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Incidence of Infectious Events in Patients with Inflammatory Bowel Disease. The Impact of Treatment with Immunomodulators and Biologics

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1. Abstract

1.1. Background and Aim: To analyse the incidence of infectious events in patients with inflammatory bowel disease (IBD) and the association to concomitant medical therapy for IBD.

1.2. Methods: We performed a retrospective medical chart review of patients with inflammatory bowel disease age 18-65 years included in the Swedish Registry of Inflammatory Bowel Disease in the catchment area of Umea University Hospital, Sweden. Data was collected from the period January 1, 2006, to January 31, 2019. An infectious event was defined as an outpatient prescription of antimicrobials or a positive diagnostic test for infection.

1.3. Results: Among the 593 included patients, 1398 events occurred. The proportion of events that occurred while on treatment with corticosteroids, immunomodulators (IM), tumour necrosis factor antagonists, combination therapy and without any immunosuppressive treatments was 8.3%, 35.8%, 17.7%, 10.0% and 47.4%. Of all patients, 60.4% had at least one infectious event, and 29.3% had > 0.3 events per year. Compared to patients not receiving immunosuppressive therapy, the median number of events per year was significantly higher in patients treated with IM (0.13; 25th-75th percentile 0-0.39 vs 0.08; 0-0.22; p=0.004) and combination therapy (0.18; 0-0.84 vs 0.08; 0-0.22; p<0.001). There was no significant difference between patients who had received immunomodulator monotherapy and patients who had received combination therapy (p = 0.172).

1.4. Conclusion: We found an increased incidence of infections associated with the use of combination therapy and immunomodulator monotherapy, but no difference between the two treatments. Overall, the incidence of infectious events was low.

2. Introduction

Inflammatory Bowel Disease (IBD) is a group of chronic conditions of presumed autoimmune aetiology, including ulcerative colitis (UC) and Crohn's disease (CD) [1, 2]. IBD is characterised by intermittent inflammation of the gastrointestinal tract with varying extension, severity and frequency of relapse.

The aim of the treatment of IBD is to induce and sustain remission. The treatment strategy varies with the subtype, extension, localization and severity of the disease, frequency of relapse and response of earlier treatments [3, 4]. The traditional therapies consist mainly of 5-aminosalicylic acid, corticosteroids and antimetabolite immunomodulators (IM), such as thiopurines and methotrexate. In more recent years, biological agents, mainly in the form of tumour necrosis factor antagonists (anti-TNF), integrin antagonists (vedolizumab) and interleukin antagonists (ustekinumab), have emerged as alternatives and complements for patients with moderate-severe disease, or when treatment goals have not been reached by traditional means [3, 4].

The treatment of IBD with drugs that interact with the immune system increases the risk for infectious disease [5, 6]. For example, systemic corticosteroids, especially in higher doses, significantly increase the risks of serious [7] and opportunistic [8] infections. Furthermore, thiopurines are associated with an increased risk of opportunistic infections in patients with IBD [8], as well as with overall infection in patients with UC [5]. But, the risk of infection when on treatment with anti TNFs is controversial. While an observational, post-mar-

keting study indicates an increased risk of serious infections compared to non-biological treatment [7], recent meta-analyses have not found an increased risk of serious infections with anti-TNF treatment compared to placebo [6, 9, 10]. However, the risk of overall6 and opportunistic [6, 11] infections seem to increase with anti-TNF treatment.

The combination of anti-TNF and IM is often used in clinical practice. The combination of infliximab and azathioprine has been found to result in higher rates of steroid-free remission than infliximab monotherapy [12, 13]. However, the knowledge of the safety of combination therapy is not fully understood. One retrospective cohort study has indicated no increased risk for serious infections compared to anti-TNF monotherapy [14], while another study demonstrates an increased risk.15 However, the risk of opportunistic infection seems to be higher with combination therapy than anti-TNF monotherapy or thiopurine monotherapy [14, 15].

