Initial Disease Course and Treatment in an Inflammatory Bowel Disease Inception Cohort in Europe: The ECCO-EpiCom Cohort

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication September 4, 2013; Accepted September 24, 2013.

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Supported by unrestricted grant from the Danish Colitis Crohn Patients Organization, the Vibeke Binder and Povl Riis' Foundation, the Scientific Council at the Herlev Hospital, the Sigrid Rigmor Moran Foundation, the Aage and Johanne Louis-Hansens Foundation, the Munkholm Foundation, the C.C. Klestrup and Henriette Klestrup Foundation, the Knud and Dagny Gad Andresens Foundation, the Else and Mogens Wedell-Wedellsborgs Foundation, the Direktør Jacob Madsen and Olga Madsens Foundation, ScanVet, the Torben og Alice Frimodt Foundation, Lægernes forsikringsforening af 1891, the Bengt Ihres Foundation, the Nanna Svartz Foundation, the Örebro University Hospital Research Foundation, the Örebro County Research Foundation, The Swedish Foundation for Gastrointestinal Research, The Swedish Research Council, The Swedish Society of Medicine, the Research Council of South-East Sweden, the County Council of Östergötland, The Swedish Organization for the Study of Inflammatory Bowel Disease, the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital, and the European Crohn's and Colitis Organization.

The authors have no conflicts of interest to disclose.

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DOI 10.1097/01.MIB.0000436277.13917.c4

Published online.

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Background: The EpiCom cohort is a prospective, population-based, inception cohort of inflammatory bowel disease (IBD) patients from 31 European centers covering a background population of 10.1 million. The aim of this study was to assess the 1-year outcome in the EpiCom cohort.

Methods: Patients were followed-up every third month during the first 12 (±3) months, and clinical data, demographics, disease activity, medical therapy, surgery, cancers, and deaths were collected and entered in a Web-based database (www.epicom-ecco.eu).

Results: In total, 1367 patients were included in the 1-year follow-up. In western Europe, 65 Crohn's disease (CD) (16%), 20 ulcerative colitis (UC) (4%), and 4 IBD unclassified (4%) patients underwent surgery, and in eastern Europe, 12 CD (12%) and 2 UC (1%) patients underwent surgery. Eighty-one CD (20%), 80 UC (14%), and 13 (9%) IBD unclassified patients were hospitalized in western Europe compared with 17 CD (16%) and 12 UC (8%) patients in eastern Europe. The cumulative probability of receiving immunomodulators was 57% for CD in western (median time to treatment 2 months) and 44% (1 month) in eastern Europe, and 21% (5 months) and 5% (6 months) for biological therapy, respectively. For UC patients, the cumulative probability was 22% (4 months) and 15% (3 months) for immunomodulators and 6% (3 months) and 1% (12 months) for biological therapy, respectively in the western and eastern Europe.

Discussion: In this cohort, immunological therapy was initiated within the first months of disease. Surgery and hospitalization rates did not differ between patients from eastern and western Europe, although more western European patients received biological agents and were comparable to previous population-based inception cohorts.

(Inflamm Bowel Dis 2013;0:1–11)

Key Words: epidemiology, outcomes research, Crohn's disease, ulcerative colitis

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are heterogenous chronic relapsing disorders of unknown etiology. Patients require anti-inflammatory and immunosuppressive treatment and, sometimes, surgery for inducing remission and long-term maintenance. Over the past few decades, new therapeutic approaches, including early and more aggressive intervention with immunomodulators and biological agents, have been introduced. These offer the possibility of a favorable modification in the natural history of IBD,[1] especially on the risk of hospitalization and surgery. To assess this possible impact on disease outcome, population-based prospective cohorts of unselected patients representing the broad spectrum of disease are needed because these cohorts offer the most accurate picture of the effectiveness regarding medication and surgery in IBD in the community setting.

From 1991 to 1993, the European Collaborative study group on Inflammatory Bowel Disease (EC-IBD) collected data from the first European population-based inception cohort. The EC-IBD study found a North–South gradient in IBD incidence in Europe,[2] with higher incidences in northern Europe, as well as delivering important information on the epidemiology of IBD in Europe.[3–6] However, it failed to provide an explanation for the geographical distribution of the diseases in Europe, possibly because countries from eastern Europe were not included in the study.

Therefore, the European Crohn's and Colitis Organization's Epidemiological Committee (EpiCom) study was initiated as a prospective population-based cohort of unselected IBD patients diagnosed in 2010 to investigate the occurrence and disease course of IBD in eastern and western Europe. Patients were recruited within well-described geographical areas from 31 centers from eastern and western Europe. Recently, the annual incidence rates were reported,[7] and the incidence of CD and UC in western European centers was found to be twice as high as that in eastern European centers. The aim of this study was to assess a possible West–East gradient in 1-year outcomes and the impact of treatment choices on disease course within the EpiCom cohort.

METHODS

Study Setting

The EpiCom cohort is a population-based, prospective, inception cohort of incident IBD patients diagnosed in 2010 in 31 centers from 8 eastern and 14 western European countries (see List of participants, Supplemental Digital Content 1, http://links.lww.com/IBD/A352). Participation in the study required a well-defined primary catchment area with up-to-date population data, including age and gender distribution. Similarly, participation required an established network of gastroenterologists, colorectal surgeons, and general practitioners within the uptake area who were contacted twice during the inclusion period to ensure complete coverage and inclusion of patients. In total, 1560 IBD patients, 550 with CD, 840 with UC, and 170 with IBD unclassified (IBDU), were recruited within well-described geographical areas covering a total background population of 10.1 million (3.3 million in eastern and 6.8 million in western Europe). Case ascertainment methods, diagnostic criteria for case definition, period of inclusion, and recorded patient data were standardized. One center from eastern Europe only included pediatric-onset IBD patients, whereas 2 centers from western Europe were unable to follow-up their patients sufficiently after the diagnosis.

