

## ORIGINAL ARTICLE

# Chronological Order of Appearance of Extraintestinal Manifestations Relative to the Time of IBD Diagnosis in the Swiss Inflammatory Bowel Disease Cohort

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**Background:** Data evaluating the chronological order of appearance of extraintestinal manifestations (EIMs) relative to the time of inflammatory bowel disease (IBD) diagnosis is currently lacking. We aimed to assess the type, frequency, and chronological order of appearance of EIMs in patients with IBD.

**Methods:** Data from the Swiss Inflammatory Bowel Disease Cohort Study were analyzed.

**Results:** The data on 1249 patients were analyzed (49.8% female, median age: 40 [interquartile range, 30–51 yr], 735 [58.8%] with Crohn's disease, 483 [38.7%] with ulcerative colitis, and 31 [2.5%] with indeterminate colitis). A total of 366 patients presented with EIMs (29.3%). Of those, 63.4% presented with 1, 26.5% with 2, 4.9% with 3, 2.5% with 4, and 2.7% with 5 EIMs during their lifetime. Patients presented with the following diseases as first EIMs: peripheral arthritis 70.0%, aphthous stomatitis 21.6%, axial arthropathy/ankylosing spondylitis 16.4%, uveitis 13.7%, erythema nodosum 12.6%, primary sclerosing cholangitis 6.6%, pyoderma gangrenosum 4.9%, and psoriasis 2.7%. In 25.8% of cases, patients presented with their first EIM before IBD was diagnosed (median time 5 mo before IBD diagnosis: range, 0–25 mo), and in 74.2% of cases, the first EIM manifested itself after IBD diagnosis (median: 92 mo; range, 29–183 mo).

**Conclusions:** In one quarter of patients with IBD, EIMs appeared before the time of IBD diagnosis. Occurrence of EIMs should prompt physicians to look for potential underlying IBD.

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**Key Words:** extraintestinal manifestations, inflammatory bowel disease, arthritis, uveitis

Crohn's disease (CD) and ulcerative colitis (UC) represent the main entities of inflammatory bowel diseases (IBDs). During their lifetime, patients with IBD are likely to suffer from extraintestinal manifestations (EIMs), which are reported with frequencies ranging from 6% to 47%.<sup>1–8</sup> The occurrence of EIM can considerably affect morbidity and mortality in patients with

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IBD.<sup>9,10</sup> EIMs are classified into 3 major groups. The first one includes manifestations that are either associated with intestinal disease activity (peripheral arthritis, erythema nodosum, oral aphthous ulcers) or not (pyoderma gangrenosum, uveitis, spondylarthropathy, primary sclerosing cholangitis [PSC]).<sup>11</sup> The second category of EIMs encompasses non-IBD-specific autoimmune diseases, such as thyroid disease, hemolytic anemia, vitiligo, or insulin-dependent diabetes mellitus. The third group includes IBD-related complications that are attributed to anatomical or metabolic abnormalities, such as osteopathy, nephrolithiasis, or thromboembolic events.

Most patients with CD and UC suffering from EIMs also present with extensive colitis and are likely to have a positive IBD family history.<sup>8,12</sup> Most EIMs tend to follow the clinical course of IBD, with the exception of axial arthropathy/ankylosing spondylitis, PSC, pyoderma gangrenosum, and uveitis.<sup>8,13–16</sup> We have recently reported that about one quarter of EIM-affected IBD patients tend to suffer from a combination of several EIMs during their disease course (up to 5 EIMs).<sup>8</sup> It seems that the appearance of 1 EIM increases the susceptibility to developing other EIMs.<sup>8</sup> The skin, joints, the biliary tract, as well as the eyes represent the organs most commonly affected by EIM. The high frequency with which these 4 organs are involved suggests a common pathogenic link; however, the underlying mechanisms are yet not completely understood.<sup>9</sup>

Despite the fact that EIMs are frequently observed in patients with IBD, data on the frequency of EIMs in large IBD populations are scarce. Furthermore, studies evaluating the chronological order of appearance of EIMs relative to the time of IBD diagnosis are lacking. As such, the proportion of patients presenting with EIMs before or after the time of IBD diagnosis has not been elucidated. The data about EIMs that precede the time of IBD diagnosis are of particular interest, since appearance of EIMs may help treating physicians to detect IBD and in doing so shorten the diagnostic delay.<sup>17</sup>

We aimed to determine the frequency of patients affected by EIM(s) before and after the time of IBD diagnosis and to assess the cumulative risk of developing one or several EIMs relative to the time of IBD diagnosis in a large national cohort of patients with IBD.