Therefore, we believe that more knowledge of the potential risks of combination therapy is needed. Previous studies have mainly focused on serious and opportunistic infections. However, the rates of any infection can also affect the adherence to treatment [16], which might impair long term outcome of IBD [17]. The aim of this study was to report the frequency of infectious events in patients with IBD that have led to an intervention from the health-care system and to study to what extent treatment with steroids, IM and anti-TNF is associated with these events. The present study aimed to focus on both factors associated with each infectious event and on the frequency of infectious events in each patient.

3. Methods

3.1. Study Population

The study population was derived from the Swedish Registry of Inflammatory Bowel Disease, SWIBREG, a nationwide registry covering 59% of the Swedish IBD population [18] Patients aged 18-65 February 1, 2019, and treated at the Department of Medicine at Umea University hospital (NUS) within the period of 2006-2019, were included. Inclusion was made January 1, 2006, for prevalent cases 18 years or older. Younger patients were included from turning 18, and incident cases from the date of the first positive finding on endoscopy, either macro- or microscopically. Patients were excluded if they lacked a UC or CD diagnosis, had been treated at NUS only as children, resided outside of Vasterbotten County or had blocked their medical charts. Exclusion was also made from the date of diagnosis of malignancy, organ transplantation surgery, or from the date patients with UC underwent colectomy.

3.2. Definitions

An infectious event was defined as an outpatient prescription of antibiotics or antimicrobials due to infectious disease and/or a positive diagnostic test for infectious disease. Antibiotics prescribed due to IBD related complications, such as fistulas or abscesses, were not considered as events, neither were antibiotics prescribed prophylactically, postoperatively or due to primary sclerosing cholangitis. Multiple events on the same date were registered as a single post, as were prescriptions and positive tests from different dates but clearly linked. Diagnostic tests were not considered as events if the result was described as borderline or commensal flora. In order to exclude positive cultures due to colonisation flora, skin and urine cultures were considered positive only if the patient received infection treatment.

In the patient data, the patients were categorized into three groups: (1) if they had never received immunosuppressive treatment, (2) if they had ever received treatment with IM but not anti-TNF (IM monotherapy) and (3) if they had ever received concomitant treatment with IM and anti-TNF (combination therapy). Only six patients had been treated with anti-TNF but not IM, and this group was not included in the treatment focused analysis.

With the term "immunosuppressive treatment", we included treatment with systemic prednisolone, thiopurines, methotrexate, anti-TNFs, anti-integrins and anti-interleukins. With the term IM we included thiopurines and methotrexate. Combination therapy was defined as concomitant treatment with an IM and an anti-TNF. Budesonide was not considered as a systemic steroid in this study.

The exposure of infliximab, vedolizumab or ustekinumab was considered to last for 8 weeks since the last infusion. The exposure of thiopurines and adalimumab was considered to last for 4 weeks since the last administration. Other treatments were considered to last until the last day of administration.

To determine if a patient was prone to being diagnosed with infection we set the primary outcome at a cut-off >0.3 infectious events per year ("at least one event every third year"). Secondary outcomes were defined as the number of events per year, prescriptions of antibiotics, antivirals and antimycotics, and positive tests for bacterial, viral and mycotic infection.

3.3. Data Collection

Data collection was made retrospectively by review of medical charts of the department of Internal Medicine at NUS dated January 1, 2006, to January 31, 2019. These charts have access to prescriptions and microbiological diagnostics from all outpatient care provided by Vasterbotten County. Data concerning date of diagnosis, number of years treated at NUS, Montreal classification19, surgery due to IBD, medical treatment for IBD, and diagnostics and outpatient antimicrobial treatment for infectious disease was collected.

The characteristics of the events were registered along with concomitant medication for IBD or immunosuppressant medication due to other reasons. Data concerning whether the event was related to surgery was also collected.