Classifications and Definitions

Incident patients diagnosed with IBD between January 1, 2010, and December 31, 2010, aged ≥15 years and living in the predefined catchment areas at the time of diagnosis were prospectively included in the EpiCom cohort. The diagnosis of CD, UC, or IBDU was based on the *Copenhagen Diagnostic Criteria*[8–10] (see List of participants, Supplemental Digital Content 1, http://links.lww.com/IBD/A352). The date of inclusion was the date of diagnosis. Disease extent for UC and disease location and behavior for CD were defined according to the *Montreal Classification*.[11]

Treatment was grouped into 5 levels of treatment of ascending therapeutic potency: 5-aminosalicylates (5-ASA) (oral and/or topical

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5-ASA treatment ± topical steroids), glucocorticosteroids (GCS) (oral steroids ± 5-ASA or topical steroids), immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, or methotrexate ± steroids), biologicals (infliximab or adalimumab in combination with any of the above), and surgery (major abdominal surgery as a result of IBD regardless of the medical treatment before surgery). Initial treatment was defined as the highest treatment step reached within the first 3 months from diagnosis. Treatment (medical or surgical) initiated during a hospitalization was defined as the highest treatment step reached within 14 days from the day of hospitalization. Immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate) were combined in one category because 94% of patients treated with immunomodulators received thiopurines.

Disease activity of UC was measured using the *simple clinical colitis index*.[12] A score of ≤2 was defined as remission, 3 to 4 as mild/moderately active disease, and ≥5 as severely active disease.[13] For CD, the *Harvey–Bradshaw index*[14] was used. A Harvey–Bradshaw index score of <5 was defined as remission, 5 to 7 as mildly active disease, 8 to 16 as moderately active disease, and ≥16 as severely active disease.[15] Causes of death and cancers were categorized according to the *International Classification of Diseases, Tenth Revision*.[16]

Data Collection and Validity

Patients were followed prospectively every third month from diagnosis and throughout the follow-up period. Data regarding demographics, disease activity, medical therapy, surgery, hospitalization, disease classification, cancers, and deaths were collected and entered prospectively in the Web-based inception cohort EpiCom database.[17] A follow-up period of 12 ± 3 months was chosen to assess the 1-year outcome of the cohort. Measures to secure data validity have been thoroughly described elsewhere.[7] In short, data validity was secured by built-in control and validation tests, locked diagnostic criteria in the database, manual data standardization, and random audits of case ascertainment and data quality.

Statistical Analysis

Statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc., Cary, NC). Demographics and disease classification between the groups were compared with chi-square test. Possible associations between primary endpoints (surgery, hospitalization, or biological treatment) and multiple covariates (age, gender, diagnosis, geographic region, disease behavior for CD, disease extent for UC, initial treatment, smoking status) were analyzed by Cox regression analyses using the proportional hazard assumption, and associations were visualized by Kaplan–Meier plots. Only events occurring after the time of diagnosis and among patients being followed-up were included in the Cox regression analysis. A P value of <0.05 was considered statistically significant. Continuous variables are expressed as median (range), unless otherwise stated.

Ethical Considerations

The study was approved by the local ethical committees according to local regulations.

RESULTS

The cohort consisted of a total number of 1367 incident IBD patients aged 15 years or older. Of these, 509 patients (37%) were diagnosed with CD, 710 (52%) with UC, and 148 (11%) with IBDU. In total, 1109 patients (81%) were diagnosed in western European and 258 (19%) in eastern European centers. Patients' sociodemographic characteristics (Table 1) did not differ between the 2 geographic regions or between the 28 participating and the 3 nonparticipating centers. A subset of 148 patients (11%) had no follow-up after diagnosis, 3 because of death and 15 because they moved away from the uptake area. The remaining 130 patients gave no consent and came from countries where follow-up in that case was not allowed.

No significant change in disease phenotype for CD patients or disease extent for UC patients was observed during the follow-up period, and the distribution of patients within the phenotypes remained constant (data not shown). Data on disease activity during follow-up were available for analysis in 328 CD patients (64%) and 448 UC patients (63%). The proportion of patients in remission rose from 11% in UC and 27% in CD at the time of diagnosis to 71% and 77%, respectively, at 1-year follow-up (Fig. 1).

Biological Therapy

A total of 93 CD (18%) patients were started on biological therapy (66 infliximab [71%] and 27 adalimumab [29%]) during the follow-up period. Of the 87 western European CD patients (21%) receiving biologicals, 21 (24%) had stricturing and 18 (20%) had penetrating disease. Six (6%) eastern European CD patients received biological therapy. Two patients (33%) had stricturing, whereas no patient had penetrating disease. Most CD patients were treated because of refractoriness to other treatments (53 [57%]) or steroid dependency (24 [26%]). Furthermore, a total of 32 UC patients (5%) were administered biological therapy (only infliximab). In western Europe, 31 patients (6%), 20 (65%) with extensive disease and 11 (35%) with left-sided colitis, were treated. Treatment was initiated mainly because of refractoriness to other treatments (23 [77%]) or steroid dependency (6 [20%]). Only 1 patient (1%) from eastern Europe with left-sided colitis received infliximab because of steroid dependency. Finally, 12 patients (8%) with IBDU received biological therapy during follow-up, most importantly because of refractoriness to other treatments (6 [50%]) or steroid dependency (3 [25%]). Treatment before biological therapy is shown in Table 2

Cox regression analysis found the type of disease, region, younger than 40 years at diagnosis, and the highest treatment step reached during the first 3 months of disease as factors predictive of biological therapy within the first year of disease. The probability of biological therapy was highest for CD (CD versus UC: hazard ratio [HR], 2.3; 95% confidence interval [CI], 1.4–3.6; IBDU versus UC: HR, 1.7; 95% CI, 0.9–3.5; $P < 0.01$). For CD, the factors were region (eastern Europe: HR, 0.2; 95% CI, 0.1–0.5; $P < 0.001$) and higher initial treatment step (per step: HR, 2.1; 95% CI, 1.6–2.9; $P < 0.001$), whereas smoking status and behavior did not show association. For UC, the factors were region (eastern Europe: HR, 0.1; 95% CI, 0.02–0.97; $P < 0.05$), age (age, <40 years; HR, 2.5;

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TABLE 1. Patient Characteristics and First-Year Outcomes of 1367 Incident IBD Patients From the EpiCom Cohort