## MATERIALS AND METHODS

### Patients

The Swiss IBD Cohort Study (SIBDCS) has been including patients with IBD meeting the diagnostic criteria according to the established guidelines from all regions of Switzerland starting in 2006.<sup>18,19</sup> The SIBDCS is supported by the Swiss National Science Foundation and approved by local ethics committees of the participating centers.<sup>20</sup> For inclusion, patients need to provide written informed consent. Patients also need to have a permanent residency status in Switzerland and/or else need to be covered by a Swiss health insurance. Patients can be included into the cohort

if the diagnosis of CD, UC, or indeterminate colitis (IC) was established at least 4 months before inclusion, or if they had at least 1 episode of symptom recurrence.<sup>20</sup> At the time of inclusion, patients undergo a thorough clinical and laboratory assessment. Clinical, socioeconomic, and psychosocial data are collected. Detailed physician questionnaires are completed by patients' treating physicians, and patient-reported outcome questionnaires that, among other things, assess quality of life, the degree of social impairment and symptom severity, are completed by patients themselves. Patients were recruited in 5 University hospitals and 2 large private practices throughout Switzerland.

### Definitions for EIMs

All EIMs were diagnosed by a physician. The following EIMs were analyzed: peripheral arthritis, axial arthropathy/ankylosing spondylitis, aphthous stomatitis, uveitis, erythema nodosum, pyoderma gangrenosum, psoriasis, and PSC.<sup>11,17,21–23</sup> Rheumatologic EIMs were diagnosed by a rheumatologist. Peripheral arthritis was defined as pain, swelling, and/or redness in one or several peripheral joints. Axial arthropathy/ankylosing spondylitis was diagnosed based on a combination of typical symptoms, characteristic clinical findings, as well as x-ray examination. All patients with uveitis were diagnosed by an ophthalmologist. Erythema nodosum was diagnosed when tender bluish-red nodules (mainly on the extensor side of the limbs) were found, and pyoderma gangrenosum was diagnosed when typical chronic ulcers with undermined necrotic bluish margins (many of them beginning as pustular or nodular lesions) persisted for several weeks or longer. The skin lesions were diagnosed by dermatologists. PSC was diagnosed based on characteristic alterations of the biliary tract in endoscopic retrograde cholangiography and/or magnetic resonance cholangiography. Oral aphthous ulcers were diagnosed by the treating gastroenterologists.

## METHODS

Data were entered into a Microsoft Access database (Access 2000; Microsoft Switzerland Ltd. Liab. Co., Wallisellen, Switzerland). The questionnaires were sent to the datacenter of the SIBDCS at the Institute of Social and Preventive Medicine, University of Lausanne, Switzerland. All data were validated by the data manager, and rigorous rules were applied to ensure data quality.

A standardized questionnaire, which included items on demographic characteristics, onset of symptoms, date of diagnosis, extent of disease, family history of IBD, smoking status, the results of laboratory tests, current therapy, and medical history (drugs, complications, and surgery), was completed by the treating physician. In addition, the standardized questionnaire assessed whether patients with IBD had ever experienced any kind of EIM, and whether the EIM(s) was/were present at the time of inclusion. The disease location was grouped according to the Montréal classification. For CD, L1 denotes disease in the terminal ileum, L2 denotes disease in the colon, L3 denotes ileocolonic

disease, and L4 denotes isolated disease in the upper gastrointestinal tract.<sup>24</sup> For UC, E1 denotes rectal disease, E2 denotes left-sided colitis, and E3 denotes extensive colitis. Since the information on the chronological order of appearance of EIM relative to the time of IBD diagnosis was not captured by the standardized questionnaires, 2 medical students (C.G. and M.S.) visited IBD centers, in which patients were included, and reviewed patient files to complete, together with the treating physician, an additional questionnaire that included items on various characteristics of EIMs. Only patients with all chronologic information regarding the appearance of EIM relative to IBD diagnosis were included. This work was performed under supervision of S.R.V. and A.M. S., who also validated all data obtained using this additional questionnaire. For the purposes of this study, data on 1249 patients with IBD, enrolled into the SIBDCS between January 2006 and March 2010, were analyzed.

