.3]
6-month change	-1.0 (1.1) N=157	-1.4 (1.4) N=1,104	0.1 [-0.1, 0.3]	-0.7 (1.2) N=64	-1.2 (1.4) 1,317	0.2 [-0.1, 0.5]
12-month	-1.0	-1.5	0.3 [0.0, 0.5]	-0.8 (1.3)	-1.5	0.3 [-0.0, 0.6]

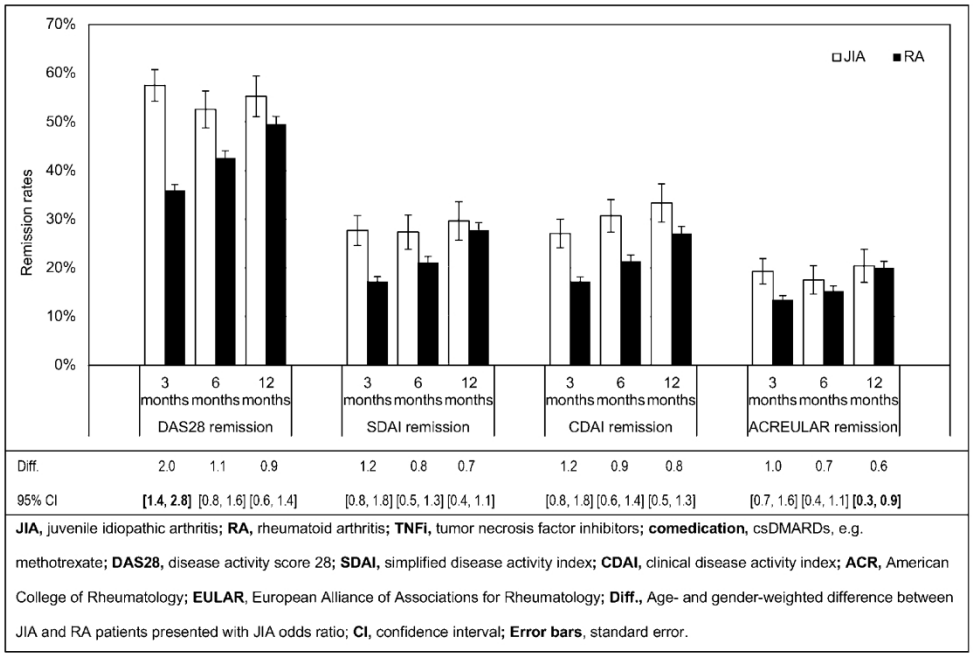
change	(1.2) N=132	(1.3) N=879		N=50	(1.5) N=1,075	
SDAI*						
Baseline	17.9 (11.0) N=292	24.6 (14.6) N=1,928	**-3.3 [-5.1, -1.5]**	17.9 (11.0) N=108	25.9 (13.6) N=2,152	**-5.9 [-8.4, -3.4]**
3-month change	-8.2 (10.1) N=185	-11.7 (13.0) N=1,311	-0.1 [-1.7, 1.5]	-5.7 (9.3) N=79	-10.4 (13.9) N=1,559	-0.0 [-2.2, 2.2]
6-month change	-8.4 (8.8) N=139	-13.2 (13.4) N=982	1.7 [-0.2, 3.5]	-5.6 (8.3) N=61	-12.3 (14.2) N=1,240	1.9 [-0.5, 4.2]
12-month change	-8.6 (9.8) N=119	-14.4 (13.1) N=775	2.5 [0.6, 4.4]	-8.7 (11.6) N=48	-14.1 (14.6) N=1,015	0.9 [-1.4, 3.3]
CDAI*						
Baseline	16.5 (10.5) N=303	22.6 (13.5) N=2,009	**-3.0 [-4.6, -1.3]**	16.3 (10.4) N=116	23.6 (12.8) N=2,244	-5.6 [-7.9, -3.3]
3-month change	-8.0 (9.8) N=207	-10.7 (12.2) N=1,425	-0.3 [-1.7, 1.2]	-4.7 (8.3) N=96	-9.5 (13.1) N=1,755	0.4 [-1.5, 2.3]
6-month change	-8.5 (8.8) N=171	-12.1 (12.6) N=1,080	0.8 [-0.7, 2.4]	-4.9 (7.7) N=67	-11.1 (13.1) N=1,405	1.7 [-0.5, 3.9]
12-month change	-8.1 (9.3) N=131	-13.2 (12.3) N=842	2.3 [0.5, 3.9]	-8.1 (10.4) N=56	-12.9 (13.6) N=1,196	0.6 [-1.4, 2.6]
PGA*						
Baseline	52.9 (25.8) N=344	51.0 (25.4) N=2,216	**4.4 [0.9, 8.0]**	50.6 (24.4) N=118	48.4 (24.2) N=2,294	4.5 [-0.6, 9.5]
3-month	-22.1	-17.6	-1.8 [-5.3, 1.8]	-11.5 (26.0)	-14.0	3.9 [-0.9, 8.7]