3.4. Statistics

Descriptive statistics were used to characterize the study population

and the infectious events. Categorical variables were analysed using Chi-squared test, and presented as frequencies and percentages. Parameters that were not normally distributed were analysed using Mann-Whitney test, and presented as median and first and third quartiles. A p-value < 0.05 was considered statistically significant, and we did not correct for multiple testing.

Analyses were performed using SPSS Statistics 25.0 (IBM Corporation, Armonk, NY).

4. Results

4.1. Study population

The study population is described in (Table 1), and the number of included and excluded patients are shown in (Figure 1).

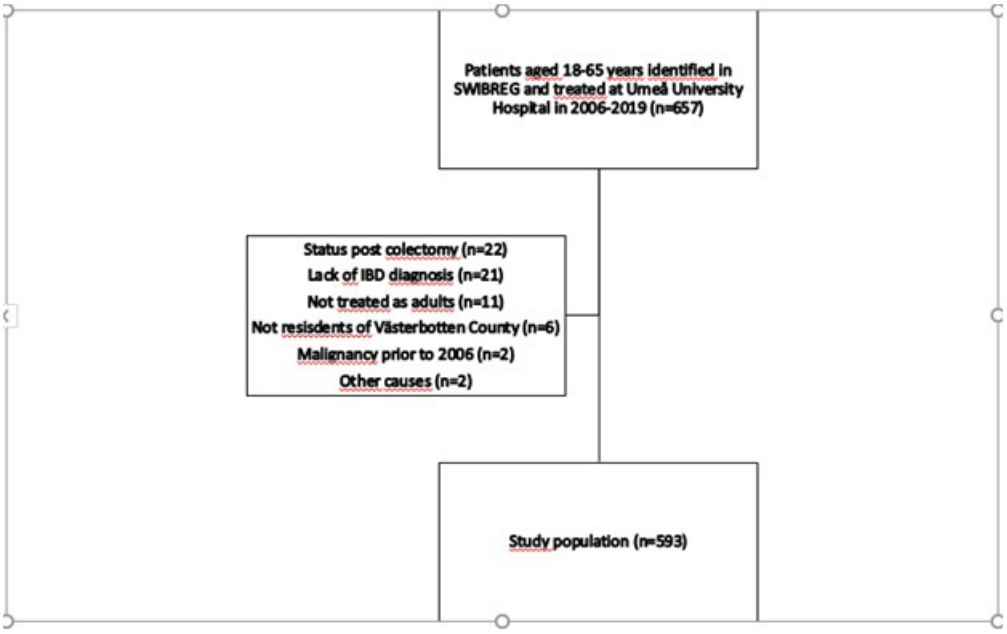

Figure 1: The recruitment of the study population

Table 1: Characteristics of patients included in the study

	All (n = 593)	UC (n = 379)	CD (n = 195)
Follow up duration, years, median (Q_1-Q_3)	9 (5-13)	9 (5-13)	10 (4-13)
Age Feb. 1st 2019, years, median (Q_1-Q_3)	42 (34-53)	43 (35-53)	40 (32-52)
Age at diagnosis, years, median (Q_1-Q_3)	26 (19-35)	26 (20-35)	24.5 (18-33)
Male sex, n (%)	329 (55.5)	213 (56.2)	107 (54.9)
UC, n (%)	379 (63.9)		
CD, n (%)	195 (32.9)		
Unclassified colitis, n (%)	19 (3.2)		
Montreal classification:			
A1, n (%)	93 (15.7)	54 (14.6)	39 (20.7)
A2, n (%)	397 (66.9)	267 (72.0)	122 (64.9)
A3, n (%)	84 (14.2)	50 (13.2)	27 (14.4)
E1, n (%)		49 (12.9)	
E2, n (%)		116 (30.6)	
E3, n (%)		206 (54.4)	
L1, n (%)			44 (22.6)
L2, n (%)			72 36.9)
L3, n (%)			73 (37.4)
L4, n (%)			10 (5.1)
B1, n (%)			102 (52.3)
B2, n (%)			46 (23.6)
B3, n (%)			44 (22.6)
p, n (%)			43 (22.1)
At any time treated with:			
Five-ASA, n (%)	485 (81.8)	359 (94.7)	107 (54.9)
Budesonide, n (%)	144 (24.3)	39 (10.3)	103 (52.8)
Systemic prednisolone, n (%)	314 (53.0)	205 (54.1)	103 (52.8)
Thiopurines, n (%)	283 (47.7)	143 (37.7)	137 (70.3)
Methotrexate, n (%)	34 (5.7)	15 (4.0)	19 (9.7)
Infliximab, n (%)	109 (18.4)	51 (13.5)	56 (28.7)