### Statistical Analysis

All statistical analyses were performed using the statistical package program Stata (version 12.1, StataCorp, College Station, TX). Quantitative data distribution was analyzed using Normal-QQ-Plots. Results of quantitative data are presented either as mean  $\pm$  SD and range (for Gaussian data) or median, interquartile range, and range (for non-Gaussian data). Categorical data were summarized as the percentage of the group total. Differences in categorical data distribution between groups were assessed using the chi-square test, or the Fisher's exact test in case of insufficient sample size.

Survival curves were calculated according to the Kaplan-Meier method to estimate probability of staying EIM free according to time from IBD diagnosis. A *P* value <0.05 was considered statistically significant.

## RESULTS

### Clinical Characteristics of the Study Population

Of the 1249 patients with IBD included in the study, 735 patients (58.8%) had CD, 483 patients (38.7%) had UC, and 31 patients (2.5%) had IC. Six hundred twenty-two patients were female (49.8%) with a median age at enrollment of 40 years (interquartile range, 30–51 yr). The clinical characteristics as well as disease location and current medication status of the study patients are shown in Table, Supplemental Digital Content 1, <http://links.lww.com/IBD/A874>. The clinical characteristics of 366 patients (248 patients with CD, 105 patients with UC, 13 patients with IC) that presented with one or more EIMs (up to 5) are depicted in Table 1.

### Frequencies and Types of EIM in the Study Population

Two hundred forty-eight patients with CD (33.7%), 105 patients with UC (21.7%), and 13 patients with IC (41.9%) suffered from at least 1 EIM that occurred either before or after the time of IBD diagnosis (Table 2). The maximum number of

**TABLE 1.** Characteristics of Patient Affected by One or More EIMs

	CD	UC	IC	IBD Total
No. patients	248	105	13	366
No. females (%)	151 (60.9)	52 (49.5)	9 (69.2)	212 (57.9)
Median age at enrollment (in yr)	41	41	38	41
Interquartile range	29–50	32–50	29–49	30–50
Range	16–77	17–82	20–71	16–82
Median disease duration (in yr)	9	9	4	8
Interquartile range	3–16	4–15	1–7	3–16
Range	0–52	0–49	0–10	0–52
Disease location, n (%)	L1: 66 (26.6) L2: 91 (36.7) L3: 81 (32.7) L4: 2 (0.8) Missing: 8 (3.2)	E1: 13 (12.4) E2: 40 (38.1) E3: 47 (44.8) Missing: 5 (4.7)		
Medication (ever treated), n (%)				
5-ASA	152 (61.3)	98 (93.3)	12 (92.3)	262 (71.6)
Steroids systemic	184 (74.2)	85 (81.0)	12 (92.3)	281 (76.8)
Budesonide	77 (31.0)	11 (10.5)	0 (0.0)	88 (24.0)
Azathioprine/6-MP	195 (78.6)	64 (61.0)	8 (61.5)	267 (73.0)
Methotrexate	72 (29.0)	13 (12.4)	2 (15.4)	87 (23.8)
TNF-antagonists	129 (52.0)	22 (21.0)	5 (38.5)	156 (42.6)
Cyclosporine/tacrolimus	5 (2.0)	10 (9.5)	1 (7.8)	16 (4.4)

**TABLE 2.** Frequency and Type of EIMs in the IBD Population Examined

	CD	UC	IC	IBD Total
EIM frequency	248	105	13	366
No. EIM(s) per patient, n (%)				
1	151 (60.9)	70 (66.7)	11 (84.6)	232 (63.4)
Two	69 (27.8)	26 (24.8)	2 (15.4)	97 (26.5)
Three	12 (4.8)	6 (5.7)	0 (0.0)	18 (4.9)
Four	7 (2.8)	2 (1.9)	0 (0.0)	9 (2.5)
Five	9 (3.6)	1 (1.0)	0 (0.0)	10 (2.7)
Type of EIM, n (%)				
Arthritis	184 (74.2)	62 (59.1)	10 (76.9)	256 (70.0)
Aphthous stomatitis	58 (23.4)	19 (18.1)	2 (15.4)	79 (21.6)
Axial arthropathy/ankylosing spondylitis	45 (18.2)	14 (13.3)	1 (7.7)	60 (16.4)
Uveitis	39 (15.7)	11 (10.5)	0 (0.0)	50 (13.7)
Erythema nodosum	31 (12.5)	13 (12.4)	2 (15.4)	46 (12.6)
Pyoderma gangrenosum	9 (3.6)	9 (8.6)	0 (0.0)	18 (4.9)
Psoriasis	7 (2.8)	3 (2.9)	0 (0.0)	10 (2.7)
PSC	5 (2.0)	19 (18.1)	0 (0.0)	24 (6.6)