	Western European Centers			Eastern European Centers		
	CD	UC	IBDU	CD	UC	IBDU
No. of patients, n (%)	405 (37)	562 (51)	142 (13)	104 (40)	148 (57)	6 (2)
Male, n (%)	209 (52)	325 (58)	70 (49)	61 (59)	84 (57)	4 (67)
Female, n (%)	196 (48)	237 (42)	72 (51)	43 (41)	64 (43)	2 (33)
Age at diagnosis, yr, n (range)	35 (16–89)	40 (15–89)	38 (16–84)	32 (15–78)	37 (15–81)	30 (20–34)
Median time to diagnosis, mo, n (range, yr)	4.6 (0–31)	2.5 (0–21)	2.3 (0–30)	3.4 (0–10)	2.3 (0–20)	2.7 (0–3)
Never smoker, n (%)	165 (43)	279 (56)	65 (52)	38 (37)	79 (54)	4 (67)
Current smoker, n (%)	137 (35)	47 (9)	19 (15)	39 (38)	16 (11)	2 (33)
Former smoker, n (%)	85 (22)	174 (35)	41 (33)	25 (25)	52 (35)	0 (0)
Disease extent, n (%)						
E1: Proctitis	—	118 (21)	—	—	32 (22)	—
E2: Left sided colitis	—	225 (41)	—	—	67 (45)	—
E3: Extensive colitis	—	210 (38)	—	—	49 (33)	—
Disease location, n (%)						
L1: Terminal ileum	118 (30)	—	—	40 (39)	—	—
L2: Colon	112 (28)	—	—	20 (20)	—	—
L3: Terminal ileum + colon	87 (22)	—	—	25 (25)	—	—
L4: Upper GI	30 (8)	—	—	2 (2)	—	—
L1+L4	23 (6)	—	—	5 (5)	—	—
L2+L4	11 (3)	—	—	3 (3)	—	—
L3+L4	18 (5)	—	—	7 (7)	—	—
Disease behavior, n (%)						
B1: nonstricturing, non-penetrating	259 (64)	—	—	70 (67)	—	—
B2: stricturing	79 (20)	—	—	20 (19)	—	—
B3: penetrating	29 (7)	—	—	6 (6)	—	—
B1p: B1 + perianal	16 (4)	—	—	1 (1)	—	—
B2p: B2 + perianal	3 (1)	—	—	0 (0)	—	—
B3p: B3 + perianal	19 (5)	—	—	7 (7)	—	—
Highest initial treatment level, n (%)						
No treatment	37 (9)	56 (10)	13 (9)	6 (6)	2 (1)	0 (0)
5-ASA	77 (19)	289 (51)	78 (55)	28 (27)	99 (67)	4 (67)
GCS	140 (35)	168 (30)	39 (27)	34 (33)	37 (25)	2 (33)
Immunomodulators	92 (23)	29 (5)	7 (5)	26 (25)	9 (6)	0 (0)
Biological therapy	26 (6)	13 (2)	4 (3)	2 (2)	0 (0)	0 (0)
Surgery	33 (8)	7 (1)	1 (1)	8 (8)	1 (1)	0 (0)
Highest level of treatment during follow-up, n (%)						
No treatment	17 (4)*	40 (7)*	8 (6)	1 (1)	2 (1)	0 (0)
5-ASA	55 (14)*	251 (45)*	70 (49)	29 (28)	92 (62)	4 (67)
GCS	78 (19)*	141 (25)*	36 (25)	24 (23)	34 (23)	1 (17)
Immunomodulators	119 (29)*	87 (15)*	12 (8)	32 (31)	17 (11)	1 (17)
Biological therapy	71 (18)*	23 (4)*	11 (8)	6 (6)	1 (1)	0 (0)
Surgery	65 (16)*	20 (4)*	5 (4)	12 (12)	2 (1)	0 (0)

*Differences between geographic regions ($P < 0.05$).

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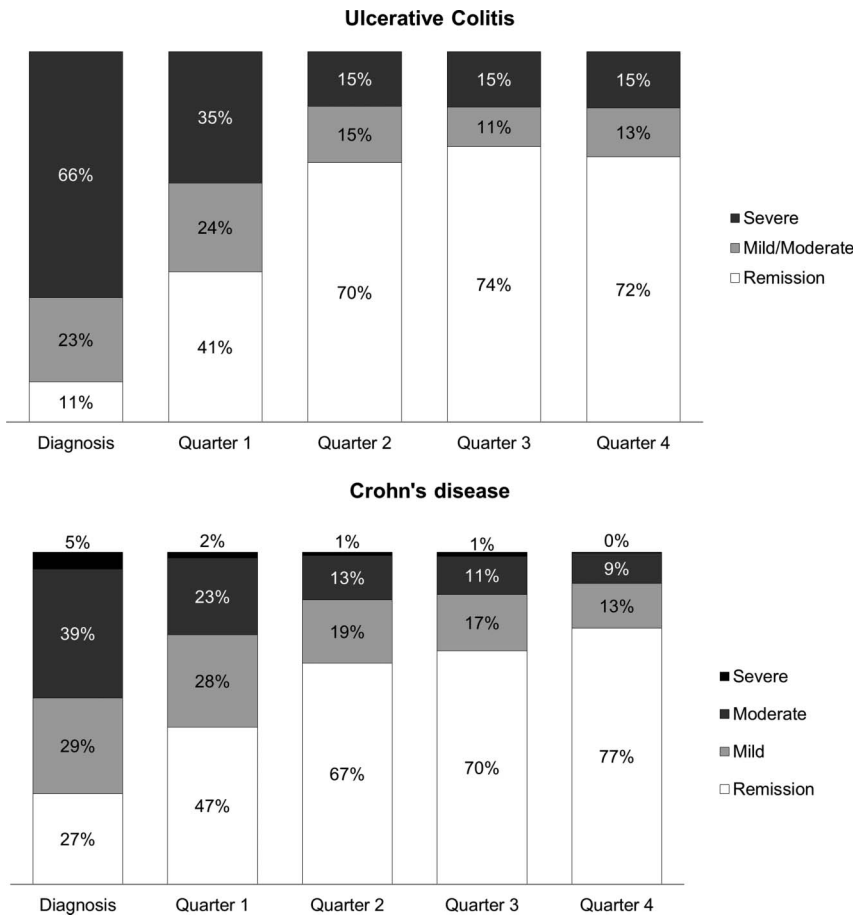

FIGURE 1. Distribution of disease activity during the first year of disease.

