

Medically Significant Infections Are Increased in Patients With Juvenile Idiopathic Arthritis Treated With Etanercept

Results From the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study

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Objective. The association between anti-tumor necrosis factor therapy and increased rates of infection is widely documented in adults with rheumatoid arthritis. Findings in children with juvenile idiopathic arthritis (JIA) have been less well documented. The aims of this analysis were to compare the rates of medically significant infections (MSIs) in children with JIA treated with etanercept (ETN) versus methotrexate (MTX) and to compare the rates between combination therapy with ETN plus MTX and monotherapy with ETN.

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Methods. A total of 852 ETN-treated children and 260 MTX-treated children had been recruited to the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN). MSIs included infections that resulted in death or hospitalization or were deemed medically significant by the clinician. This on-drug analysis followed the patients until the first MSI, treatment discontinuation, the last followup, or death. Cox proportional hazards models, which were adjusted using propensity deciles, were used to compare rates of MSI between cohorts. Sensitivity analyses were conducted specifically with regard to serious infections (SIs), which were defined as those requiring hospitalization or treatment with intravenous antibiotics/antivirals.

Results. The ETN-treated cohort was older and had a longer disease duration, but the disease activity was similar between the cohorts. A total of 133 first MSIs were reported (109 with ETN and 24 with MTX). Patients receiving ETN had higher rates of MSI than did the controls (propensity decile adjusted hazard ratio 2.13 [95% confidence interval 1.22–3.74]). The risk of MSI was higher whether patients were receiving combination or monotherapy. Sensitivity analysis showed no between-group difference in the rate of SIs, which were much less common.

Conclusion. ETN therapy is associated with an increased risk of MSI; however, this increased risk disappears when considering only SIs, which suggests that either there were differences in the severity of infections and/or there was a possible reporting bias.

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory disease in children. The term describes a group of disorders characterized by joint

inflammation that can cause long-term disability and poor quality of life (1,2). Tumor necrosis factor (TNF) is a proinflammatory cytokine that is increased in patients with JIA and is also involved in host defense against infections (3,4). Anti-TNF drugs for the treatment of JIA were introduced more than 14 years ago. A number of studies of adults with rheumatoid arthritis (RA) have shown that while helpful in controlling inflammation, these drugs could increase the rates of serious infection (SI), particularly within the first 6 months of therapy, although the background risk of infection is also increased in RA irrespective of treatment (5–7).

There have been few studies investigating the risk of infection in patients with JIA, and these have produced inconsistent findings. A US study using data from the Medicaid program, which contains medical and pharmacy administrative claims records for children from low-income families, showed a doubling of the rate of hospitalized bacterial infection in patients with JIA as compared to a cohort of children with attention deficit hyperactivity disorder (incidence rate 2.8 versus 1.0 per 100 person-years) (8). Within the group of patients with JIA, the infection risk did not differ according to whether patients were taking methotrexate (MTX) or anti-TNF, although exposure in the latter group was limited.

Similarly, a series of prospective observational studies, including those from national JIA registers, found no increased risk of infection in patients with JIA treated with etanercept (ETN) or ETN in combination with MTX as compared to MTX alone, although the studies were limited by their small sample sizes and/or short duration of followup (2,9,10). One such study showed an incidence rate of serious infection of 2.1 per 100 person-years in patients treated with ETN, which is similar to the rate reported in JIA patients in the US study regardless of treatment (9).

A number of case reports, however, have identified serious infections in patients treated with ETN (3,11,12). Furthermore, a study of the German JIA registry found more SIs in patients receiving ETN plus MTX combination therapy than in patients receiving ETN monotherapy, but this difference did not reach statistical significance (13).

With the existing literature showing differing results and many studies being limited by small sample sizes and limited followup time, the relationship between anti-TNF use and infection risk in JIA remains unclear. The aims of the present study were 1) to compare the rates of medically significant infection (MSI) in JIA patients recruited to the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN) (those treated with ETN versus those treated with MTX), 2) to

compare the rates of MSI in those receiving ETN alone versus those receiving ETN plus MTX, 3) to determine whether the risk of infection changes over time, and 4) to identify risk factors for infection within this population.