Adalimumab, n (%)	67 (11.3)	17 (4.5)	50 (25.6)
Other anti-TNF, n (%)	8 (1.3)	6 (1.6)	2 (1.0)
Vedoluzimab, n (%)	13 (2.2)	9 (2.4)	4 (2.1)
Ustekinumab, n (%)	11 (1.9)	0 (0.0)	11 (5.6)
Combination therapy (IM + anti-TNF), n (%)	120 (20.2)	48 (12.7)	71 (36.4)

NOTE: The sum of the numbers of treatments exceeds the number of patients, as each patient might have received several different treatments and treatment combinations.

Abbreviations: n number, UC ulcerative colitis, CD Crohn's disease, y years, Q1 first quartile, Q3 third quartile, A1 age at diagnosis ≤16 years, A2 age at diagnosis 17-40 years, A3 age at diagnosis >40 years, E1 ulcerative proctitis, E2 left-sided colitis, E3 extensive colitis, L1 terminal ileum, L2 colon, L3 ileocolon, L4 upper gastrointestinal tract, B1 nonstricturing, nonpenetrating, B2 stricturing, B3 penetrating, p perianal, Five-ASA 5-aminosalicylic acid, IM immunomodulator, anti-TNF tumour necrosis factor antagonist.

Patients with CD more often had been treated with IM (p <0.001), anti-TNF (p <0.001) and combination therapy (p <0.001) than those with UC (Table 1). IM monotherapy (patients who had received IM but never anti-TNF) was also more common among CD than UC patients (32.3% vs. 24.0%, p = 0.034). There was no difference in the proportion of patients who had at least once been exposed to systemic corticosteroids between patients with UC and CD (p = 0.773).

Compared to patients not receiving immunosuppressive treatment, patients receiving IM monotherapy more often had CD (40.6% vs. 19.9%, p < 0.001), and had more severe disease characteristics in terms of extensive UC (60.0% vs. 40.2%, p = 0.004) and stricturing and/or penetrating CD (40.3% vs. 8.6%, p = 0.001). Those who received combination therapy more often had CD (59.2% vs. 19.9%, p <0.001) and had more severe disease characteristics in terms of age of onset ≤16 years (24.8% vs. 13.8%, p 0.032), extensive UC (79.2 vs. 40.2%, p <0.001) and structuring and/or penetrating CD (73.2% vs. 8.6%, p<0.001) than those not receiving immunosuppressive treatment.

Furthermore, compared to patients receiving IM monotherapy, those receiving combination therapy more often had CD (p = 0.002), and had more severe disease characteristics in terms of age of onset ≤16 years (p = 0.006), extensive UC (p = 0.020) and stricturing and/or penetrating CD (p <0.001). There was no difference in the proportion of patients that at least once had received systemic corticosteroids between the groups receiving IM monotherapy and combination therapy (71.0% vs. 72.5%, p = 0.780).

4.2. Infectious Events Overall

The infectious events are characterized in (Table 2). Almost half of all infectious events was not associated with any immunosuppressive treatment. The most common treatment that was associated with an infectious event was thiopurines. Only one of ten infectious events was associated with combination therapy.

