Anti-TNF Treatment for Extraintestinal Manifestations of Inflammatory Bowel Disease in the Swiss IBD Cohort Study

Stephan R. Vavricka, MD,[1,2] Martin Gubler, MD,[1] Claudine Gantenbein, MD,[1] Muriel Spoerri, MD,[1] Florian Froehlich, MD,[3,4] Frank Seibold, MD,[5] Marijana Protic, MD,[6] Pierre Michetti, MD,[7] Alex Straumann, MD,[8] Nicolas Fournier, PhD,[9] Pascal Juillerat, MD, MSc,[10] Luc Biedermann, MD,[2] Jonas Zeitz, MD,[2] Benjamin Misselwitz, MD,[2] Michael Scharl, MD,[2] Henriette Heinrich, MD,[2] Christine N. Manser, MD,[2,11] Ekaterina Safroneeva, PhD,[12] Raja Affendi Raja Ali, MD,[13] Gerhard Rogler, MD, PhD,[2] Alain M. Schoepfer, MD,[4] and Thomas Greuter, MD,[2] Swiss IBD Cohort Study Group

Background: Extraintestinal manifestations (EIMs) in patients with inflammatory bowel disease (IBD) are frequently observed. Little is known about the efficacy of anti–tumor necrosis factor (TNF) in EIM management. We assessed the effect of 3 anti-TNF agents (infliximab, adalimumab, and certolizumab pegol) on EIM evolution.

Methods: Data on 1249 patients from the Swiss IBD Cohort Study (SIBDCS) were analyzed. All EIMs were diagnosed by relevant specialists. Response was classified into improvement, stable disease, and clinical worsening based on the physician's interpretation.

Results: Of the 366 patients with at least 1 EIM, 213 (58.2%) were ever treated with an anti-TNF. A total of 299 treatments were started for 355 EIMs. Patients with EIM were significantly more often treated with anti-TNF compared with those without EIM (58.2% versus 21.0%, $P < 0.001$). Infliximab was the most frequently used drug (63.2%). In more than 71.8%, a clinical response of the underlying EIM to anti-TNF therapy was observed. In 92 patients (43.2%), anti-TNF treatments were started for the purpose of treating EIM rather than IBD. Response rates to anti-TNF were generally good and best for psoriasis, aphthous stomatitis, uveitis, and peripheral arthritis. In 11 patients, 14 EIM occurred under anti-TNF treatment.

Conclusions: Anti-TNF was frequently used among patients with EIM. In more than 40%, anti-TNF treatments are started to treat EIM rather than IBD. Given the good response rates, anti-TNF seems to be a valuable option in the treatment of EIM, whereas appearance of EIM under anti-TNF does not seem to be a source of considerable concern.

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Key Words: extraintestinal manifestations, inflammatory bowel disease, arthritis, uveitis, anti-TNF

Inflammatory bowel diseases (IBD) with the 2 main subtypes, Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract. The etiopathogenesis of IBD is incompletely understood, although it is considered to be a multifactorial disease, which arises from a complex interplay between genetic, environmental, and immunological factors with an abnormal host immune response to environmental stimuli.[1,2] Extraintestinal manifestations (EIMs) of IBD are

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From the [1]Division of Gastroenterology and Hepatology, Triemli Hospital Zurich, Zurich, Switzerland; [2]Division of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland; [3]Division of Gastroenterology and Hepatology, University Hospital Basel, Basel, Switzerland; [4]Division of Gastroenterology and Hepatology, University Hospital Lausanne—CHUV, Lausanne, Switzerland; [5]Division of Gastroenterology, Lindenhof Spital, Bern, Switzerland; [6]Division of Gastroenterology and Hepatology, Spital Tiefenau, Bern, Switzerland; [7]Crohn and Colitis Center, Clinique La Source-Beaulieu, Lausanne, Switzerland; [8]Praxis Römerhof, Olten, Switzerland; [9]Institute of Social and Preventive Medicine (IUMSP), University of Lausanne, Lausanne, Switzerland; [10]Department of Gastroenterology, Clinic for Visceral Surgery and Medicine, Inselspital, University Hospital of Bern, Bern, Switzerland; [11]Department of Gastroenterology, See Spital, Horgen, Switzerland; [12]Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland; and [13]Division of Gastroenterology, The National University of Malaysia Medical Centre, Kuala Lumpur, Malaysia.

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Swiss IBD Cohort Study Group Members are listed in Appendix 1.

Address correspondence to: Stephan R. Vavricka, MD, Division of Gastroenterology and Hepatology, Triemli Hospital Zurich, Birmensdorferstrasse 497, 8063 Zurich, Switzerland (e-mail: stephan.vavricka@triemli.zuerich.ch).