PATIENTS AND METHODS

Patients. All patients must fulfill criteria for JIA as defined by the International League of Associations for Rheumatology (ILAR) criteria (14) and are registered in the BSPAR-ETN, a national prospective observational cohort study set up in 2004 to monitor the long term safety and effectiveness of ETN in patients with JIA. UK national guidelines from the National Institute of Clinical Excellence recommend that ETN is restricted to patients who were 4–17 years old with active polyarticular disease in whom MTX treatment had failed. Active polyarticular disease was defined as the presence of 5 or more joints with active arthritis and 3 or more joints with limited range of motion (15).

A detailed explanation of the study methods has been described previously (16). Briefly, once a patient starts ETN therapy, he or she is invited to join the study, and hospitals intended to recruit the children within 6 months of starting the study drug. A comparison cohort of biologics-naïve children who are starting MTX are also recruited using similar methods. The study was approved by the West Midlands Research Ethics Committee, and written informed consent from patients or their parents (as appropriate) was provided in accordance with the Declaration of Helsinki.

Data collection and followup. Baseline data (defined as at time of start of ETN or MTX) are collected by the pediatric rheumatologist or clinical research nurse using a web-based questionnaire and include demographics, disease status including disease duration and activity measures, ILAR disease classification, drug history, and comorbidities.

Patients are followed up at 6 months, 12 months, and annually thereafter and data are collected on current treatments, changes to antirheumatic therapy, as well as detailing serious and nonserious adverse events, including any events which occurred in the months prior to enrollment. Patients are flagged with the National Health Service Information Service to detail any reported cancers and deaths, including cause.

Adverse events are coded in the database using MedDRA (the Medical Dictionary for Regulatory Activities), which is a clinically validated international medical terminology to standardize communication of events between industry and regulators (17). All adverse events are recorded and clinical staff members are required to indicate whether an event is serious and why by way of a tick box list (see below).

Definition of outcome. MSIs were defined as any infection classified as “serious” by the consultant for 1 of the following reasons: 1) life-threatening, 2) caused significant disability, 3) caused death, 4) led to hospitalization, 5) required intravenous (IV) antibiotics or IV antivirals, or 6) was deemed “medically significant” by the consultant. SIs were defined as any infection classified as above, but not including the final, “medically significant,” category. To remove the possibility of prior infection becoming a risk factor for future infections, only the first MSI and/or SI was included in the analysis.

Statistical analysis. Baseline comparisons between cohorts were made using chi-square tests for categorical data and

Table 1. Baseline characteristics of the registered patients taking ETN or ETN plus MTX*

Characteristic	ETN cohort (n = 852)	MTX cohort (n = 260)	<i>P</i>	ETN monotherapy (n = 399)	ETN plus MTX combination therapy (n = 453)	<i>P</i>
Age, median (IQR) years	11 (8–14)	8 (3–12)	0.0001	12 (9–14)	11 (7–14)	0.439
Sex, no. (%) female	572 (67)	182 (70)	0.387	267 (67)	305 (67)	0.898
Disease duration, median (IQR) years	3 (2–6)	1 (0–1)	0.0001	3 (2–7)	3 (1–6)	0.0735
ILAR classification, no. (%)			<0.0001			0.001
Systemic arthritis	104 (13)	13 (5)	–	32 (8)	72 (16)	–
Oligoarthritis, persistent	32 (4)	23 (9)	–	20 (5)	12 (3)	–
Oligoarthritis, extended	140 (17)	60 (23)	–	76 (20)	64 (14)	–
Polyarthritis, RF negative	293 (35)	95 (37)	–	144 (37)	149 (34)	–
Polyarthritis, RF positive	91 (11)	25 (10)	–	34 (9)	57 (13)	–
Psoriatic arthritis	58 (7)	15 (6)	–	31 (8)	27 (6)	–
Enthesitis-related arthritis	62 (7)	11 (4)	–	23 (6)	39 (9)	–
Undifferentiated arthritis	49 (6)	14 (5)	–	26 (7)	23 (5)	–
Comorbid conditions, no. (%)			0.006			0.380
0	563 (66)	196 (75)	–	268 (67)	295 (65)	–
1	165 (19)	44 (17)	–	80 (20)	85 (19)	–
≥2	124 (15)	20 (8)	–	51 (13)	73 (16)	–
No. of joints with active arthritis, median (IQR)	5 (2–10)	6 (3–12)	0.0005	4 (2–9)	6 (3–10)	0.0001
Limited joint count, median (IQR)	4 (2–9)	5 (2–7)	0.4804	4 (1–8)	5 (2–10)	0.0044
C-HAQ score, median (IQR), range 0–3	1.1 (0.4–1.8)	1.0 (0.4–1.8)	0.8023	1 (0.3–1.6)	1.3 (0.5–1.8)	0.062
Pain, median (IQR) on 10-cm VAS	4.7 (2–7)	5 (2–7)	0.5019	4.6 (1.1–6.8)	4.8 (2.3–7.0)	0.1104
ESR, median (IQR) mm/hour	16 (6–36)	21 (10–50)	0.0010	11 (5–29)	20 (8–48)	0.0001
CRP, median (IQR) mg/liter	7 (4–32)	8 (5–26)	0.5914	6 (4–16)	12 (5–43)	0.0001
Physician's global assessment, median (IQR) on 10-cm VAS	3.5 (2.5–5.5)	4.0 (2.5–6.0)	0.1608	3 (1.5–5.0)	4 (2.7–6.0)	0.0001
Patient's/parent's global assessment, median (IQR) on 10-cm VAS	4.6 (2.0–6.9)	4.5 (1.5–6.5)	0.4344	4 (1.3–6.2)	5 (2.3–7.0)	0.0012
JADAS-71, median (IQR)	15.4 (9.0–22.3)	16.7 (10.2–25.4)	0.1121	12.7 (6.8–19.4)	16.5 (11.2–23.3)	0.0001
Concurrent oral steroid use, no. (%)	184 (22)	47 (18)	0.614	59 (15)	125 (28)	<0.0001
Concurrent MTX use, no. (%)	453 (53)	260 (100)	–	0 (0)	453 (100)	–

