

# Inflammatory Bowel Disease in Juvenile Idiopathic Arthritis Patients Treated with Biologics

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**ABSTRACT. Objective.** Evolving inflammatory bowel disease (IBD) is a matter of interest in patients with juvenile idiopathic arthritis (JIA) and might be associated with JIA therapy.

**Methods.** Data from the German biologics registry (Biologika in der Kinderreumatologie; BiKeR) from 2001 to 2013 were analyzed.

**Results.** There were 3071 patients with 8389 patient-years (PY) of observation followed. IBD was diagnosed in 11 patients, 8 with Crohn disease and 3 with ulcerative colitis. IBD incidence in patients with JIA was 1.31/1000 PY and higher than published IBD incidences in pediatric populations. Compared with the total BiKeR cohort, patients with IBD more commonly had enthesitis-related arthritis, extended oligoarthritis, psoriatic arthritis, and also rheumatoid factor (RF)-negative polyarthritis. No IBD occurred in patients with systemic JIA or RF-positive polyarthritis. In patients treated with methotrexate (MTX), the IBD incidence was significantly lower compared with patients not treated with MTX. Etanercept (ETN) monotherapy, but not the combination of ETN and MTX, was associated with an increased incidence of IBD.

**Conclusion.** Incidence of IBD in patients with JIA is higher than in the population. MTX turned out to be protective, even in combination with ETN. (J Rheumatol First Release September 15 2015; doi:10.3899/jrheum.140472)

## Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS  
METHOTREXATE

BIOLOGICS  
ETANERCEPT  
INFLAMMATORY BOWEL DISEASE

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory disease in children, with an incidence of up to 15 cases/year per 100,000 children<sup>1,2,3</sup>. There are several treatment options, because of the differences in the pathogenesis and the clinical features of the 8 JIA subtypes. Treatment recommendations depend on clinical features, such as disease severity and prognostic factors, but also on the efficacy of the medical treatment, including the risk of side effects<sup>4,5,6</sup>. In some patients with only a few affected joints, intraarticular injections with corticosteroids and

symptomatic therapy with nonsteroidal antiinflammatory drugs (NSAID) can be sufficient. Most patients with polyarticular and systemic-onset JIA are often treated initially with disease-modifying antirheumatic drugs (DMARD), most commonly methotrexate (MTX)<sup>7</sup>. In the case of ineffectiveness or intolerance to first-line therapy or severe comorbidity, e.g., uveitis, biologic treatment options exist. The tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) receptor immunoglobulin fusion protein etanercept (ETN) has been shown to be effective in all JIA subtypes, except systemic-onset JIA<sup>8,9,10,11</sup>. TNF- $\alpha$  is involved as a proinflammatory cytokine in the pathophysiology of inflammation, so its inhibition can be effectively used for JIA treatment<sup>12</sup>.

Inflammatory bowel disease (IBD) is a matter of interest in patients with JIA because cases have been described of IBD onset upon treatment with ETN<sup>13,14,15,16,17</sup>. TNF- $\alpha$  secretion is also involved in the pathogenesis of IBD<sup>18</sup>. The TNF- $\alpha$  antibodies adalimumab (ADA) and infliximab (IFX) are both approved for the treatment of moderate to severe Crohn disease (CD) and ulcerative colitis (UC)<sup>19</sup>, while ETN failed to be effective in patients with CD<sup>20</sup>.

IBD occurring in patients with JIA might be a comorbidity because it has been described for adults with spondyloarthropathies<sup>21</sup>. Otherwise, arthritis could represent an extraintestinal manifestation of IBD occurring later. It is unclear whether IBD incidence in patients with JIA is

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increased as a consequence of JIA therapy with ETN or for other reasons. The primary objective of our work was to find out how drug exposure could influence the occurrence of an IBD in patients with JIA.

## MATERIALS AND METHODS

Data from the German biologics registry (Biologika in der Kinderrheumatologie; BiKeR) were used as described previously<sup>11,22</sup>. The German BiKeR registry was a prospective cohort study conducted in accordance with the International Conference on Harmonization good clinical practices and the Declaration of Helsinki. The protocol had been approved by the ethics committee of the Aerztekammer Nordrhein, Duesseldorf, Germany, and by local ethics committees, if applicable according to local regulations. Written consent was obtained by the patients and their parents prior to the collection of the data. Data were collected through pseudonymization. All patients of the German JIA BiKeR registry who were newly starting treatment with biologicals or MTX from 2000 to April 2013 were included in our study. While patients treated with ETN were initially followed by registry, the documentation was extended to further biologicals after abatacept (ABA), ADA, and tocilizumab (TCZ) were approved. Some patients' data from an earlier publication were included<sup>13</sup>.