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frequently observed with a prevalence ranging from 6% to 47%.[3–10] EIMs considerably affect morbidity and mortality in patients with IBD.[11,12] EIMs mostly affect joints (peripheral arthritis, axial arthropathy [AS]), the skin (erythema nodosum [EN], pyoderma gangrenosum [PG]), the eyes (uveitis), and the hepatobiliary tract (primary sclerosing cholangitis [PSC]). Although some EIMs are associated with IBD activity such as type 1 arthritis or EN, other EIMs such as PG, AS, uveitis, PSC, or type 2 arthritis do not parallel intestinal disease activity.[10,13–16] Although different EIMs tend to cluster in up to one quarter of EIM-affected patients, suggesting a common pathogenic link, little is known about their underlying pathomechanisms.[11,17] However, both intestinal and extraintestinal IBD manifestations are believed to share tumor necrosis factor (TNF)-dependent mechanisms.[18]

There is limited evidence regarding the efficacy of particular EIM treatments. This lack of good evidence is probably related to the difficulty of analyzing EIM treatments in a cross-sectional manner as only a few patients will suffer from EIM at the time of study enrollment.[18] Although introduction of biologics considerably changed the management of EIM in IBD, there are only few and small studies supporting evidence for the efficacy of anti-TNF: Infliximab may be efficacious in cutaneous, ocular, and joint manifestations with clinical response for PG, EN, aphthous stomatitis,[19–24] and peripheral arthritis and AS, respectively.[19,21,25] The strongest evidence for efficacy of infliximab has been shown in PG management.[26] In addition, there is some evidence for the efficacy of adalimumab in patients with CD presenting with EIM.[27] The CARE study (Crohn's Treatment with Adalimumab: Patient Response to a Safety and Efficacy Study), an open label multicenter phase IIIb trial showed a significant decrease in the frequency of arthralgia, arthritis, oral aphthous ulcers, and EN at week 20.[28] In contrast, anti-TNF treatment for PSC is not recommended given the lack of evidence for clinical efficacy. If anti-TNF has to be used for underlying IBD activity, the course of PSC is influenced neither positively nor negatively.[29,30] Current (limited) knowledge on anti-TNF efficacy has been nicely summarized by Peyrin-Biroulet et al recently.[31] However, because of significant variations between the analyzed studies (regarding study design, studied EIM, and study outcome) data have not been meta-analyzed.

Given this limited evidence for efficacy of anti-TNF treatment in IBD patients with EIM, we investigated the role of anti-TNF agents in the large nation-wide Swiss IBD Cohort Study (SIBDCS) and analyzed the influence of 3 available anti-TNF agents (infliximab, adalimumab, and certolizumab pegol) on the evolution of different EIMs.

METHODS

Patients

The SIBDCS is a nation-wide cohort study from all regions of Switzerland, which has been including patients with IBD meeting the diagnostic criteria according to the established guidelines. Enrollment started in 2006. The SIBDCS is supported by the Swiss National Science Foundation and is approved by the local ethics committees of the participating centers. The patients have to meet the following inclusion criteria: (1) written informed consent, (2) permanent residency status in Switzerland and/or coverage by a Swiss health insurance, (3) diagnosis of CD, UC, or IBD unclassified established at least 4 months before enrollment or at least 1 episode of symptom recurrence. Assessment includes a thorough clinical and laboratory analyses (including information about IBD diagnosis, clinical course, disease activity, surgery, medication, and EIM). A detailed questionnaire about IBD diagnosis, clinical course, and disease activity is completed by patients' treating physicians. Patient-reported outcome questionnaires are completed by each individual patient. Annual follow-up questionnaires are completed by both the responsible physicians and their patients.

Definition of EIM and Anti-TNF Outcome

All EIMs had to be diagnosed by a relevant specialist: Diagnosis of skin manifestations was established by a dermatologist, of joint affections by a rheumatologist, of eye manifestations by an ophthalmologist, and of PSC by a gastroenterologist. We analyzed the following EIM: peripheral arthritis, uveitis, PG, EN, aphthous stomatitis, AS, psoriasis, and PSC. Diagnosis of EIM relied on previously published criteria.[17] Evolution of EIM under anti-TNF treatment was judged according to the relevant specialist's global assessment that was based on patient history, clinical findings, and laboratory parameters (in the case of PSC). The course of a particular EIM under anti-TNF treatment was classified into the following 3 categories: clinical improvement, stable disease unaffected by anti-TNF, and clinical worsening.