* ETN = etanercept; MTX = methotrexate; IQR = interquartile range; ILAR = International League of Associations for Rheumatology; RF = rheumatoid factor; C-HAQ = Childhood Health Assessment Questionnaire; VAS = visual analog scale; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; JADAS-71 = Juvenile Arthritis Disease Activity Score in 71 joints.

Mann-Whitney tests for continuous data. For patients in the ETN cohort, person-years of followup began from date of first treatment to the first MSI, the most recent followup recorded, or death, whichever came first. Events were included only if patients were receiving ETN monotherapy or ETN plus MTX combination therapy, with a 90-day lag time window added to the date of stopping ETN to allow for a washout period. Patients in the ETN cohort were able to contribute followup time to both the monotherapy and combination therapy cohorts depending on their MTX use at any given time. For patients in the MTX cohort, person-years of followup started at date of first treatment until first MSI, most recent followup, or death, whichever came first. Patients who registered on MTX and later switched to ETN were followed in the MTX cohort until ETN start, at which point they were censored from that cohort, then subsequent followup time was counted in the ETN cohort as above.

Crude rates of MSI are presented per 100 person-years with 95% confidence intervals (95% CIs). Cox proportional hazard models were used to compare rates of MSI between the MTX- and ETN-treated cohorts. A further comparison was made between patients receiving ETN monotherapy and patients receiving ETN with MTX in combination. Such comparisons were further stratified into 6 monthly time intervals from the

beginning of therapy to 2 years of treatment. To avoid inconsequential infections being misclassified as “medically significant,” a sensitivity analysis was conducted on SIs defined by any one of the first 5 criteria (i.e., not “medically significant”) using identical methods.

A series of propensity scores stratified into deciles were used to adjust for potential confounding effects of baseline differences between the cohorts (ETN plus MTX combination versus MTX, ETN only versus MTX, and ETN plus MTX combination versus ETN only) including age, sex, disease severity (determined using baseline scores on the Childhood Health Assessment Questionnaire [C-HAQ] [18] and the Juvenile Arthritis Disease Activity Score in 71 joints [19]), disease duration, baseline oral steroid use, and ILAR category (systemic versus non-systemic). In this context, logistic regression is used to calculate the probability of a person being assigned to one of two treatment groups given a set of observed covariates. This score would then serve to reduce selection bias by balancing groups based on these covariates. Two time-varying covariates were included to estimate the probability of an ETN plus MTX combination patient becoming an ETN only patient, and an ETN only patient becoming an ETN plus MTX combination patient. These were included as covariates in the ETN plus MTX versus