EIMs was 5 (9 patients with CD and 1 patient with UC). Of 248 patients with CD with EIM, 60.9% had 1 EIM, 27.8% had 2 EIM, 4.8% had 3 EIM, 2.8% had 4 EIM, and 3.6% had 5 EIM. During the course of their disease, 105 patients with UC who ever presented with EIMs suffered from 1 (66.7%), 2 (24.8%), 3 (5.7%), 4 (1.9%), or 5 EIMs (1.0%). In all patients with IBD with EIMs, peripheral arthritis was the most prevalent (70.0%), followed by aphthous stomatitis (21.6%), axial arthropathy/ankylosing spondylitis (16.4%), uveitis (13.7%), erythema nodosum (12.6%), pyoderma gangrenosum (4.9%), PSC (6.0%), and psoriasis (2.7%).

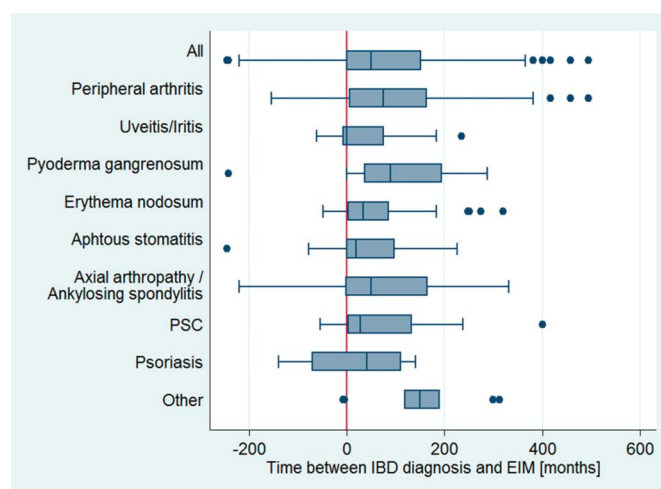
**Distribution of Different EIMs According to Their Chronological Appearance**

The 3 most frequent EIMs, which were likely to appear as first EIM (N = 232) were peripheral arthritis (65%), axial arthropathy/ankylosing spondylitis (6.3%), and aphthous stomatitis (6.6%). If patients were diagnosed with a second EIM (N = 97), aphthous stomatitis (25.4%), uveitis (20.9%), and axial arthropathy/ankylosing spondylitis (15.7%) were the most frequent EIM in our cohort. The most prevalent EIMs that were likely to appear as a third EIM (N = 18 affected patients) were aphthous stomatitis (32.4%) followed by erythema nodosum (29.7%) and axial arthropathy/ankylosing spondylitis (13.5%).

We then examined the time intervals in which the EIMs appeared before and/or after the time of IBD diagnosis. Figure 1 illustrates the chronological order of appearance of different EIMs in relation to the time of IBD diagnosis. Peripheral arthritis was diagnosed before the time of IBD diagnosis in 19.7% of patients. Axial arthropathy/ankylosing spondylitis was diagnosed in 39.1% of patients before IBD was diagnosed. Of note, the 25th percentile for axial arthropathy/ankylosing spondylitis lies at minus 2 months related to IBD diagnosis. Furthermore, 5 patients

experienced axial arthropathy/ankylosing spondylitis during the same month IBD was diagnosed. Aphthous stomatitis was diagnosed before IBD in 27.8% of patients, uveitis in 52.2% of patients, erythema nodosum in 14.3% of patients, pyoderma gangrenosum in 14.3% of patients, psoriasis in 50% of patients, and PSC in 23.8% of patients. Of note, musculoskeletal and dermatologic EIMs more frequently appeared after the time of IBD diagnosis rather than before (P = 0.010).

The Kaplan–Meier survival curves indicate the probability of staying free of EIMs in patients with CD and UC (1218 patients in total) over time (Fig. 2A). EIMs were more prevalent in



**FIGURE 1.** Appearance of different EIM relative to the time of IBD diagnosis. Data are presented as horizontal boxplots. The box comprises the 25th and 75% percentile; the vertical line in the box corresponds to the median.