95% CI, 1.1–5.7; $P = 0.03$), and initial treatment step (per step: HR, 3.7; 95% CI, 2.1–6.4; $P < 0.001$), while smoking status and disease extent did not show association. Survival plots for disease extent and behavior are shown in Figure 2.

Surgery

During follow-up, 77 CD patients (15%) had a resection performed (including 5 hemicolectomies and 3 total colectomies). The resections were performed in 65 western European CD patients (16%) compared with 12 eastern European CD patients (12%) (Fig. 3). Stricturing disease occurred in 28 western European patients (44%) and penetrating disease in 22 (34%) compared with 4 (33%) and 7 (58%), respectively, eastern European patients ($P = 0.20$). Twenty-two UC patients (3%) were colectomized during follow-up: 20 (4%) in western (6 [30%] with left-sided colitis, 13 [65%] with extensive colitis, and 1 [5%] with proctitis) compared with 2 patients (1%) with left-sided colitis from the eastern Europe. Five patients (4%) with IBDU from western Europe were operated: 4 (80%) total colectomies and 1 (20%) hemicolectomy. Medical treatment before surgery is shown in Table 2. A second operation was performed in 4 patients (4%) (3 CD and 1 UC). One resection and 2 hemicolectomies were performed on the CD patients, of which 1 had stricturing and 2 had penetrating disease. One UC patient had a rectum resection.

For IBD patients combined, the Cox regression analysis identified the type of disease (CD versus UC: HR, 3.6; 95% CI, 2.1–6.3; IBDU versus UC: HR, 1.3; 95% CI, 0.5–3.4; $P < 0.001$) and receiving any medical treatment within the first 3 months of disease (no treatment: HR, 2.1; 95% CI, 1.01–4.49; $P < 0.05$) as being significantly associated with the risk of surgery within the first year of disease. For CD patients, the analysis revealed disease behavior (B2 versus B1: HR, 11.3; 95% CI, 4.9–25.9; B3 versus B1: HR, 18.6; 95% CI, 7.6–45.3; $P < 0.001$) as an associated factor, as well as smoking status at diagnosis (nonsmokers: HR, 2.0; 95% CI, 1.01–3.91; $P = 0.03$). For UC patients, only disease extent was associated with the risk of surgery (E2: HR, 2.0; 95% CI, 0.2–18.0; E3: HR, 7.3; 95% CI, 1.0–55.7; $P = 0.02$). Survival plots for disease extent and behavior are shown in Figure 2.

Hospitalization

Overall, hospitalization (any IBD related) occurred in 98 CD patients (19%), 92 UC patients (13%), and 13 IBDU patients (9%). In western Europe, 81 CD patients (20%) were hospitalized for the first time after a median of 5.1 months (range, 0–15 months), 24 (30%) having stricturing and 19 (23%) penetrating disease. During the hospitalization, 34 (42%) underwent a resection, 18 (22%) were started on GCS,

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TABLE 2. Treatment Steps Reached Before Biological Therapy or Surgery in a European Inception Cohort of IBD Patients

	Western European Centers			Eastern European Centers		
	CD	UC	IBDU	CD	UC	IBDU
Highest treatment step before biological therapy, n (%)						
No treatment	6 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5-ASA	4 (5)	0 (0)	1 (8)	1 (17)	0 (0)	0 (0)
GCS	15 (17)	22 (71)	7 (58)	3 (50)	0 (0)	0 (0)
Immunomodulators	56 (64)	9 (29)	4 (33)	2 (33)	1 (100)	0 (0)
Surgery	6 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Highest treatment step before surgery, n (%)						
No treatment	26 (40)	0 (0)	0 (0)	7 (58)	0 (0)	0 (0)
5-ASA	4 (6)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)
GCS	14 (22)	5 (25)	3 (60)	1 (8)	0 (0)	0 (0)
Immunomodulators	12 (18)	7 (35)	0 (0)	4 (33)	2 (100)	0 (0)
Biological therapy	9 (14)	8 (40)	1 (20)	0 (0)	0 (0)	0 (0)

CD, Crohn's disease; GCS, glucocorticosteroids; IBDU, inflammatory bowel disease unclassified; UC, ulcerative colitis.

5 (6%) on immunomodulators, 2 (2%) on 5-ASA, 3 (4%) on biological therapy, although 19 (23%) had no change in current treatment. In eastern Europe, 17 CD patients (16%) were hospitalized after a median of 4.0 months (range, 0–15 months), 6 (35%) with stricturing and 5 (30%) with penetrating disease. Six patients (35%) had a resection, 5 (29%) were started on GCS, 1 (6%) on immunomodulators, 1 (6%) on 5-ASA, and 4 (24%) did not change their current treatment.