Table 2. Infections reported during the course of the study

Site or type of infection	Medically significant infections (n = 133)	Serious infections (n = 64)
Upper respiratory tract	38	11
Herpesvirus (includes varicella zoster and herpes zoster)	20	11
General infection not otherwise specified	16	6
Lower respiratory tract	15	11
Skin and soft tissue	15	8
Urinary tract	8	4
Abdominal and gastrointestinal	4	2
Eye and eyelid	4	2
Epstein-Barr virus	3	3
Candidal	2	2
Bone and joint	1	1
Mumps	1	1
Rubeola	1	1
Streptococcal	1	1
Dental and oral soft tissue	1	0
Ear	1	0
Acarodermatitis	1	0
Viral	1	0

ETN monotherapy model. Finally, a series of univariate Cox regressions were performed on baseline variables to identify possible predictors of both MSI and SI in the whole cohort.

All analyses were performed using Stata version 11 software (StataCorp). Missing data were accounted for by way of multiple imputation (20 imputations), using the *ice* package in Stata (20).

RESULTS

A total of 1,112 patients were included in this analysis (852 receiving ETN and 260 receiving MTX). This included 14 patients who had discontinued ETN prior to enrolling with the study. The baseline characteristics of both cohorts are displayed in Table 1 and show that the ETN cohort was older, had a longer disease duration, and had a higher proportion with a diagnosis of systemic arthritis. Disease activity was similar between the cohorts. Patients in the ETN cohort had a higher overall prevalence of comorbid conditions, with the most common in both cohorts being uveitis (10%), eczema (8%), and asthma (8%). Patients starting ETN in combination with MTX presented with higher disease activity scores and concurrent steroid use than those starting ETN monotherapy. The mean followup time on medication was 2.6 years in the ETN cohort and 3.0 years in the MTX cohort.

Risk of medically significant infections. There were 184 MSIs (158 in those receiving ETN and 26 in those receiving MTX), 133 of which were first events (109 in the ETN group and 24 in the MTX group). Thirty percent of first MSIs (similar rates in both MTX and ETN) were reported to have occurred following drug initiation but prior to study enrollment; these were included in the analysis. The most common MSIs were varicella and respiratory tract infections (Table 2). Of the 109 first MSIs in

the ETN cohort, 103 occurred in patients currently taking ETN (48 during monotherapy and 55 during combination therapy with MTX). The overall incidence of MSIs was 4.8 per 100 person-years (95% CI 4.0–5.6). As compared to the MTX-treated patients, the ETN-treated patients showed an increase in the rate of MSIs, with a crude incidence rate of 5.5 per 100 person-years (95% CI 4.5–6.6) versus 3.4 per 100 person-years (95% CI 2.2–5.0) for MTX. Within the ETN cohort, patients receiving monotherapy had an incidence rate of 4.3 per 100 person-years (95% CI 3.2–5.7), as compared to 7.2 per 100 person-years (95% CI 5.4–9.3) in the ETN plus MTX cohort (Table 3).

The unadjusted hazard ratio (HR) for the ETN-treated patients versus the MTX-treated patients was 1.46 (95% CI 0.93–2.28). Within the entire BSPAR-ETN cohort, univariate predictors of MSI included younger age, systemic JIA (versus nonsystemic disease), baseline oral steroid use, concurrent MTX use at baseline, and having 2 or more comorbid conditions at baseline (Table 4). Adjusting for potential confounders using propensity deciles found a fully adjusted hazard ratio of 2.13 (95% CI 1.22–3.74), showing an increased risk of MSI in patients treated with ETN as compared to MTX. There was a trend toward a higher risk of MSI in ETN-treated patients receiving combination MTX therapy as compared to those receiving ETN monotherapy, but this difference did not reach significance (HR 1.42 [95% CI 0.89–2.25]) (Table 3).

Risk of serious infections. Results of the sensitivity analysis reported 64 first SIs, with 46 occurring while patients were receiving ETN (22 receiving monotherapy and 24 receiving combination therapy). The most common SIs reported, again, included varicella and pneumonia

Table 3. Crude incidence rates and hazard ratios for infection in patients taking ETN versus MTX*