change	(26.3) N=241	(26.9) N=1,624		N=99	(26.3) N=1,826	
6-month change	-23.0 (24.9) N=195	-19.5 (27.7) N=1,234	0.9 [-3.1, 4.9]	-10.0 (24.6) N=69	-13.8 (26.5) N=1,463	5.5 [-0.1, 11.0]
12-month change	-21.9 (28.6) N=154	-20.9 (27.6) N=963	4.0 [-0.7, 8.6]	-16.0 (25.4) N=58	-14.5 (26.4) N=1,250	1.3 [-4.9, 7.5]
PHGA*						
Baseline	35.7 (18.0) N=322	39.4 (19.7) N=2,078	-0.8 [-3.5, 1.9]	29.8 (16.7) N=118	39.1 (18.4) N=2,304	-8.7 [-12.2, -5.1]
3-month change	-35.6 (25.7) N=229	-29.6 (26.2) N=1,579	-7.5 [-11.7, -3.4]	-32.3 (24.8) N=97	-25.8 (25.8) N=1,844	**-10.2 [-15.6, -4.8]**
6-month change	-37.4 (24.3) N=186	-31.8 (26.3) N=1,176	-6.3 [-10.7, 1.9]	-26.9 (24.1) N=69	-27.9 (25.5) N=1,476	-3.5 [-9.9, 3.0]
12-month change	-35.3 (26.1) N=148	-32.8 (26.4) N=940	-4.8 [-10.0, 0.4]	-34.1 (25.5) N=57	-29.6 (24.8) N=1,254	**-9.9 [-16.8, -3.1]**

*Mean (SD)

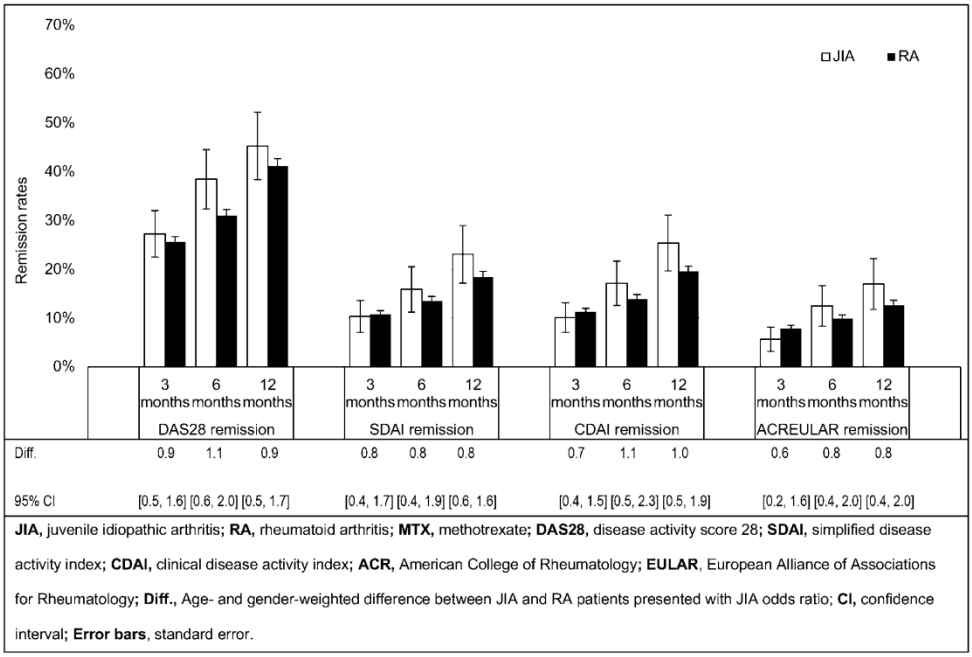
Adjusted difference between groups in change of disease activity from baseline to 3-, 6- and 12-months follow-up, [JIA change minus RA change], JIA-RA [95% CI]. **Significant p-values are in bold text.