The total JIA cohort of the registry was used to describe baseline demographic and clinical characteristics. Demographics were compared in patients with JIA with and without IBD. Patient data including adverse events were reported by the patient's local physician. Data of reported adverse events in the registry were explored to identify cases of IBD according to the European Society for Pediatric Gastroenterology Hepatology and Nutrition ESPGHAN Revised Porto Criteria. Medication at the time of development of IBD was reported, and IBD incidence with and without different drugs was compared by performing chi-square tests. Statistics were calculated with Microsoft Excel and Access.

## RESULTS

From a total of 3071 patients in the registry and a total observation time of 8389 patient-years (PY), 11 cases of proven IBD were documented. Until March 31, 2013 (data lock), a total of 1739 patients starting ETN and 1126 patients starting treatment with MTX but never exposed to a biologic agent were identified in the database. There were 1912 patients who received 1 biologic only, and 298, 87, 18, 2, and 2 patients who received 2, 3, 4, 5, and 6 biologics, respectively. TNF inhibitors were used as the first-line therapy in 1880 patients, and as second-line therapy in 232 and third-line therapy in 56. ETN was the first biologic agent in 1698 patients (97.6%), second in 32 (1.8%), and third in 9 (0.5%).

There were 398 patients who were exposed to ADA (total exposure time 369 PY), and 44, 47, 47, and 50 patients who received ABA (25 PY), anakinra (68 PY), IFX, (37 PY), or TCZ (61 PY), respectively. The IBD incidence in patients with JIA in the registry was 1.31/1000 patients.

Among 11 patients with IBD (27% males), 8 had CD and 3 had UC, which matches the sex distribution of IBD subtypes in the pediatric population<sup>23</sup>. The IBD diagnosis was confirmed histologically according to the ESPGHAN Revised Porto Criteria for the diagnosis of IBD<sup>24</sup> (Table 1). Two further cases of CD, 1 with extended oligoarthritis JIA and 1 with enthesitis-related arthritis (ERA) JIA, were reported, but had to be excluded because of missing

diagnostic details. One patient was reported to have CD because of clinical, sonographic, and laboratory findings. One patient was reported to have developed CD with no further details given.

JIA categories in patients with IBD were extended oligoarthritis (n = 3), seronegative polyarthritis (n = 4), ERA (n = 2), and psoriatic JIA (n = 2). HLA-B27 was positive in 2 patients and not performed in 1 patient, and antinuclear antibodies (ANA) were positive in 7 patients developing an IBD. The characteristics of patients experiencing IBD were compared with the total JIA cohort (Table 2). There was no significant difference in sex, HLA-B27 positivity, or ANA positivity. The mean age at onset of JIA was  $6.1 \pm 3.9$  years. Mean age at onset of IBD was  $13.4 \pm 3.4$  years. Mean time between onset of JIA and onset of IBD was  $7.2 \pm 4.0$  years.

At admission to the registry, all of the 11 patients with JIA with new IBD were treated with NSAID and MTX. Seven patients were treated with steroids, 3 with sulfasalazine (SSZ), 2 with azathioprine, and 1 with leflunomide (LEF). At the time of IBD diagnosis, 9 patients were treated with ETN, 5 with NSAID, 3 with steroids, 2 with SSZ, and 1 with LEF. Two patients received MTX when IBD developed, 1 of them in combination with ETN; the other took MTX monotherapy and was never exposed to biologicals. One patient developed IBD upon SSZ therapy after discontinuation of MTX therapy.

Analyzing the number of events and the exposure time of drugs revealed 5 IBD events occurring in 4575 years of exposure to NSAID (1.09/1000 PY), 3 in 1981 years of exposure to corticosteroids (1.51/1000 PY), 2 in 195 years of exposure to SSZ (10.26/1000 PY), 2 in 5455 years of exposure to MTX (0.37/1000 PY), 1 in 212 years of exposure to LEF (4.72/1000 PY), and 9 in 3557 years of exposure to ETN (2.53/1000 PY). In all 9 cases of IBD exposed to ETN, it was the first-line biologic therapy. One of the patients with reported but not proven CD had had monotherapy with ETN, and the other had received combination therapy with ETN and MTX. No occurrence of IBD was observed upon treatment with the other biologicals. However, many fewer patients were followed with much shorter observation times compared to treatment with ETN.