	Entire BSPAR-ETN cohort		ETN cohort alone	
	Patients taking MTX	Patients taking ETN	Patients receiving ETN as monotherapy	Patients receiving ETN plus MTX combination therapy
Medically significant infections				
Person-years of exposure, based on first-event analysis	714	1,883	1,116	767
Mean duration of followup, years	3.0	2.6	2.4	1.8
No. of first MSI	24	109	48	55
Crude incidence rates of MSI (95% CI), per 100 person-years	3.4 (2.2–5.0)	5.5 (4.5–6.6)	4.3 (3.2–5.7)	7.2 (5.4–9.3)
Unadjusted HR (95% CI) for first MSI				
Versus MTX monotherapy	Reference	1.46 (0.93–2.28)	1.22 (0.75–2.00)	1.70 (1.05–2.76)
Versus ETN monotherapy	–	–	Reference	1.47 (0.99–2.17)
Fully adjusted HR (95% CI) for first MSI†				
Versus MTX monotherapy	Reference	2.13 (1.22–3.74)	2.09 (1.07–4.07)	2.28 (1.21–4.30)
Versus ETN monotherapy	–	–	Reference	1.42 (0.89–2.25)
Serious infections				
Person-years of exposure, based on first-event analysis	746	2,060	1,209	851
No. of first SI	13	46	22	24
Crude incidence rates of SI (95% CI), per 100 person-years	1.7 (0.9–3.0)	2.2 (1.6–3.0)	1.8 (1.1–2.8)	2.8 (1.8–4.2)
Unadjusted HR (95% CI) for first SI				
Versus MTX monotherapy	Reference	1.18 (0.59–2.35)	1.06 (0.49–2.27)	1.21 (0.57–2.58)
Versus ETN monotherapy	–	–	Reference	1.23 (0.66–2.29)
Fully adjusted HR (95% CI) for first SI†				
Versus MTX monotherapy	Reference	1.36 (0.60–3.07)	1.29 (0.48–3.50)	1.30 (0.51–3.30)
Versus ETN monotherapy	–	–	Reference	1.29 (0.63–2.62)

* Serious infections were those requiring hospitalization or intravenous administration of antibiotics/antivirals. ETN = etanercept; MTX = methotrexate; BSPAR-ETN = British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study; MSI = medically significant infection; 95% CI = 95% confidence interval; HR = hazard ratio; SI = serious infection.

† Fully adjusted using propensity deciles (includes age, sex, Childhood Health Assessment Questionnaire score, Juvenile Arthritis Disease Activity Score in 71 joints, concurrent steroid use, and International League of Associations for Rheumatology category).

Table 4. Univariate HRs for predictors of MSIs and SIs in the entire BSPAR-ETN cohort*

Predictors	MSIs, HR (95% CI)	SIs, HR (95% CI)
Sex		
Male	Reference	Reference
Female	1.04 (0.72–1.51)	1.11 (0.64–1.91)
Age at baseline	0.91 (0.88–0.95)†	0.90 (0.85–0.96)†
Disease duration at baseline	0.97 (0.92–1.02)	1.00 (0.93–1.08)
JIA at baseline		
Nonsystemic	Reference	Reference
Systemic	2.14 (1.41–3.25)†	2.57 (1.46–4.54)†
Oral corticosteroid use at baseline	2.11 (1.49–3.00)†	2.13 (1.29–3.51)†
MTX use at baseline	1.80 (1.22–2.66)†	1.90 (1.06–3.40)
C-HAQ score at baseline	1.23 (0.89–1.69)	1.26 (0.80–1.99)
JADAS-71 at baseline	1.01 (0.99–1.02)	1.01 (0.99–1.04)
No. of comorbid conditions at baseline		
0	Reference	Reference
1	1.23 (0.80–1.88)	1.29 (0.70–2.40)
≥2	1.66 (1.06–2.58)†	1.88 (1.01–3.50)†

* HRs = hazard ratios; MSIs = medically significant infections; SIs = serious infections; BSPAR-ETN = British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study; 95% CI = 95% confidence interval; JIA = juvenile idiopathic arthritis; MTX = methotrexate; C-HAQ = Childhood Health Assessment Questionnaire; JADAS-71 = Juvenile Arthritis Disease Activity Score in 71 joints.

† $P < 0.05$.