Table 2: Characterization of medical treatment for IBD at the time of event and event characteristics

Ongoing treatment at the time of event	Number of events, n (%) n = 1398	Number of patients with events n = 358
No immunosuppression	663 (47.4)	223
Systemic corticosteroids	116 (8.3)	44
Thiopurines	469 (33.5)	136
Methotrexate	31 (2.2)	11
Anti-TNF	247 (17.7)	70
Vedolizumab	11 (0.8)	6
Uztekinumab	7 (0.5)	3
Combination therapy (Immunomodulators + anti-TNF)	140 (10.0)	48
Combination therapy + systemic corticosteroids	17 (1.2)	7
Characteristic of events	Number of events, n (%) n = 1398	Number of patients with events n = 358
Prescription of:		
Antibiotics	1039 (70.9)	319
Antivirals	100 (6.8)	47
Antimycotics	158 (10.8)	55
Positive test for:		
Bacterial infection	311 (21.2)	134
Viral infection	77 (5.3)	48
Mycotic infection	46 (3.1)	26

Seventy-seven percent (n=1080) of the events were related to bacterial infection (prescription of antibiotics and/or positive bacterial test), while 11.8% (n=16) and 12.2% (n=17) of the events were related to viral and mycotic infections respectively. The most common infections diagnosed with culture was Escherichia coli (n=65), staphylococcus aures (n=64), candida albicans (n=28), haemophilus influenza (n=15), Streptococcus pneumonia (n=10), klebsiella pneumonia (n=9), and chlamydia trachomatis (n=7). Two patients had mycoplasma pneumoniae and two patients had chlamydia TWAR. Overall, only one patient had a diagnosis of mycobacterium tuberculi infection and that patient was diagnosed during combination therapy.

4.3. Infectious Events Per Patient

Overall, the median number of infectious events per year was 0.11 (25th-75th percentile; 0-0.32). Sixty per cent of the patients had at

least one event during the follow-up time. Among patients who at some time had been treated with immunosuppressive medication, 36.7% of the events occurred during a period when they did not receive these treatments. There was a significant positive correlation between number of infectious events and age (rs 0.180; p<0.001).

The median number of infectious events per year was significantly higher among patients with CD compared to patients with UC (0.15; 25th-75th percentile 0-0.42 vs 0.09; 25th-75th percentile 0-0.30; p=0.039). The difference was not significant when comparing CD and UC within each treatment group (IM monotherapy or combination therapy).

Among patients that at some time had been treated with IM or combination therapy, the median number of events per year and the proportion of patients with an event rate >0.3 events per year were significantly higher than among those who had never received immunosuppressive therapy (Table 3). Compared to patients not receiving immunosuppressive therapy, patients who had combination therapy significantly more often had been prescribed antibiotic, antiviral and antimycotic treatment, and more often were diagnosed with bacterial, viral or fungal infection (Table 3). IM monotherapy was associated with a higher frequency of prescription of antibiotics and antimycotics, and more often were diagnosed with bacterial or mycotic infection than patients not receiving immunosuppressive treatment. No significant differences in primary or secondary outcome could be found between patients receiving IM monotherapy and combination therapy, except for positive tests for viral infection which was more common in the combination therapy group (5.8% vs 14.2%; p=0.019).

When excluding events that occurred during treatment with corticosteroids the result did not change.

Table 3: Outcomes according to treatment at any time during the study period.