The incidence of IBD was significantly lower in patients treated with MTX but significantly higher in patients treated with ETN or SSZ (Table 3). No statistical difference could be shown for treatment with corticosteroids, LEF, or NSAID.

Comparison of ETN monotherapy (1501 PY) with the combination treatment of ETN with MTX (1610 PY) showed that the incidence of an IBD event in patients receiving monotherapy with ETN (5.33/1000 PY) was much higher than with combination therapy (0.62/1000 PY). The combination of ETN with MTX did not significantly increase the IBD incidence compared with MTX monotherapy (2670 PY, IBD incidence 0.37/1000 PY).

The 9 patients with ETN at the time of IBD diagnosis had

Table 1. Patient overview including histological findings.

No.	Sex	JIA Type	Age at JIA Onset, Yrs	IBD Type	Age at IBD Onset, Yrs	Pretreatment at Registry Start	Medication at IBD Onset	Treatment after IBD	IBD Outcome	IBD Diagnosis	Histology after 3 Mos
1	M	PsA	1.0	CD	17.8	MTX, NSAID	ETN, NSAID	Stop: ETN; start: MES	No R	H	Segmental ileocolitis with epitheloid cell-like granuloma
2	F	RF- JIA	5.4	CD	10.2	MTX, CS, NSAID	ETN	Stop: ETN; start: ADA, MES, CS	No R	H	Oesophagitis, epitheloid cell reaction, and isolated giant cells; active and chronic duodenitis with microgranulomata, active and chronic colitis with epitheloid cell reaction
3	F	eoJIA	4.1	UC	12.0	MTX, LEF, NSAID	ETN, LEF	Stop: ETN; start: MES, ADA, CS	R	H	Erosive colitis, colonic cryptic defect
4	F	eoJIA	6.7	CD	11.7	MTX, CS, NSAID	ETN, NSAID	Stop: ETN; start: ADA, SSZ, CS	R	H	Colonic cryptic defect, loss of goblet cells, cryptitis, inflammatory infiltrate
5	F	RF- JIA	2.0	CD	12.2	MTX, NSAID	ETN	Stop: ETN; start: ADA, CS, AZA	No R	H	Ileocolitis, epitheloid cell-like granuloma
6	F	ERA	10.0	UC	17.2	MTX, AZA, SSZ, CS, NSAID	SSZ, NSAID	SSZ ongoing	NA	H	Chronic colitis with few ulcerative and inflammatory reactive, small adenomatous polypus
7	M	PsA	10.3	CD	17.9	MTX, SSZ, NSAID	MTX, SSZ	MTX and SSZ ongoing	No R	H	Aphthous ulcers in the terminal ileum
8	F	RF- JIA	3.1	UC	11.9	MTX, AZA, CS, NSAID	ETN, CS, NSAID	Stop: ETN; start: MTX, IFX, SSZ	R	H	Pancolitis ulcerosa, microgranuloma
9	F	eoJIA	9.6	CD	11.4	MTX, CS, NSAID	ETN	Stop: ETN; start: MTX, CS, SSZ	No R	H	Ileal chronic inflammatory infiltrate, active lymphatic system, and Peyer patch; colonic cryptic defect and abscesses, erosions, chronic gastritis
10	M	ERA	12.4	CD	16.4	MTX, SSZ, CS, NSAID	MTX, ETN, CS, NSAID	No change	R	H	Findings suitable histologically for Crohn disease
11	F	RF- JIA	2.7	CD	8.2	MTX, CS, NSAID	ETN, CS	Stop: ETN; start: SSZ	R	H	Gastritis and duodenitis, ileitis terminalis, chronic fluoride colonic inflammation

JIA: juvenile idiopathic arthritis; IBD: inflammatory bowel disease; M: male; F: female; PsA: psoriatic arthritis; RF: rheumatoid factor; eoJIA: extended oligo-articular JIA; ERA: enthesitis-related arthritis; CD: Crohn disease; UC: ulcerative colitis; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drugs; CS: corticosteroid; LEF: leflunomide; AZA: azathioprine; SSZ: sulfasalazine; ETN: etanercept; MES: mesalazine; ADA: adalimumab; IFX: infliximab; R: remission; H: histological; NA: unknown.

a mean (median) exposure time of 1.71 (1.29) years with a wide range of 0.34–5.03 years before onset of IBD symptoms. Of interest, in 8 of them, IBD was reported after MTX was discontinued. IBD symptoms started within a mean (median, range) time of 2.05 (1.29, 0.50–6.08) years after discontinuation of MTX. ETN has been discontinued in 8 patients within a mean (median, range) time of 5.5 (0.9, 0.0–22.3) weeks after onset of IBD.