Table 5. HRs for infection in patients taking ETN versus MTX, by time interval*

	No. of first infections		No. of patients at risk		Fully adjusted HR (95% CI)	
	MTX	Taking ETN	MTX	Taking ETN	MTX	Taking ETN
MSIs						
Time points						
0–6 months	9	48	260	852	Reference	2.00 (0.89–4.46)
6–12 months	6	26	211	716	Reference	1.09 (0.43–2.78)
12–18 months	4	18	160	564	Reference	2.68 (0.58–12.42)
18–24 months	1	16	138	470	Reference	4.13 (0.51–33.50)
SIs						
Time points						
0–6 months	5	24	260	852	Reference	0.93 (0.32–2.73)
6–12 months	5	12	215	738	Reference	0.36 (0.11–1.231)
12–18 months	2	9	166	595	Reference	1.61 (0.19–13.86)
18–24 months	1	9	143	506	Reference	1.37 (0.15–12.19)

* Hazard ratios (HRs) were fully adjusted using propensity deciles (including age, sex, Childhood Health Assessment Questionnaire score, Juvenile Arthritis Disease Activity Score in 71 joints, concurrent steroid use, and International League of Associations for Rheumatology category). ETN = etanercept; MTX = methotrexate; 95% CI = 95% confidence interval.

(Table 2). The rate of SI in patients taking ETN was 2.2 per 100 person-years (95% CI 1.6–3.0). There was no difference in the rate of first SI across the cohorts (Table 3). Univariate predictors of SI were similar to those for MSI and included younger age, systemic JIA, baseline oral steroid use, and having 2 or more comorbid conditions at baseline (Table 4).

The unadjusted HR for SIs in the ETN-treated patients versus the MTX-treated patients was 1.18 (95% CI 0.59–2.35) (Table 5). The fully adjusted HR showed a similar result, with an HR of 1.36 (95% CI 0.60–3.07). This was also true for monotherapy and combination therapy as compared to MTX and compared to each other (Table 3).

Time-varying risk of infections. Compared to the overall rate of MSIs, the risks observed within each 6-month window from the start of therapy were similar and did not vary over time ($P = 0.36$ for the test for interaction for MSIs and $P = 0.93$ for the test for interaction for SIs) (Table 5).

DISCUSSION

Biologic drugs that interfere with primary functions of the immune system are being used more widely and at an earlier stage of many diseases in children and young people (21). The potential for such medications to increase the risk of serious infection has been explored in one of the largest long-term followup studies of infection risks to date. From the data in the BSPAR-ETN, the risk of MSI appears to be increased in children with JIA receiving ETN as compared to those receiving MTX, both in those receiving ETN plus MTX in combination and in those receiving ETN monotherapy. However, compared to studies in adult populations with RA, we did not

observe a marked increase in infection during the first few months of treatment, with a subsequent reduction in risk over time (5).

An explanation of the higher risk of MSI in ETN-treated patients may be that the background risk of infection differed between the cohorts. ETN-treated patients also had more comorbid conditions at baseline and had a longer history of disease, which may have predisposed them to developing MSIs. Indeed, we know from studies in RA that baseline comorbidity and other disease features are predictors of future adverse events (22,23). We allowed for channeling bias (increased risk of MSI because of the influence of baseline differences on choice of treatments) and demonstrated that the risk was increased even after accounting for these baseline differences between groups. MSI risk in the ETN cohort increased after adjusting for confounding as compared to the unadjusted risk, and this appeared to be driven by age. Younger children were more prone to infection (Table 4), and because children in the ETN cohort were older, the risk appeared to be lower in the unadjusted analysis.

The risk of SIs was not different between the treatment groups, despite the rates of MSIs being markedly higher in the ETN cohort. The absolute risk of SIs was very low, consisting of only a small proportion of all MSIs reported; however, the observed rate of SIs was similar to that reported by Beukelman et al within their JIA cohort, and the crude incidence in both ETN- and MTX-treated patients was higher than that reported in their non-JIA US cohort (8). It was not always possible to deduce why a physician would mark a nonhospitalized infection as significant based on the data supplied, but recorded reasons included missed school, prolonged oral antibiotic therapy, or temporary cessation of arthritis treatment. It is possible

that infections experienced while taking ETN may still be more severe or persistent, even though they did not always result in hospitalization. It is also possible that the results were influenced by a reporting bias, where physicians are more likely to report significant infections to the registry or to classify infections as significant among children receiving ETN rather than those receiving MTX. We also allowed a 90-day lag window with regard to the date of ETN cessation, which may have contributed to a greater number of infections in this cohort; however, only 1 additional infection occurred during this 90-day period.