JIA, juvenile idiopathic arthritis; **RA**, rheumatoid arthritis; **TNFi**, tumor necrosis factor inhibitors; **comedication**, csDMARDs, e.g. methotrexate; **MTX**, methotrexate; **ESR,** erythrocyte sedimentation rate; **CRP,** C-reactive protein; **SJC-28,** swollen joint count with 28 joints; **TJC-28,** tender joint count with 28 joints; **DAS28,** disease activity score-28;; **SDAI,** simplified disease activity index; **CDAI,** clinical disease activity index; **PGA,** patient global assessment; **PHGA,** physician global assessment;



JIA, juvenile idiopathic arthritis**; RA,** rheumatoid arthritis**; TNFi,** tumor necrosis factor inhibitors**; comedication,** csDMARDs, e.g. methotrexate**; DAS28,** disease activity score 28**; SDAI,** simplified disease activity index**; CDAI,** clinical disease activity index**; ACR,** American College of Rheumatology**; EULAR**, European Alliance of Associations for Rheumatology**; Diff.,** Age- and gender-weighted difference between JIA and RA patients presented with JIA odds ratio; **CI,** confidence interval**; Error bars**, standard error.

Figure 1: Remission rates after 3, 6 and 12 months in adult JIA and RA patients treated with TNFi ± comedication



JIA, juvenile idiopathic arthritis**; RA,** rheumatoid arthritis**; MTX,** methotrexate**; DAS28,** disease activity score 28**; SDAI,** simplified disease activity index**; CDAI,** clinical disease activity index**; ACR,** American College of Rheumatology**; EULAR**, European Alliance of Associations for Rheumatology**; Diff.**, Age- and gender-weighted difference between JIA and RA patients presented with JIA odds ratio; **CI,** confidence interval**; Error bars**, standard error.

Figure 2: Remission rates after 3, 6 and 12 months in adult JIA and RA patients treated with MTX monotherapy