Data Collection and Management

Data were entered into a Microsoft Access database (Access 2000; Microsoft Switzerland Ltd. Liab. Co., Wallisellen, Switzerland). All completed questionnaires were sent to the data center of the SIBDCS located at the Institute of Social and Preventive Medicine, University of Lausanne, Switzerland. All data were validated by the responsible data manager. Collected data consisted of 2 standardized questionnaires, one completed by the responsible physician, the other by each individual patient. The former included the following items: demographic characteristics, onset of symptoms, date of diagnosis, extent of disease, IBD family history, smoking status, results of laboratory tests, current therapy, and medical history. Furthermore, this questionnaire assessed past and present EIM. The latter questionnaire completed by each patient included the following items: patient demographics, IBD diagnosis, and current medications. Because information about appearance of EIM in relation to the time of IBD diagnosis and evolution of EIM under anti-TNF treatment was not captured by those standardized questionnaires, we further reviewed each individual's patient chart at the responsible IBD center to complete, together with the treating physician and the relevant specialist, an additional questionnaire, which included items on various characteristics of EIM and their evolution under anti-TNF treatment. All 1249 patients with IBD who were

enrolled into the SIBDCS between January 2006 and March 2010 were eligible for this study. For outcome analysis, only those patients with both EIM and current or past anti-TNF treatment were included. EIMs were only taken into account if present at the time of anti-TNF treatment.

Statistical Analysis

For all statistical analyses, IBM software SPSS version 23.0.0 (2014 SPSS Science, Inc., Chicago, IL) was used. Metric data are shown as medians with their total range. Categorical data are summarized as the percentage of the group total. Comparisons between categorical data were performed using Chi-square test, or the Fisher's exact test in case of small sample size ($n < 10$). Multivariate logistic regression analysis regarding prediction of anti-TNF response was performed by first taking into account all covariates with a univariate P value of <0.15, removing insignificant covariates, and then adding remaining covariates one by one, checking the model significance and consistency at each step. A 2-sided P value of <0.05 was regarded as statistically significant.

RESULTS

Patient Demographics

Of the 1249 patients who were enrolled into the SIBDCS between January 2006 and March 2010, 366 (29.3%) suffered from at least 1 EIM that occurred either before or after the time of IBD diagnosis. Of those, 213 patients (58.2%) were ever treated with one or several anti-TNF agents, whereas 153 (41.8%) had never received these drugs. Patients with EIM were significantly

TABLE 1. Demographic Data According to IBD Subtype

	UC (n = 40)	CD (n = 165)	IBD-U (n = 6)	Total (n = 213)
Sex				
No. of males, n (%)	18 (45.0)	59 (35.8)	0 (0)	77 (36.2)
Age at IBD diagnosis	29.0 (13.8–61.5)	24.5 (4.0–58.7)	28.3 (18.3–36.8)	25.2 (4.0–61.5)
Age at enrollment	30.4 (20.4–64.8)	39.6 (16.1–73.8)	32.5 (20.6–44.7)	39.2 (16.1–73.8)
Duration of IBD at enrollment	9.9 (0.3–20.2)	9.8 (0.3–36.6)	4.4 (0.8–7.4)	9.0 (0.3–36.6)
Disease location, n (%)	E1: 2 (5.0)	L1: 33 (20.0)		
	E2: 20 (50.0)	L2: 53 (32.1)		
	E3: 13 (32.5)	L3: 35 (21.2)		
	Missing: 5 (12.5)	L4: 2 (1.2)		
		L1+L4: 1 (0.6)		
		L2+L4: 1 (0.6)		
		L3+L4: 2 (1.2)		
		Missing: 38 (23.0)		
Cohort follow-up time, mo	81.6 (0.0–102.0)	83.7 (0.0–108.0)	87.8 (60.7–97.2)	83.7 (0.0–108.0)
Previous medication, n (%)				
5-ASA	37 (92.5)	107 (64.8)	6 (100.0)	152 (71.4)
AB	19 (47.5)	103 (62.4)	4 (66.7)	128 (60.1)
Steroids	39 (97.5)	156 (94.5)	6 (100.0)	203 (95.3)
IM	35 (87.5)	158 (95.8)	6 (100.0)	201 (94.4)
Comedication concomitant with anti-TNF, n (%)				
5-ASA	12 (30.0)	22 (13.3)	1 (16.7)	35 (16.4)
AB	0 (0.0)	15 (9.1)	0 (0.0)	15 (7.0)
Steroids	19 (47.5)	52 (31.5)	3 (50.0)	75 (35.2)
IM	5 (12.5)	52 (31.5)	4 (66.7)	61 (28.6)
Smoking status, n (%)				
No	37 (92.5)	101 (61.2)	4 (66.7)	142 (66.7)
Yes	2 (5.0)	61 (37.0)	2 (33.3)	67 (31.5)
unknown	1 (2.5)	3 (1.8)	0 (0.0)	4 (1.9)

IBD subtype of 2 patients unknown. Disease location L1 (disease isolated to ileum), L2 (disease isolated to large bowel), L3 (disease involving ileum and colon), L4 (disease isolated to upper gastrointestinal tract), E1 (proctitis, inflammation limited to the rectum), E2 (left-sided distal, inflammation limited to the splenic flexure), E3 (pancolitis, inflammation extends to the proximal splenic flexure).
5-ASA, 5-aminosalicylic acid;AB, antibiotics; IBD-U, IBD unclassified; IM, immunomodulators (methotrexate, azathioprine, and cyclosporine).