Regardless of treatment allocation, children with systemic JIA, those receiving steroids (which were also used more commonly among those with systemic disease), and those with multiple comorbid conditions were more prone to developing an MSI. Corticosteroids are an important risk factor for infection across all indications (24) and have been identified as a predictor of infection in children with JIA (8). The use of steroids in adults with RA has been seen as one of the most important predictors of SIs (5,25). The relationship with multiple comorbidities (which included such diseases as uveitis, growth abnormalities, chronic skin conditions, and atopy) may also be a marker of more severe chronic disease, which in itself may also be a risk factor for infection (20,21). However, the C-HAQ score, another marker of disease severity, was not associated with risk of infection in this cohort.

The lack of time-varying risk of infection between cohorts is inconsistent with the results of studies in adults with RA, which have suggested up to an 80% increased risk within the first 6 months of anti-TNF therapy, which then decreased over time (5). Reasons for this have been explored in RA (9) and may be related to comorbid conditions among the treated population as well as changes in a given patient over time, such as reductions in steroid dosage or improvements in disease activity. It is possible that the different comorbidities experienced by adults with RA (such as chronic obstructive pulmonary disease, ischemic heart disease, and renal failure) as well as other exposures that are uncommon in this pediatric population (e.g., smoking) are, in themselves, stronger risk factors for infection regardless of treatment and are more evident early in the treatment course, resulting in "healthier" cohorts over time.

Historically, adult RA cohorts have also had a mean of more than 10 years of disease duration (compared to only 3 years in the current study of JIA) and much longer than that among comparison cohorts receiving nonbiologic therapies. Thus, the other cohorts may have accrued more damage and disability, which again would make them more prone to infection upon starting anti-TNF therapy. Many studies in adults have included a combination of incident and prevalent usage of MTX and other disease-

modifying antirheumatic drugs in their comparison cohorts, which may have attenuated the risk in those not receiving biologic drugs. Finally, it should also be noted that the numbers of infections per time interval were low, and therefore drawing firm conclusions about time-varying risk in JIA should be explored further in larger data sets.

The main strengths of the BSPAR-ETN are related to the size of the cohort, with more than 1,100 patients included in this study, the detailed followup procedures used, and the prospective study design, which minimizes potential recall bias.

As a nonrandomized observational treatment study, the BSPAR cohort is subject to the limitations common to all such research. Due to the study protocol, it was not possible to enroll patients before they started ETN (or MTX). It is therefore possible that the study may have missed patients who started and then stopped the study drug, either because of an adverse event or disease remission, prior to study enrollment. Although not an exclusion for the study, it may be possible that some of these children declined to participate.

To minimize this patient exclusion and ensure that we analyzed incident users of drug, we aimed to recruit all patients within 6 months of starting ETN or MTX, and we included in the analysis all time and events reported from the start of treatment. Reassuringly, our study did capture both children who had already discontinued ETN prior to enrollment and those who had already experienced an adverse event, including infection, in the months between starting the drug and giving consent for study, suggesting that capture of cases was inclusive, but we cannot exclude the possibility that some children were missed.

There were missing data across all covariates, although there was not a complete lack of information for any patient, and we were therefore able to use multiple imputation to account for these data. For example, results from our univariate analysis support the important role of corticosteroids in infection risk. However, concurrent steroid use and steroid dosage were not recorded as accurately during the early years of this study as during more recent years, and therefore we were unable to include the actual steroid dosage in our model. One study showed that infection risk in JIA patients was similar in those treated with MTX and those treated with anti-TNF; however, those receiving high-dose glucocorticoids showed an increased risk irrespective of anti-TNF or MTX use (8). It would therefore be important to understand further the impact of the steroid dose in the context of infections. Finally, followup completion rates are still relatively low, with a median followup time of 2.9 years overall. We therefore cannot comment on infection risk with long-term use based on these study data.

In conclusion, this study showed that the risk of MSI is increased in patients receiving ETN as compared to those starting MTX; however, this increased risk disappears when serious infections requiring intravenous antibiotics/antivirals or hospitalization are taken into consideration. Given the higher infection rates reported in adults receiving anti-TNF therapy and the low absolute risk of SI observed in our data set, further research in larger cohorts is needed to study the effects of ETN in JIA over a longer time period, especially since JIA itself may be associated with an increased risk independently of treatment. It would also be important to study the effect of glucocorticoids on the SI rate in these patients and further study the underlying risk of infection in the JIA population as a whole.

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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 published. Dr. Hyrich 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. Southwood, Hyrich.

Acquisition of data. Southwood.

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