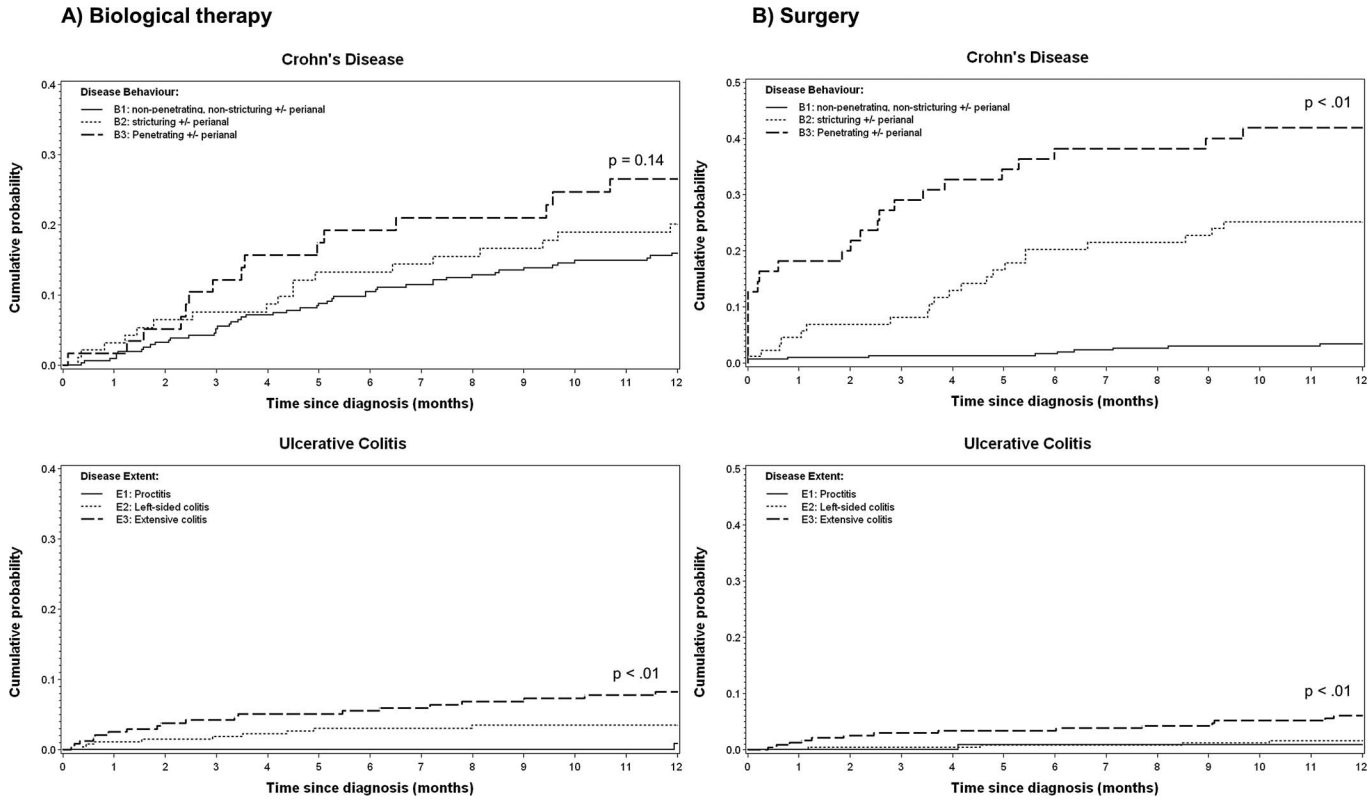

FIGURE 2. Cumulative probability for biological therapy (A) and surgery (B) during the first year of disease.

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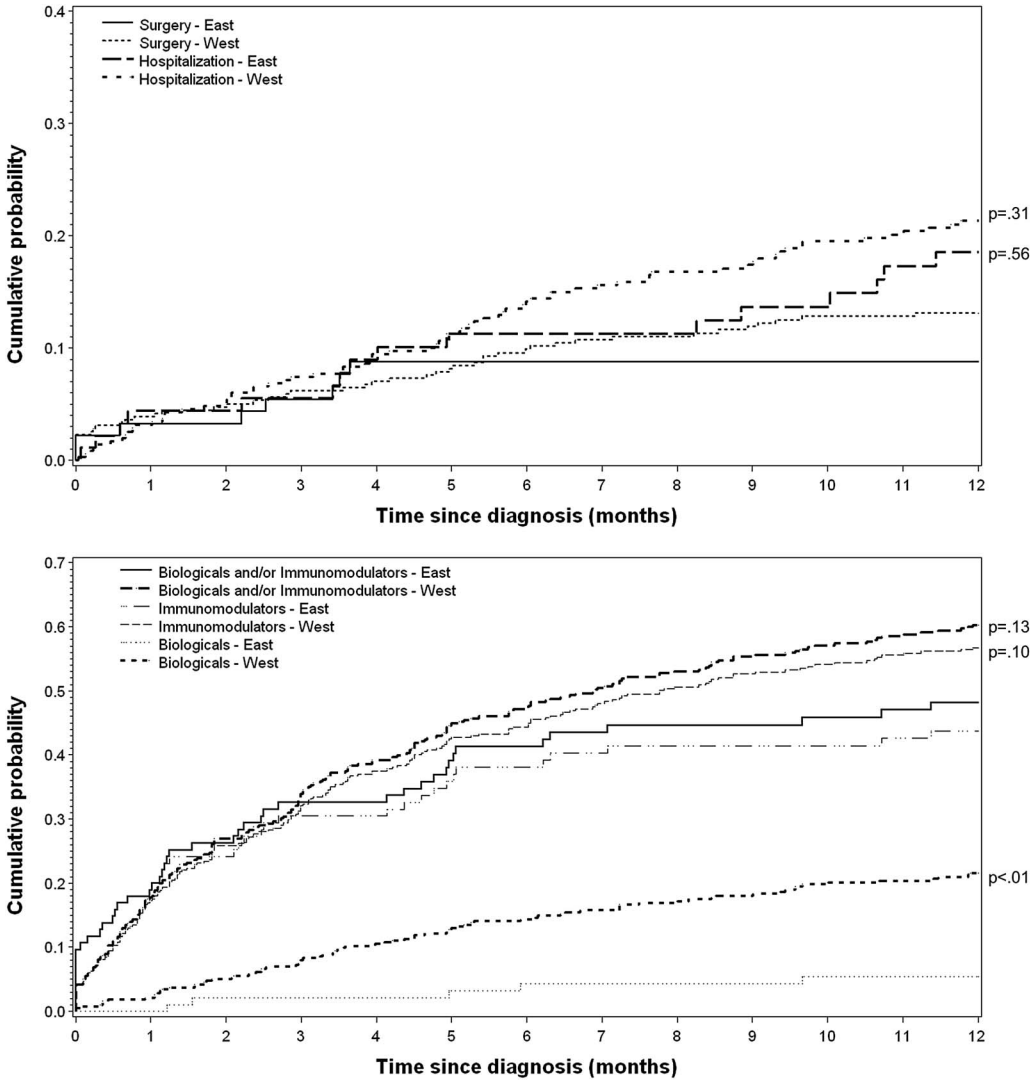

FIGURE 3. Cumulative probabilities for needing immunomodulators, hospitalization and surgery for CD patients during the first year of disease.