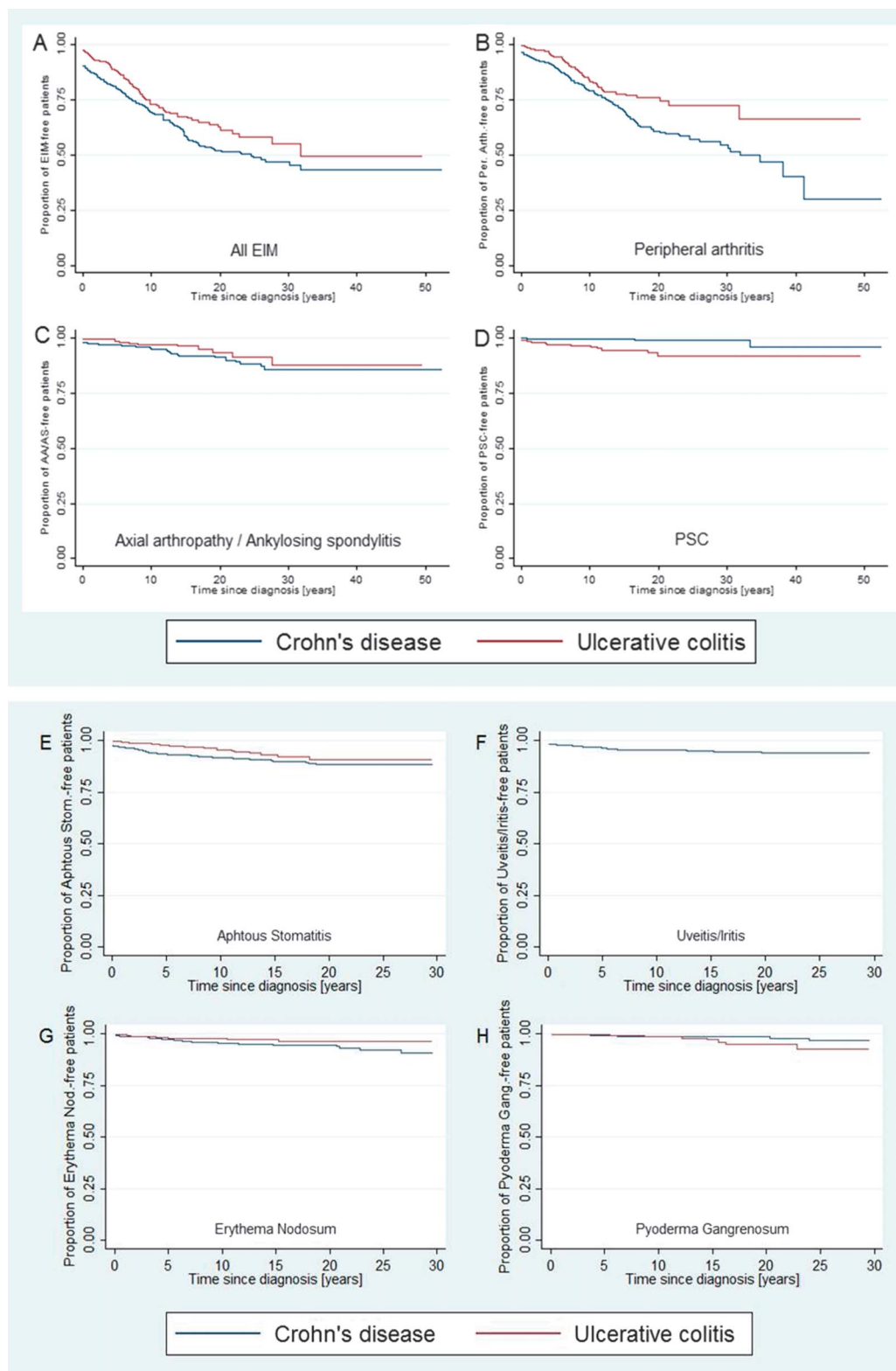


FIGURE 2. (A), EIM-free survival (total of 1218 patients): CD (blue curve) and UC (red curve). Kaplan–Meier estimates for all EIM (panel A), for arthritis (panel B), for axial arthropathy/ankylosing spondylitis (panel C), and for PSC (Panel D). (B), EIM-free survival (total 1218 patients with IBD): CD (blue curve) and UC (red curve). Kaplan–Meier estimates for aphthous stomatitis (panel E), for uveitis/iritis (panel F), for erythema nodosum (panel G), and for pyoderma gangrenosum (panel H).



patients with CD when compared with patients with UC (Fig. 2A). Only PSC (Fig. 2D) and pyoderma gangrenosum (Fig. 2H) occurred more often in patients with UC. Peripheral arthritis (Fig. 2B) and axial arthropathy/ankylosing spondylitis (Fig. 2C) were the most prevalent EIMs in our cohort of patients with IBD. After 30 years of disease duration, 54.0% of patients with CD and 73.0% of patients with UC were free of peripheral arthritis.