TABLE 2. Frequency of Different EIMs According to IBD Subtype

	UC (n = 40)	CD (n = 165)	IBD-U (n = 6)	Total (n = 213)
Age at first EIM	36.8 (17.7 to 58.1)	35.2 (4.5 to 66.0)	32.8 (27.7–37.9)	35.3 (4.5 to 66.0)
Duration from IBD to EIM	4.9 (−0.4 to 16.8)	3.9 (−17.7 to 34.2)	4.0 (0.0–8.0)	4.4 (−17.7 to 34.2)
No. of EIM, n (%)				
1	27 (67.5)	88 (53.3)	6 (100.0)	122 (57.3)
2	11 (27.5)	53 (32.1)	0 (0.0)	65 (30.5)
3	1 (2.5)	9 (5.5)	0 (0.0)	10 (4.7)
4	1 (2.5)	6 (3.6)	0 (0.0)	7 (3.3)
5	0 (0.0)	9 (5.5)	0 (0.0)	9 (4.2)
EIM, n (%)				
Arthritis	24 (60.0)	131 (79.4)	5 (83.3)	161 (75.6)
Uveitis	4 (10.0)	29 (17.6)	0 (0.0)	33 (15.5)
PG	2 (5.0)	9 (5.5)	0 (0.0)	11 (5.2)
EN	7 (17.5)	18 (10.9)	0 (0.0)	26 (12.2)
Stomatitis	4 (10.0)	46 (27.9)	0 (0.0)	50 (23.5)
AS	9 (22.5)	35 (21.2)	1 (16.7)	46 (21.6)
PSC	4 (10.0)	6 (3.6)	0 (0.0)	10 (4.7)
Psoriasis	1 (2.5)	7 (4.2)	0 (0.0)	8 (3.8)

IBD subtype of 2 patients unknown.
IBD-U, IBD unclassified.

more often treated with anti-TNF compared with those patients without EIM (213/366, 58.2% versus 185/883, 21.0%, $P < 0.001$). Seventy-seven patients of those 213 treated with anti-TNF were men (36.2%), 40 patients had UC (18.8%), 165 had CD (77.5%), and 6 had IBD unclassified (2.8%). In 2 patients, exact IBD subtype was unclear or subtype classification changed over time. Median age at IBD diagnosis was 25.2 years (4.0–61.5) with a median age of 39.2 years (16.1–73.8) at enrollment into the SIBDCS. Median duration of IBD at enrollment was 9.0 years (0.3–36.6). The clinical characteristics of these 213 patients are summarized in Table 1 according to the underlying IBD subtype.

Frequency and Types of EIM

Most of the 213 patients included in our analysis suffered from 1 EIM (122/213, 57.3%), whereas 30.5% of patients (65/213) had 2 EIMs, 4.7% (10/213) had 3 EIMs, and 3.3% (7/213) had 4 EIMs. The maximum number of EIMs was 5 (9/213, 4.2%). The most frequently reported EIMs were peripheral arthritis (161/213, 75.6%), aphthous stomatitis (50/213, 23.5%), and AS (46/213, 21.6%). Median duration from IBD to EIM was 4.4 years (−17.7 to 34.2). A detailed overview over the different EIMs according to IBD subtype is provided in Table 2.