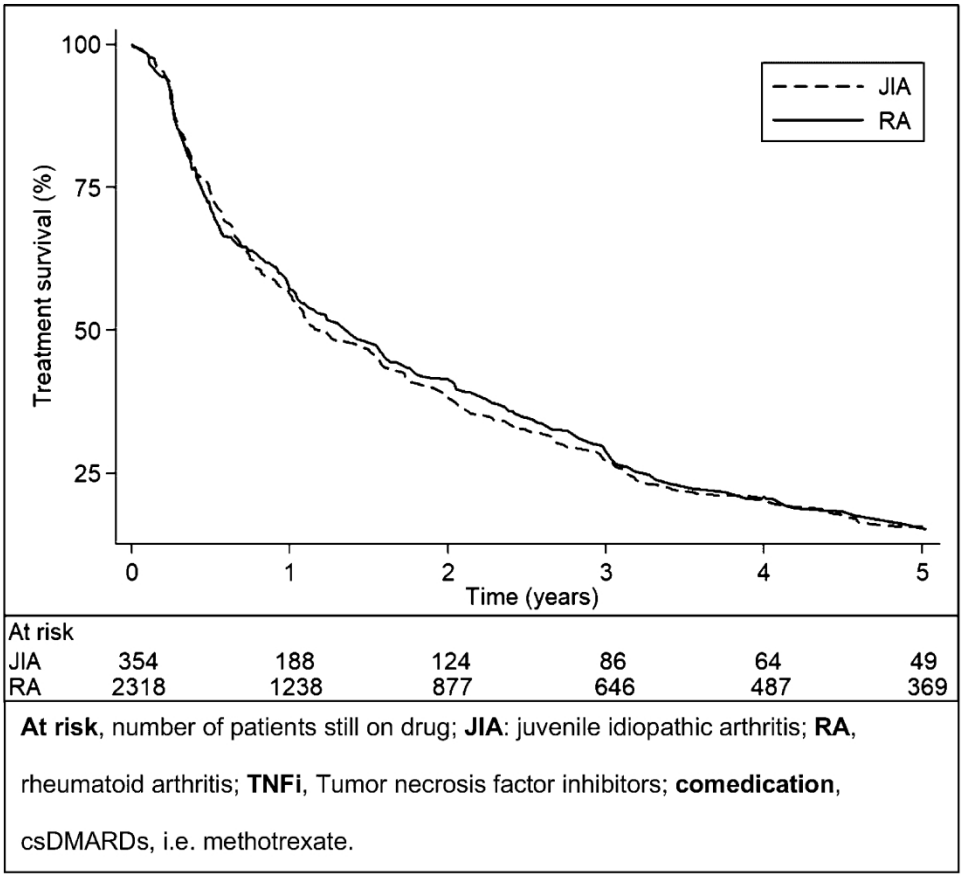
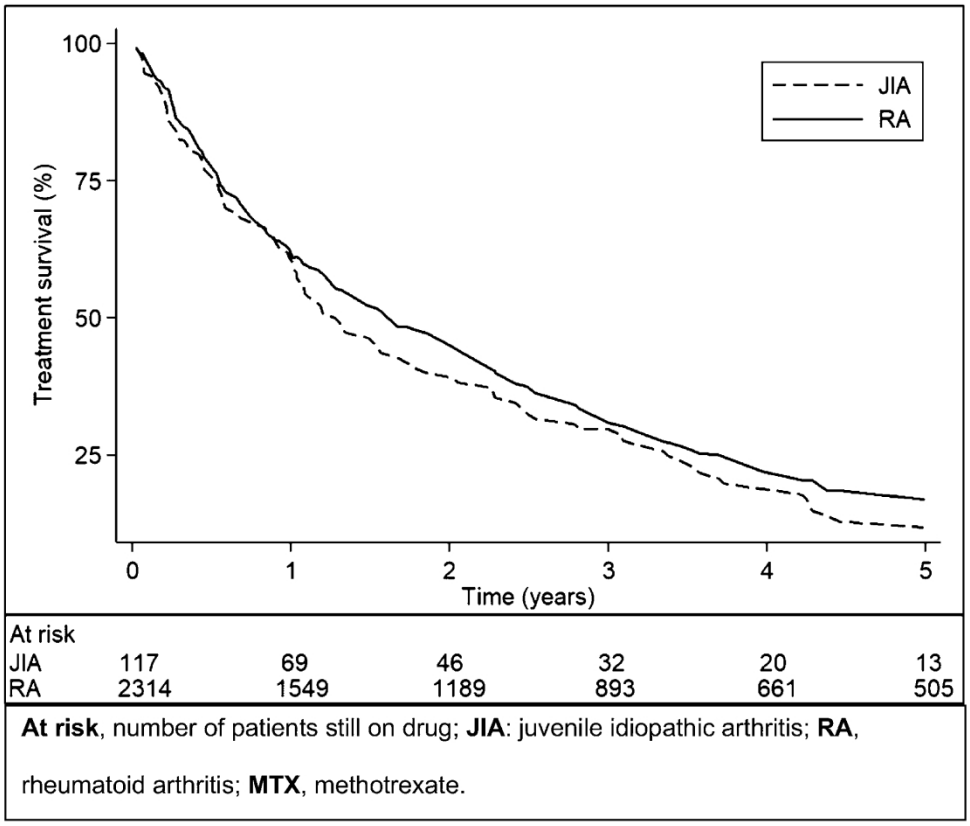


Figure 3a: Five-year age- and gender-weighted drug survival of TNF ± comedication in JIA and RA



At risk, number of patients still on drug; **JIA**: juvenile idiopathic arthritis; **RA**, rheumatoid arthritis; **MTX**, methotrexate.

Figure 3b: Five-year age- and gender-weighted drug survival of MTX monotherapy in JIA and RA