Regarding UC, 80 patients (14%) were hospitalized in western Europe after a median of 3.6 months (range, 0–14), 29 (36%) with left-sided colitis and 43 (54%) with extensive colitis. Ten patients (13%) were colectomized, 26 (33%) were started on GCS, 16 (20%) on immunomodulators, 5 (6%) on biological agents, 3 (4%) on 5-ASA, and 20 (25%) did not change their current treatment during hospitalization. In eastern Europe, 12 UC patients (8%) were hospitalized after a median of 2.4 months (range, 0–15) (regional difference $P < 0.01$), 3 (35%) with left-sided colitis and 8 (67%) extensive colitis. One patient (8%) was colectomized, whereas 4 (33%) were started on immunomodulators, 3 (25%) on GCS, and 1 (8%) on 5-ASA. Three patients (25%) had no change in treatment. Thirteen IBDU patients (9%) from western Europe were hospitalized after a median of 5.6 months (range, 0–10). Of these patients, 4 (31%) had surgery during hospitalization, 3 (23%) were started on biological agents, 3 (23%) on GCS, and 1 (8%) on 5-ASA. Two patients (15%) had no change in the treatment.

For CD patients, disease behavior was associated with the risk of hospitalization (B2: HR, 2.9; 95% CI, 1.8–4.9; B3: HR, 5.2; 95% CI, 3.0–9.1; $P < 0.001$). For UC patients, region (eastern Europe: HR, 0.5; 95% CI, 0.23–0.99; $P < 0.05$) and the higher initial treatment step were associated with higher risk (immunomodulators: HR, 4.8; 95% CI, 1.1–22.1; biologicals, HR, 5.5; 95% CI, 1.1–27.8; $P < 0.001$).

Medical Treatment

The cumulative probabilities for and time to treatment steps within the first year of disease are shown in Figure 4. The highest treatment step reached during the follow-up is shown in Table 1. The distribution of CD and UC patients within the 6 treatment steps during the follow-up period is shown in Figure 5. A subset of 105 CD patients (21%) received only 5-ASA as the initial treatment (western Europe: 77 [19%], eastern Europe: 28 [27%]). During follow-up, the majority of patients (49 [64%] in western Europe

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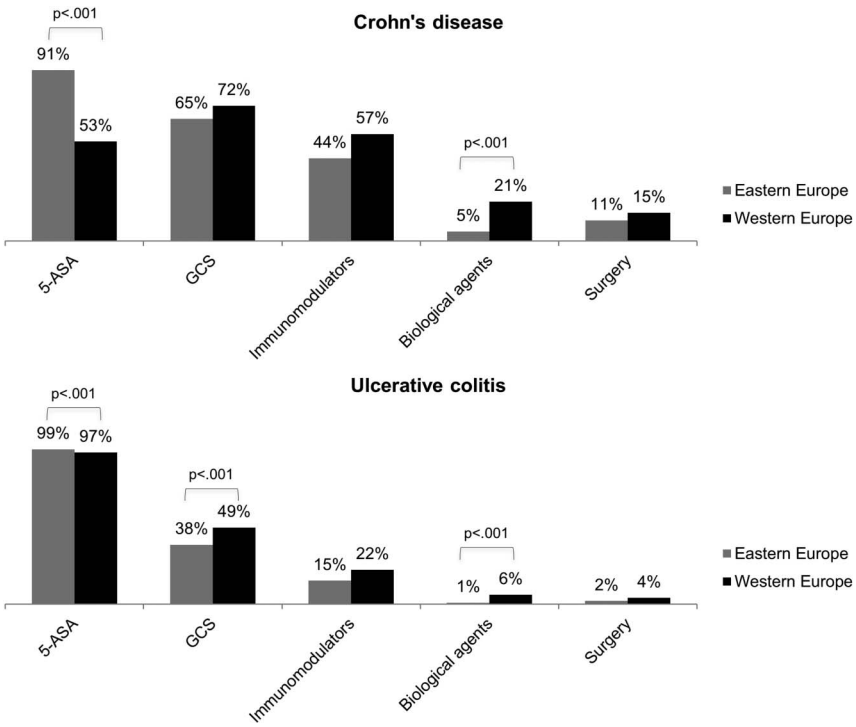

Median time to treatment	CD		UC	
	Western Europe	Eastern Europe	Western Europe	Eastern Europe
5-ASA	1 d. (-6-12 mo.)	0 d (-1-11 mo.)	0 d. (-7-12 mo.)	0 d. (0-2 mo.)
GCS	1 d. (-4-12 mo.)	0 d. (-1-11 mo.)	1 d. (-4-12 mo.)	3 d. (0-10 mo.)
Immunomodulators	2 mo. (-2-12 mo.)	1 mo. (0-11 mo.)	4 mo. (0-12 mo.)	3 mo. (1-12 mo.)
Biological agents	5 mo. (0-15 mo.)	6 mo. (1-1 mo.)	3 mo. (0-15 mo.)	12 mo.
Surgery	3 mo. (-2-15 mo.)	1 mo. (0-15 mo.)	5 mo. (0-14 mo.)	6 mo. (1-11 mo.)

FIGURE 4. Cumulative probabilities for treatment steps during the first year of disease in a European inception cohort.

and 27 [96%] in Eastern Europe) remained on 5-ASA monotherapy. More patients had nonpenetrating, nonstricturing disease (44 [90%] in western Europe; $P < 0.01$ and 21 [78%] in eastern Europe; $P = 0.66$) compared with patients not treated with 5-ASA monotherapy only during follow-up, while disease location did not differ (data not shown). In western Europe 12 (16%) received GCS, 11 (14%) received immunomodulators, 3 (4%) received biological agents, and 2 (3%) underwent surgery. However, 49 (64%) did not step up the treatment pyramid. In eastern Europe, only 1 (4%) patient stepped up to GCS, whereas 28 (96%) remained constant.

Cancer

During follow-up,s 6 patients (0.4%, 2 with CD and 4 with UC) were diagnosed with cancer, a median time of 2 months after IBD diagnosis (range, 0–14 months). One UC patient with extensive colitis had colon cancer diagnosed simultaneously with the IBD diagnosis, whereas the remaining patients had extraintestinal cancer. One CD patient received azathioprine before cancer diagnosis.

Death

Eight patients died during follow-up (0.6%, 5 CD, 2 UC, 1 IBDU) at a median 9 months (range, 2–14 months) after the diagnosis. Two CD patients died as a result of sepsis after IBD surgery, while 6 patients died of non-IBD–related causes.