## DISCUSSION

In this large cohort study, we report on the chronologic occurrence of different EIMs relative to the time of IBD diagnosis. EIMs are common in patients with IBD, and we demonstrate that EIMs can appear in one quarter of patients before IBD is diagnosed.

In accordance with data from Veloso et al and our previous study, we found a higher frequency of EIMs in patients with CD compared with patients with UC.<sup>7,8</sup> Veloso et al did not differentiate between the different types of EIM over time but pooled them together to evaluate the EIM prevalence during a 20-year follow-up period. Lakatos et al<sup>25</sup> evaluated 873 Hungarian patients with IBD (254 patients with CD, average disease duration 9.2 yr; 619 patients with UC, average disease duration 11.2 yr) and found that a total of 21.3% had EIM (UC: 15.0%, CD: 36.6%). Although the disease duration between the Hungarian cohort and the Swiss cohort was comparable, we observed a higher EIM frequency in our cohort, particularly regarding the joint manifestations.

Importantly, we found that in one quarter of patients, the EIM appeared before IBD was diagnosed. When analyzing the specific EIM, we found that peripheral arthritis (in 19.7%), axial arthropathy/ankylosing spondylitis (in 39.1%), aphthous stomatitis (in 27.8%), uveitis (in 52.2%), erythema nodosum (in 14.3%), pyoderma gangrenosum (in 14.3%), psoriasis (in 50%), and PSC (in 23.8%) all may appear before IBD is diagnosed. This finding has important clinical implications since the awareness of this fact might decrease the diagnostic delay in patients with IBD. We recently showed that diagnostic delay is a particular concern especially in patients with CD where one fourth of patients require >24 months from symptoms onset until CD diagnosis are established.<sup>17</sup> This finding is of particular importance since during this period bowel damage can already occur.<sup>26</sup>

The development of 1 EIM appears to increase the susceptibility of developing other EIM.<sup>27</sup> An overlap of EIM has particularly been observed with peripheral arthritis, erythema nodosum, affections of the biliary tract, and the eyes, which support the hypothesis of a common pathogenic pathway. Supporting that concept, Bhagat et al<sup>28</sup> reported an autoimmune reaction toward an isoform of tropomyosin (tropomyosin-related peptide), which is expressed in the eye (nonpigmented ciliary epithelium), skin (keratinocytes), joints (chondrocytes), biliary epithelium, and the gut. We found a relevant proportion of our patients with CD and UC suffering from several (up to 5) EIM; the prevalence of multiple EIM was again higher in patients with CD compared

with patients with UC. Genetic analyses may help understanding the increased risk for multiple EIM in some patients. Patients with UC who display HLA-B8, DR3 phenotype were found to have a 10-fold higher risk of PSC,<sup>29</sup> and patients with UC with HLA DRB1\*0103 (DR103) had a higher risk of ocular and articular manifestations.<sup>30</sup>

Our study has several strengths and also limitations. We report in a large cohort study, including a detailed additional chart review, on the chronologic appearance between EIM and IBD diagnosis. We further depict the cumulative risk of developing one or several EIM relative to the time of IBD diagnosis. Besides the large patient sample size, the prospective patient inclusion using physician questionnaires is probably less prone to under-reporting of EIM prevalence compared with databases where EIM are retrospectively identified using the *International Classification of Diseases* codes. A potential limitation may be that the Swiss IBD cohort is not population based; some selection bias is therefore likely to be present. For instance, patients included by private practitioners are underrepresented compared with patients included by hospitals (20% of patients with IBD are recruited by colleagues in private practice compared with 80% of patients recruited by physicians working in hospitals). Furthermore, the relative number of patients suffering from EIM is lower in this study (29.3%) when compared with our previously published study (38.1%).<sup>8</sup> This is related to the fact that in this study, only patients with known chronologic appearance between EIM and IBD diagnosis were included.

In summary, we demonstrate in a large national cohort that EIMs are frequent and appear in one quarter of patients before IBD is diagnosed. Knowledge of this phenomenon may result in increased awareness for underlying IBD, thereby facilitating diagnosis and reducing diagnostic delay.

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