Type of Anti-TNF Treatment and Treated EIM in the Study Population

One hundred forty-seven patients (69.0%) were treated with 1 TNF blocker, whereas in 46 patients 2 different TNF blockers were initiated successively (21.6%) and in the remaining 20 patients (9.4%) a total of 3 anti-TNF courses were started. Thus, a total of 299 anti-TNF therapies were initiated in these 213 patients with 355 EIM. Infliximab was used in 63.2% (n = 189), adalimumab in 22.4% (n = 67), and certolizumab pegol was used in 14.4% (n = 43). CD patients with EIM were significantly more frequently treated with anti-TNF compared with patients with UC (165/248, 66.5% versus 40/105, 38.1%, $P < 0.001$). Anti-TNF agents were started in 49.3% of patients (n = 105) to treat intestinal IBD activity, in 43.2% (n = 92) of patients to treat EIM, and in 0.5% (n = 1) of patients to treat both intestinal activity and EIM. In the remaining 15 patients (7.0%), the exact indication for anti-TNF treatment could not be identified. In 224 of the 299 anti-TNF treatments (74.9%), the underlying EIMs were recorded in detail: Among the most frequently reported were peripheral arthritis (158/224, 70.5%), aphthous stomatitis (32/224, 14.3%), AS (34/224, 15.2%), and uveitis (25/224, 11.2%). Further treated EIMs were PG (12/224, 5.4%), PSC (8/224, 3.6%), EN (10/224, 4.5%), and psoriasis (6/224, 2.7%). Order of frequency of treated EIM showed significant differences when those patients reporting EIM as an indication for anti-TNF treatment were compared with those reporting IBD as the underlying disease; PG and AS were more often treated when anti-TNF were initiated for EIM, whereas EN and stomatitis were more often treated when anti-TNF treatments were started for intestinal disease activity. No anti-TNF therapy was initiated to treat underlying PSC. For details see Figure 1. As it is known that EIM can manifest under anti-TNF therapy, we analyzed their first presentation according to the time point of anti-TNF introduction. In 11 patients, a total

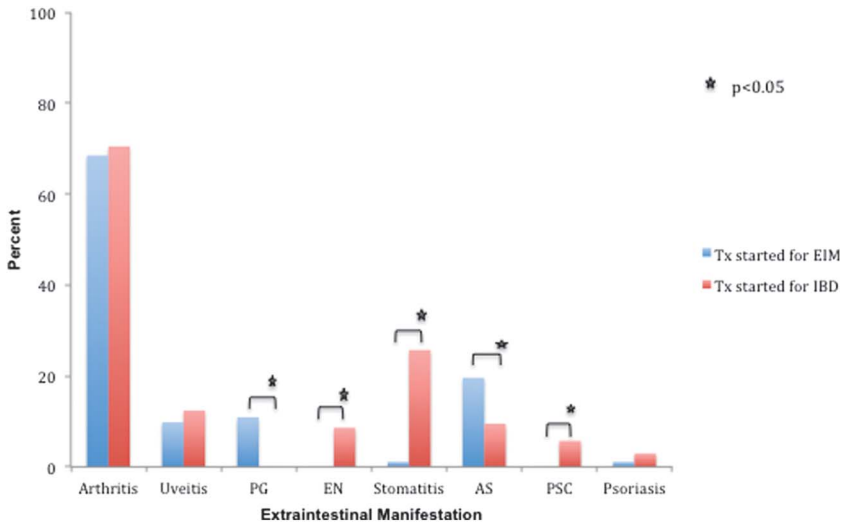

FIGURE 1. Frequency of treated EIM according to anti-TNF indication. Y-axis depicts the percentage of patients treated for each individual EIM. X-axis shows individual EIM according to whether underlying EIM or IBD was treated. As some patients were treated for several EIMs, the sum may exceed 100%. Patients who were treated with anti-TNF for EIM had significantly more often AS and PG. In contrast, patients who received anti-TNF for intestinal disease activity more often had stomatitis and EN. No anti-TNF treatment was initiated to treat PSC.

of 14 different EIMs developed under anti-TNF treatment: 4 patients suffered from newly diagnosed peripheral arthritis, 1 patient had peripheral arthritis and AS, 3 patients suffered from PG, 1 patient from aphthous stomatitis, 1 patient from psoriasis, and 1 patient from peripheral arthritis, uveitis, and aphthous stomatitis. Most (11/14, 76.9% of EIM) was observed under infliximab, 2 under adalimumab, and 1 under certolizumab pegol. Most of the EIM improved during continuation of anti-TNF treatment (64.3%), whereas only in 1 patient a clinical worsening (PG) was documented. In the majority (94.4%), EIM did not manifest under anti-TNF treatment.

Clinical Evolution of EIM Under Anti-TNF Treatment

We assessed the clinical evolution of EIM under anti-TNF treatment. In 71.8% (163/227) of all anti-TNF therapies, patients demonstrated a clinical improvement of the underlying EIM. In 26.4% (60/227), no response was observed, whereas in only 1.8% (4/227) a worsening of EIM was seen under anti-TNF treatment. For the remaining 72 anti-TNF treatments, the exact evolution of EIM could not be identified. Infliximab showed an improvement rate of 74%, adalimumab of 70%, and certolizumab pegol of 56%. The difference between intravenous (infliximab) and subcutaneous anti-TNF agents (adalimumab, certolizumab pegol) was only slight, and not statistically significant. For details see Figure 2. Anti-TNF agent did not predict treatment outcome in a logistic regression model (see Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B491). The best response rates were reported for psoriasis (6/6, 100%), EN (8/10, 80%), aphthous stomatitis (25/32, 78.1%), peripheral arthritis (116/158, 73.4%), and uveitis (18/25, 72.0%). Only PG showed a response rate of less than 60%. If only those 93 patients who were actually treated for EIM (92 patients for EIM alone, 1 patient for EIM and IBD) were included in outcome analysis, peripheral arthritis and uveitis showed even higher rates of improvement. For details see Figures 3 and 4. There was no difference in anti-TNF response when patients with concomitant immunosuppressive treatment were compared with those without (70.2% versus 73.6%, $P = 0.577$). Moreover, concomitant immunosuppressive treatment was no predictor for anti-TNF outcome in a logistic regression model (for details see Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B491). Use of anti-TNF and overall anti-TNF response rates of EIM associated with IBD activity and EIM not associated with intestinal disease were comparable; overall response rates were 74.3% and 65.5%, respectively, $P = 0.165$ (see Supplementary