DISCUSSION

We show that in an unselected, population-based, inception cohort of mild-to-severe IBD cases, surgery and hospitalization rates do not differ between eastern and western Europe, even though a significantly greater proportion of western European IBD patients received biological agents. Disease activity improved during the first year after diagnosis as the proportion of patients in clinical remission increased throughout the follow-up period for both UC and CD. The risks of surgery and treatment with biological agents were higher for CD than UC patients. Stricturing or penetrating disease the highest risk for surgery and hospitalization for CD, and extensive disease carried the highest risk for colectomy in UC. Surgery and hospitalization rates for UC and CD within the first year of disease are comparable with the previous population-based inception cohorts at the start of the millennium, despite an earlier and more aggressive treatment with immunomodulators.

The strength of the EpiCom cohort is the prospective inclusion and follow-up of incident IBD patients diagnosed within well-defined geographic areas. Diagnostic criteria, case ascertainment methods, and intervals of follow-up visits and recorded data were standardized, and patients were thereby made comparable in observation time. Several measures previously described[7] ensured that all centers performed a population-based cohort study with good data quality and validity. The EpiCom cohort thereby

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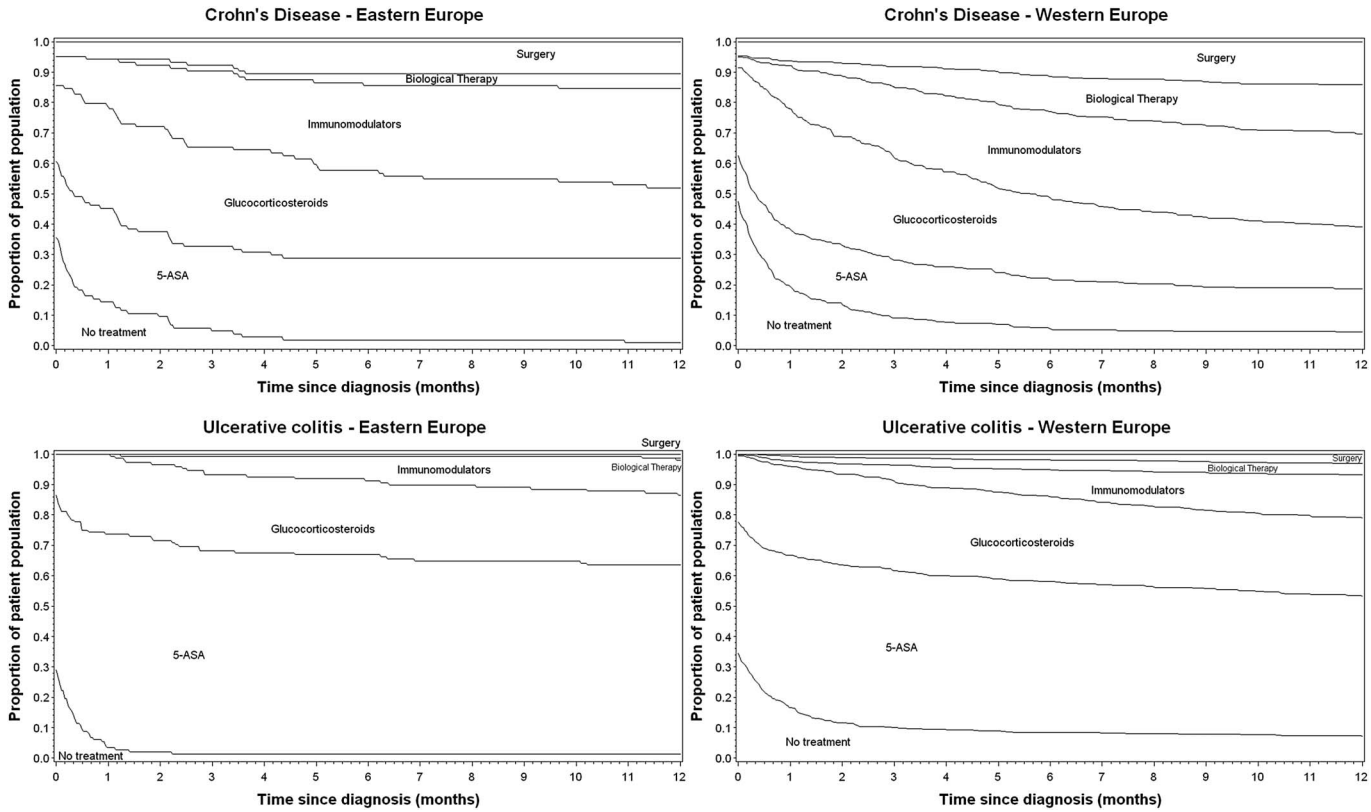

FIGURE 5. Distribution of CD and UC patients within treatment steps during the first year of disease in the EpiCom cohort.

constitutes a unique cohort of patients diagnosed after the introduction of biological agents and in the era of earlier and more aggressive treatment with immunomodulators or biological agents. The patients are unselected and represent the whole spectrum of disease severity; therefore, the choices of treatment in this cohort are the results of community effectiveness, outside the setting of randomized controlled trials, but implemented with a knowledge of the consensus of the European Crohn's and Colitis Organization.[18,19]

Limitations of the present study include the heterogeneity of the participating centers in terms of health care systems. Choices regarding medical and surgical treatment are strongly linked to extramedical considerations, and therefore, the differences observed between eastern and western Europe might have been caused by considerable variations between health care systems across Europe. Furthermore, 10% of the cohort was not available for follow-up because of local restrictions. However, they did not differ in terms of characteristics and disease classification. Finally, the distribution of participating centers is skewed, with more centers located in western Europe. As the eastern European centers are mostly low-incident areas,[20] a majority of patients in this study are from western Europe. However, and similar to previous findings,[21] the patient populations from eastern and western Europe were similar in terms of socioeconomic characteristics, disease classification and diagnostic procedures used, and time to diagnosis.[7] Therefore, we have no reason to believe the disease course being influenced by the region of origin.