No patient went into remission after discontinuation only of ETN. All were treated for IBD, receiving standard care, including 4 patients who received ADA and 1 patient who received IFX.

## DISCUSSION

The IBD incidence in patients with JIA in the registry was 1.31/1000 PY and thus much higher than published IBD

incidences in pediatric populations<sup>23,25,26,27,28</sup>. Because the methodology of those analyses was different from our method, direct comparison seems inappropriate.

According to our observation, patients with the newly approved JIA categories — extended oligoarthritis, ERA, and psoriatic arthritis (PsA) — were especially at risk because 64% of the patients with IBD belonged to these 3 JIA categories while their percentage in the total registry cohort was only 38%. This observation is in line with the historical classification of PsA, late-onset HLA-B27-positive oligo-articular juvenile chronic arthritis, and arthritides in the context of IBD upon the covering term of the spondyloarthropathies, suggesting that these entities have common clinical and genetic features<sup>29</sup>. Subclinical gut inflammation similar to CD has been found in 40–60% of patients with spondyloarthropathies, even if the number of symptomatic

**Table 2.** Patient characteristics. Comparing patients with and without clinical characteristic using chi-square test. Differences were not statistically significant. Values are n (%).

Characteristics	Total JIA Cohort, of BiKeR patients	JIA without IBD	JIA with IBD
Male	998 (32.5)	995 (32.4)	3 (27.3)
ANA+	1414 (46.0)	1407 (45.8)	7 (63.6)
HLA-B27+	617 (20.1)	615 (20.0)	2 (18.2)
sJIA	197 (6.4)	197 (6.4)	0
RF- JIA	908 (29.6)	904 (29.4)	4 (36.4)
RF+ JIA	198 (6.4)	198 (6.5)	0
poJIA	501 (16.3)	501 (16.4)	0
eoJIA	502 (16.3)	499 (16.2)	3 (27.3)
ERA	427 (13.9)	425 (13.8)	2 (18.2)
PsA	237 (7.7)	235 (7.7)	2 (18.2)
ucJIA	100 (3.3)	100 (3.3)	0

JIA: juvenile idiopathic arthritis; BiKeR: Biologika in der Kinderrheumatologie (German biologics registry); IBD: inflammatory bowel disease; ANA: antinuclear antibodies; sJIA: systemic JIA; RF: rheumatoid factor; poJIA: persistent oligoarticular JIA; eoJIA: extended oligoarticular JIA; ERA: enthesitis-related arthritis; PsA: psoriatic arthritis; ucJIA: unclassified JIA.

IBD is estimated at only 7%<sup>21</sup>. Thus, according to former published cases<sup>14,15,16,17</sup>, the conclusion can be drawn that onset of IBD upon ETN therapy may be coincidental to preexisting spondyloarthropathies.

No IBD has been reported so far in patients with rheumatoid factor-positive polyarthritis and in patients with systemic arthritis. The increased IBD incidence after SSZ must be reviewed with the consideration that it is often used in patients with ERA, and the relationship of joint and gut inflammation has been previously described in pediatric spondyloarthropathy patients<sup>21</sup>. On the other hand, only 2

patients with IBD were carriers of HLA-B27.

Interestingly, patients with JIA treated with MTX showed a marked lower incidence of IBD in our registry, while those patients treated with ETN monotherapy or SSZ seemed at higher risk. However, the higher IBD incidence with SSZ (2 patients) must be evaluated carefully because of small numbers.

MTX has shown efficacy for treatment of IBD in adults and seems also to be effective in juvenile-onset IBD<sup>30,31</sup>. Thus, it may be protective against the new occurrence of IBD manifestations in patients with JIA of our cohort. Further, IBD events more often occurred after the discontinuation of MTX (9 events) than upon treatment with MTX (2 events). Pretreatment with MTX is required for the approval of treatment of polyarticular JIA with ETN. Thus, nearly all of the patients of the BiKeR registry who have been exposed to ETN were pretreated with MTX. Upon successful treatment of arthritis with ETN, MTX was eventually withdrawn, often without the risk of flare of arthritis.

The incidence of an IBD event is higher in patients treated with ETN monotherapy, compared with the combination treatment of MTX and ETN. All of the 8 patients treated with ETN monotherapy who had experienced an IBD event were previously treated with MTX. Thus, the discontinuation of MTX upon good clinical response of the arthritis in patients treated with ETN can lead to the occurrence of IBD in patients at risk. Because the rate of IBD events is not significantly different in patients treated with MTX monotherapy compared with those treated with the combination of MTX and ETN, there is no reason to conclude that ETN treatment itself causes IBD. This conclusion is based on 2670 years of exposure to MTX monotherapy and 1610 years of exposure to a combination of MTX and ETN in the BiKeR registry with the occurrence of 1 event of IBD, respectively.