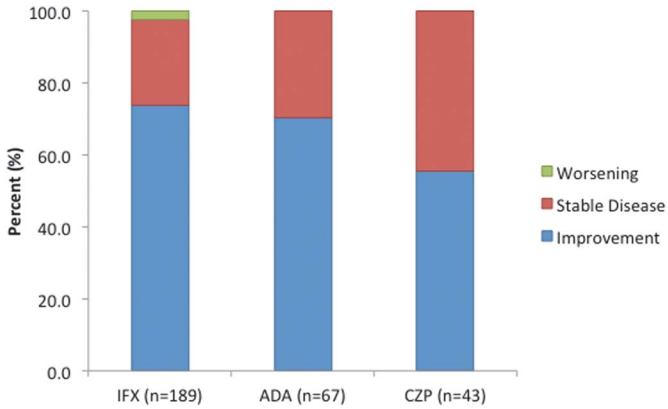

FIGURE 2. Overall outcome of anti-TNF treatment. Infliximab (IFX) showed an improvement rate of 74%, adalimumab (ADA) of 70%, and certolizumab pegol (CZP) of 56%.

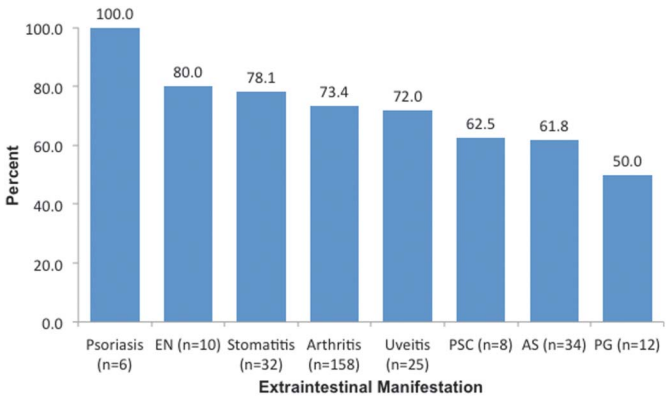

FIGURE 3. Overall anti-TNF response rates (213 patients). Response rates were best for psoriasis (6/6, 100%), EN (8/10, 80%), and stomatitis (25/32, 78.1%).

Table 2, Supplemental Digital Content 1, http://links.lww.com/IBD/B491). Furthermore, IBD activity did not predict anti-TNF outcome in a logistic regression model (see Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B491). Indeed, the only predictor for negative anti-TNF response was the presence of UC/IBD unclassified, even in a multivariate analysis corrected for age, sex, and previous anti-TNF use (odds ratio 0.337 [0.144–0.793], $P = 0.013$). For details see Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B491.

DISCUSSION

In this retrospective analysis of the Swiss IBD Cohort Study, we report on the use of anti-TNF agents in IBD patients with EIM in Switzerland and EIM evolution under such therapy. More than half of the patients presenting with EIM were treated with anti-TNF. The presence of EIM was significantly associated with the use of anti-TNF. In more than 40% of patients, anti-TNF treatments were started for the purpose of treating underlying EIM. Response rates to anti-TNF were generally good with overall improvement rates of more than 70%. Best response rates were seen for psoriasis, aphthous stomatitis, uveitis, and peripheral arthritis.

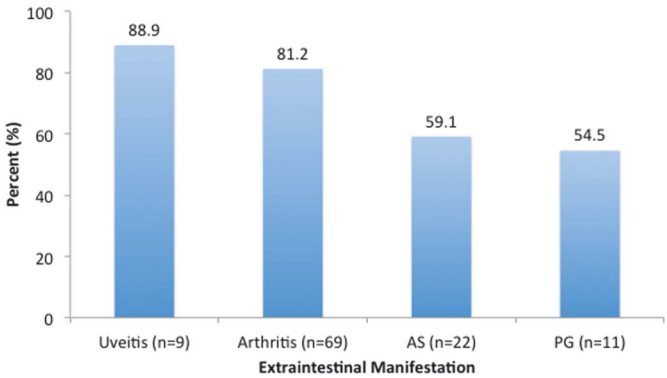

FIGURE 4. Anti-TNF response rates in those patients treated for EIM (93 patients, 113 EIMs). Psoriasis and stomatitis showed response rates of 100%; however, both were excluded from analysis because of the low number (n = 1).