Surgery rates in eastern and western Europe did not differ and are comparable to previous population-based cohorts from the previous decade in each region. One previous eastern European cohort reported 1-year surgery rates of 10% for CD and 0.5% for UC,[22] while western European and North American cohorts have reported surgery rates of 10% to 14%[10,23,24] for CD and 3% to 6%[10,25,26] for UC. The geographic regions were similar in terms of disease behavior and localization for CD and extent for UC, as well as in diagnostic approach and the availability of diagnostic procedures.[7] Surgery rates for both CD and UC have been declining during the past 3 decades,[10,23,27,28] possibly because of more aggressive medical therapy, a change in physicians' attitudes toward surgery, or a reduction of doctors and patients delay from onset of symptoms to diagnosis. Increased and early use of thiopurines has been associated with reductions in surgery rates for CD, with median times to thiopurine treatment of 2 years[29] and 11 months.[27]

However, in this cohort of unselected IBD patients, more than half of CD patients and 1 of 5 UC patients were treated with immunomodulators within the first quarter of disease with no difference between eastern and western Europe and no apparent effect on the 1-year outcome. Nonetheless, disease activity decreased during the follow-up period, and patient-reported, health-related quality of life improved as well (Burisch et al, unpublished data, 2013). The recent findings in a highly selected cohort of severe CD patients randomized to either early treatment with thiopurines (within 6 months of diagnosis) or conventional

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therapy confirm this observation as no benefit of early thiopurine treatment was found.[30] These findings, including the fact that disease behavior and extent were main predictors of surgery, could indicate that a proportion of CD patients already at diagnosis have complications ultimately requiring surgery, which is unavoidable with current therapies including biological agents. Thus, very early disease course may represent a different entity and the impact of aggressive medical therapy only having its effect on disease course beyond the first year.

Only few data on the risk of hospitalization within the first year of disease exist from population-based cohorts. In a Danish cohort of patients diagnosed between 1962 and 1987, 83% of patients with CD were hospitalized within the first year of disease,[31] whereas recent data from North America show hospitalization rates of 24% for CD,[23] thus similar to the rates found in this study. Interestingly, although surgery rates have shown a decline over time for UC and CD, hospitalization rates have been found to remain constant or are decreasing in cohorts from the post–biological era.[23,32] Whether the unchanged risk of hospitalization is caused by side effects (i.e., serious infections[33,34]) to immunosuppressive treatment remains unknown. In this cohort, we unfortunately did not have data available on the reason for hospitalization other than that of surgery.

Regarding biological therapy, a regional difference was noted as almost no patients in eastern Europe received biological therapy within the first year of disease. Biological therapy is being used more frequently since its introduction in 1998[35,36] and has had a beneficial influence on surgery and hospitalization rates in UC[37] and CD.[38] The introduction of biologicals was not significantly delayed in eastern Europe,[39] and therefore, this observation is likely to be caused by differences between health care systems across Europe. The majority of participating centers were IBD specialist centers, but differences in prescription restrictions and requirements before the initiation of biological therapy might require a longer follow-up in this cohort to truly compare the geographical regions. In this population-based inception cohort, the higher use of biological therapy in western Europe apparently did not result in lower surgery rates compared with eastern Europe. Overall, the surgery rates have not changed significantly compared with reports from around the time of introduction of biological agents. Long-term follow-up of the EpiCom cohort is necessary to accurately determine whether the disease course—despite the differences noted in treatment choices, e.g., biological therapy—is in fact similar in eastern and western Europe. The same is true for the question of whether early and aggressive treatment with immunomodulators and biologicals can change the natural history and risk of progression of IBD.[3,24,25,40–42]

A surprisingly large group of CD patients received only 5-ASA as the initial treatment in both regions (27% eastern Europe and 19% western Europe) with the majority of these patients remaining on 5-ASA monotherapy throughout the observation time. Furthermore, nearly all eastern European CD patients (91%) received treatment with 5-ASA during the first year of disease compared with approximately half of western European CD patients (53%). For UC, the cumulative probability was similarly high in eastern and western Europe; however, 5-ASA treatment was initiated much earlier, within the first 2 months, in all eastern European patients. Current guidelines do not recommend 5-ASA in the treatment of CD[19] as the efficacy of 5-ASA for inducing remission in CD patients in a recent meta-analysis could not be proven.[43] However, 5-ASA has shown to be comparable to thiopurines in preventing clinical and surgical relapses in postoperative CD patients.[44] Also, in a Danish cohort, a mild phenotype of 5-ASA–dependent CD patients benefited from a long-term 5-ASA monotherapy and had a lower cumulative probability of first intestinal surgery.[45,46] Interestingly, in the former EC-IBD study, a similarly high proportion of mild-to-moderate active luminal CD patients were, by the physicians, chosen to be treated with 5-ASA only.[47]

In conclusion, this prospective, unselected, population-based, inception cohort from 2010 to 2011 with 1 year of follow-up contains indolent and aggressive types. In this setting, we find similar surgery rates for CD and UC and hospitalization rates for CD in eastern and western Europe, comparable to population-based cohorts from the past decade. This similar disease course is in spite of more early and aggressive treatment with immunomodulators, and almost no patients in eastern Europe receiving biological agents because of differences in health care systems in eastern Europe. Very early disease course may be different from the subsequent disease course. Follow-up of the EpiCom cohort will reveal if the observed difference in treatment regimen will change the natural disease course and phenotypes over time or merely postpone outcomes such as surgery.

ACKNOWLEDGMENTS

The authors are grateful to B. Vucelic (Croatia), M. Brinar (Croatia), N. Procopiou (Cyprus), B. Järventaus (Finland), V. Tsianos (Greece), K. Stroggili (Greece), Z. Vegh (Hungary), S. Kramli (Hungary), D. Mcnamara (Ireland), S. Byrne (Ireland), D. Valpiani (Italy), A. Santini (Italy), G Kiudelis (Lithuania), I. Valantiene (Lithuania), L. Sanromán (Spain), D. Martinez-Ares (Spain), L. Granberg (Sweden), B. Almer (Sweden), U.B. Widén (Sweden), and C. Tysk (Sweden) for their contribution to the study.

All authors have participated in study design and data acquisition, have critically reviewed the draft manuscript for intellectual content, and approved the final version for publication. J. Burisch had full access to all the data in the study and takes full responsibility for the veracity of the data and statistical analysis. J. Burisch and P. Munkholm analyzed and interpreted the data. J. Burisch drafted the manuscript. P. Munkholm supervised the study.

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