**Table 3.** Incidence rates related to drug exposure. Data are given as exposed and not exposed to the drug without considering concomitant medication. Occurrence of IBD was positively associated to the exposure to SSZ and ETN, while MTX was protective.

Drug Exposure		IBD Cases, n	Exposure Yrs	Incidence/ 1000 PY	OR*	95% CI*	p*
NSAID	+	5	4575	1.09	0.69	0.21–2.28	NS
	-	6	3814	1.57			
CS	+	3	1981	1.51	1.21	0.32–4.58	NS
	-	8	6409	1.25			
SSZ	+	2	195	10.26	9.34	2.05–43.51	< 0.05
	-	9	8195	1.10			
LEF	+	1	212	4.72	3.86	0.49–30.27	NS
	-	10	8178	1.22			
MTX	+	2	5455	0.37	0.12	0.03–0.55	< 0.05
	-	9	2935	3.07			
ETN	+	9	3557	2.53	6.11	1.32–28.32	< 0.05
	-	2	4833	0.41			

\* Chi-square test was performed for comparison of incidences with and without medication, respectively. IBD: inflammatory bowel disease; SSZ: sulfasalazine; ETN: etanercept; MTX: methotrexate; PY: patient-years; NSAID: nonsteroidal antiinflammatory drug; CS: corticosteroid; LEF: leflunomide; NS: not significant.

Increased numbers of unexpected paradoxical events involving TNF inhibitor therapy have been described, including not only onset of IBD but also new onset or exacerbation of psoriasis, uveitis, or aseptic granulomatous disease such as sarcoidosis<sup>32</sup>. This phenomenon of paradoxical inflammation has an estimated incidence of more than 10% in patients receiving TNF inhibitors<sup>33</sup>.

In our study, IBD occurred only during treatment with ETN, but not with other TNF inhibitors or biologics. In published cases, the onset of IBD with ETN therapy has been described more frequently than with other TNF inhibitors such as IFX<sup>14,15,16,17</sup>. It was proposed that instead of leading to apoptosis in lamina propria T cells as IFX and ADA do, ETN leads to cytokine production, which includes TNF- $\alpha$  and interferon- $\gamma$ . Further, binding of TNF- $\alpha$  to ETN is known to prolong the plasma half-life of the cytokine. These factors may favor the inflammation in the bowel mucosa and may result in granuloma formation, and thus lead to the development of new-onset IBD<sup>34,35,36</sup>. In patients with rheumatoid arthritis (RA), increased peripheral T cell activity both to self-antigens and to microbial antigens has been shown after ETN therapy<sup>37</sup>.

A common genetic pathway with an association between IBD and JIA has been demonstrated in large-scale studies<sup>38,39,40</sup>. RA, JIA, and IBD have common genetic features. The *REL* locus, *PRDM1/ATG5* locus, and *FCGR2A* locus are found to be associated with all of them<sup>41</sup>. In addition, in patients with RA and UC, the *IL2/IL21*, *TNFRSF14*, and *IRF5* loci are common. In patients with CD and RA, associations to the *IL2RA* locus have been found. In pediatric patients with IBD, CD was associated with a higher prevalence of RA (OR 15.7), systemic lupus erythematosus (OR 41.0), and hypothyroidism (OR 2.9)<sup>40</sup>.

A limitation of our approach to compare rates of adverse events between cohorts of patients treated with MTX and ETN with those treated with other nonbiologic DMARD and other biologics is that much lower exposure years for agents other than ETN and MTX have been documented in the registry. This has to be considered when judging the real risk of IBD from biologics.

Although the patient numbers reported here are, to our knowledge, the highest numbers available of patients with JIA exposed to biologics and followed prospectively to date, they may still be too small to finally answer this question. A common data analysis of all national registries and international cooperation within the Pharmachild registry may overcome this problem.

Because of the small number of cases, we were unable to use linear regression models to calculate the influence of distinct variables such as the JIA categories. This disadvantage may also be overcome by international collaboration.

The incidence of IBD in patients with JIA seems to be higher than in the general pediatric population. MTX therapy seems to be protective, while ETN seems not to be protective. While case numbers are still too small, further observation is

necessary to explore IBD in patients with JIA. Because of the limited number of cases, no further statistical analysis was performed.

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