Peripheral arthritis was the most frequently observed EIM, which was treated with anti-TNF, followed by aphthous stomatitis, AS, uveitis, and skin manifestations (such as EN, PG, and psoriasis). The order of EIM frequency was consistent with a previous study from the SIBDCS, which analyzed the total frequency of EIM in the Swiss cohort.[10] Thus, the most frequent EIMs are also the ones which are most frequently treated with anti-TNF. Psoriasis for example, which is the least frequently occurring EIM in the Swiss cohort (1.5% according to Vavricka et al[10]), was also the least frequently anti-TNF-treated EIM. However, the low prevalence of psoriasis contrasts other EIM studies such as the one by Yates et al[32] who showed a prevalence of 11.2% in CD and 5.7% in patients with UC, respectively. Despite the limited evidence for anti-TNF agents in EIM management, anti-TNF treatments were started in more than 40% to treat underlying EIM rather than intestinal disease activity. When anti-TNF was started for EIM, order of frequency of treated EIM was significantly different compared with the condition, when therapy was initiated for IBD: PG and AS were significantly more often treated when anti-TNF was started for EIM, whereas anti-TNF therapy was rarely initiated for EN or stomatitis. This finding nicely illustrates the concept of IBD dependence of some, but not all EIMs. In addition, relative frequency of PG treatment is consistent with the fact that the evidence for infliximab's efficacy in EIM management is the strongest for PG.[26] No treatment was started for PSC, which may be due to very contradictory data hitherto.[33]

Although there is some evidence to support anti-TNF treatment in peripheral arthritis, AS, and PG,[20,26,34] data for most EIM are limited and are partially based on small case series or reports of severe and difficult-to-treat patients.[21,35,36] Hence, our finding of an overall response rate of more than 70% advances our knowledge about the efficacy of anti-TNF. Anti-TNF outcome was best for psoriasis, aphthous stomatitis, uveitis, and peripheral arthritis in those patients who were treated for EIM rather than IBD. Response rates for uveitis and arthritis were comparable with those very recently published in a comprehensive review by Peyrin-Biroulet et al, although our study population relevantly exceeds the number of patients in the studied trials (response for uveitis 1/1 and 2/2, response for arthritis 19/31 and 8/10). Response rates for AS were slightly higher in the mentioned review (response for AS 5/7, response for inflammatory back pain 7/11), although our patient numbers again were higher. Response rates for stomatitis were comparable. If we look at all patients with stomatitis being treated with anti-TNF, our study population again relevantly exceeds patient number studied in the systematic review (3 versus 33).[31] Excellent response rates for psoriasis are consistent with previous studies showing successful use of anti-TNF in psoriasis management.[37,38] In contrast to the mentioned review by Peyrin-Biroulet, where no or only minimal evidence for

other biological agents such as certolizumab was found, we herein report on 43 cases treated with certolizumab pegol showing good clinical response rates, which were not significantly different from those of infliximab or adalimumab.

Our study has several strengths and some limitations as well. With 213 patients receiving a total of 299 anti-TNF treatments for 355 EIM, it represents one of the largest analyses of EIM management. Questionnaires evaluating EIM and anti-TNF treatment outcome were physician and patient based and therefore less prone to underreporting. However, we used a retrospective uncontrolled, noninterventional study design, which limits interpretation of treatment outcome. Assessment of anti-TNF outcome was not standardized and based on physician's interpretation of patient history, clinical findings, and laboratory parameters (in the case of PSC) only. Furthermore, as the SIBDCS is not strictly population based, a selection bias may be present. A clear limitation of our analysis is that we did not include psoriasiform anti–TNF-associated skin lesions, which is now a frequently reported phenomenon.[39] However, we included many patients with enrollment and anti-TNF treatment before 2009; at that time, anti–TNF-induced psoriasiform skin lesions were believed to be an extremely rare event.[40] In addition, only 13 cases have been identified at the University Hospital Zurich between 2007 and 2013.[41] The single case of psoriasis under anti-TNF treatment in our analysis is rather a coincidence than a misinterpreted anti–TNF-induced skin lesion given the fact that improvement was observed with continuation of anti-TNF treatment. Because of the retrospective nature, it was not possible to clearly distinguish the 14 EIMs that occurred under anti-TNF treatment from anti-TNF side effects. Neither antidrug antibodies nor drug levels were checked in these patients. Furthermore, a nonnegligible proportion of patients received concomitant immunomodulators or steroids, so there may be an additional effect. However, similar results were seen, when those patients with concomitant therapy were excluded from analysis. In addition, concomitant immunosuppressive treatment did not predict anti-TNF outcome in logistic regression model.

In conclusion, anti-TNF agents were frequently used in patients with EIM and were started in more than 40% to treat EIM rather than IBD. Given the good response rates, the anti-TNF agents such as infliximab, adalimumab, and certolizumab pegol seem to be a valuable option in the treatment of EIM, whereas appearance of EIM as a side effect does not seem to be a source of considerable concern. In any case, to clearly establish the role of TNF inhibitors for treatment of EIM, randomized controlled trials are needed.

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Appendix I. Members of the SIBDCS Study Group

Claudia Anderegg, Peter Bauerfeind, Christoph Beglinger, Stefan Begré, Dominique Belli, José M. Bengoa, Luc Biedermann, Beat Bigler, Janek Binek, Mirjam Blattmann, Stephan Boehm, Jan Borovicka, Christian P. Braegger, Nora Brunner, Patrick Bühr, Bernard Burnand, Emanuel Burri, Sophie Buyse, Matthias Cremer, Dominique H. Criblez, Philippe de Saussure, Lukas Degen, Joakim Delarive, Christopher Doerig, Barbara Dora, Gian Dorta, Mara Egger, Tobias Ehmann, Ali El-Wafa, Matthias Engelmann, Jessica Ezri, Christian Felley, Markus Fliegner, Nicolas Fournier, Montserrat Fraga, Pascal Frei, Remus Frei, Michael Fried, Florian Froehlich, Christian Funk, Raoul Ivano Furlano, Suzanne Gallot-Lavallée, Martin Geyer, Marc Girardin, Delphine Golay, Tanja Grandinetti, Beat Gysi, Horst Haack, Johannes Haarer, Beat Helbling, Peter Hengstler, Denise Herzog, Cyrill Hess, Klaas Heyland, Thomas Hinterleitner, Philippe Hiroz, Claudia Hirschi, Petr Hruz, Rika Iwata, Res Jost, Pascal Juillerat, Vera Kessler Brondolo, Christina Knellwolf, Christoph Knoblauch, Henrik Köhler, Rebekka Koller, Claudia Krieger-Grübel, Gerd Kullak-Ublick, Patrizia Künzler, Markus Landolt, Rupprecht Lange, Frank Serge Lehmann, Andrew Macpherson, Philippe Maerten, Michel H. Maillard, Christine Manser, Michael Manz, Urs Marbet, George Marx, Christoph Matter, Valérie McLin, Rémy Meier, Martina Mendanova, Christa Meyenberger, Pierre Michetti, Benjamin Misselwitz, Darius Moradpour, Bernhard Morell, Patrick Mosler, Christian Mottet, Christoph Müller, Pascal Müller, Beat Müllhaupt, Claudia Münger-Beyeler, Leilla Musso, Andreas Nagy, Michaela Neagu, Cristina Nichita, Jan Niess, Natacha Noël, Andreas Nydegger, Nicole Obialo, Carl Oneta, Cassandra Oropesa, Ueli Peter, Daniel Peternac, Laetitia Marie Petit, Franziska Piccoli-Gfeller, Julia Beatrice Pilz, Valérie Pittet, Nadia Raschle, Ronald Rentsch, Sophie Restellini, Jean-Pierre Richterich, Sylvia Rihs, Marc Alain Ritz, Jocelyn Roduit, Daniela Rogler, Gerhard Rogler, Jean-Benoît Rossel, Markus Sagmeister, Gaby Saner, Bernhard Sauter, Mikael Sawatzki, Michela Schäppi, Michael Scharl, Martin Schelling, Susanne Schibli, Hugo Schlauri, Sybille Schmid Uebelhart, Jean-François Schnegg, Alain Schoepfer, Frank Seibold, Mariam Seirafi, Gian-Marco Semadeni, David Semela, Arne Senning, Marc Sidler, Christiane Sokollik, Johannes Spalinger, Holger Spangenberger, Philippe Stadler, Michael Steuerwald, Alex Straumann, Bigna Straumann-Funk, Michael Sulz, Joël Thorens, Sarah Tiedemann, Radu Tutuian, Stephan Vavricka, Francesco Viani, Jürg Vögtlin, Roland Von Känel, Alain Vonlaufen, Dominique Vouillamoz, Rachel Vulliamy, Jürg Wermuth, Helene Werner, Paul Wiesel, Reiner Wiest, Tina Wylie, Jonas Zeitz, and Dorothee Zimmermann.