	Group 1 No immunosuppressive therapy, n = 181	Group 2 IM monotherapy, n = 155	Group 3 Combination therapy, n = 120	Group 1 vs group 2 p	Group 1 vs group 3 p	Group 2 vs group 3 p
≥0.3 events per year, n (%)	33 (18.2)	49 (31.6)	47 (39.2)	0.004	<0.001	0.192
Events per year, median (Q_1-Q_3)	0.08 (0.00-0.23)	0.13 (0.00-0.40)	0.18 (0.00-0.53)	0.004	<0.001	0.172
Prescriptions of antibiotics due to infection per year, median (Q_1-Q_3)	0.00 (0.00-0.17)	0.08 (0.00-0.30)	0.10 (0.00-0.31)	0.014	0.003	0.55
≥1 prescription of antivirals, n (%)	9 (4.9)	13 (8.4)	14 (11.7)	0.207	0.032	0.365
≥1 prescription of antimycotics, n (%)	7 (3.9)	20 (12.9)	13 (10.8)	0.002	0.018	0.6
≥1 positive test for bacterial infection, n (%)	23 (12.7)	40 (25.8)	37 (30.8)	0.002	<0.001	0.357
≥1 positive test for viral infection, n (%)	7 (3.9)	13 (8.4)	19 (15.8)	0.081	<0.001	0.056
≥1 positive test for mycotic infection, n (%)	2 (1.1)	10 (6.5)	6 (5.0)	0.008	0.04	0.61
≥1 positive test for infection, n (%)	29 (16.0)	49 (31.6)	49 (40.8)	0.001	<0.001	0.113

5. Discussion

In this retrospective observational study in patients with IBD under 65 years of age, we found an overall low incidence of infectious events during the study period. Approximately 60% of the patients had at least one infectious event defined by either having been prescribed antimicrobial treatment or a positive test for bacteria, virus or fungi during a median follow up of 9 years. Almost half of all infectious events in our study occurred when the patient was not on any immunosuppressive therapy. The concomitant treatment associated with most infectious event was thiopurines but only one of ten infectious events was associated with combination therapy.

As suspected, this study shows that the risk of an infection is significantly higher among IBD patients treated with IM monotherapy and combination therapy than among patients not treated with immunosuppressive agents. This is consistent with previous studies showing an increased risk for overall infectious diseases during treatment with IM or anti-TNF [5, 6]. However, in comparison to previously reported data [14, 15] our results do not indicate any difference in infection rates with combination therapy compared to IM monotherapy, apart from an increased proportion of patients with at least one positive test for viral infection associated with combination therapy. Differences in study population and study design may partly explain the different outcomes in our study compared to earlier studies.

As stated by Kirchgesner et al [15], most observational studies analysing the association of IBD treatment and infection rates do not properly consider the use of corticosteroids, which is a major risk factor for infections [5, 8]. In the present study, only 8.3% of the events occurred during systemic corticosteroid treatment. Although the proportions of patients that had received systemic corticosteroids were similar between the IM and combination therapy groups, there could be differences in doses, frequency and duration of prednisolone treatment, affecting the event rate.

The increased risk for infection on patients on IM therapy showed in our study support that IM therapy should carefully be controlled in patients with IBD and 6-thoguanine nucleotide levels should not exceed therapeutic intervals. Also, in a patient with combination therapy who reached remission a lower dose of IM could be considered [20]. Also, to prevent antibodies against infliximab a 6-thigoguanine nucleotide level of 125 pmol/8z108/l RBC may be sufficient. [21].

A special worry highlighted when planning immunosuppressive treatment is the risk of primary or reactivated mycobacterium tuberculi infection [22]. But in the Western world tuberculosis is still un-

common. For example, only 0.2% of patients treated with anti-TNF for rheumatoid arthritis were diagnosed with tuberculosis after treatment [23] and in a prospective study from Japan that followed 570 patients one year no case of active tuberculosis was observed [24]. In consistency, in the present study only one patient was diagnosed with tuberculosis during the study and that patient was diagnosed on combination therapy.

The strength of this study lies in the unselected population, as Vasterbotten County provides universal healthcare for all its citizens. This enables observation of consequences of treatments in the context they are actually used. Furthermore, the medical charts give access to all prescriptions and microbiologic diagnostics from all departments in Vasterbotten County, which should ensure an inclusion of the vast majority of events.

The major drawback of this study is the inability of an observational study to exclude the impact of confounders. One major difference between the treatment groups is the severity of the IBD itself. We have taken measures to exclude events directly related to the patients' IBD, e.g. those connected to fistulas, primary sclerosing cholangitis and surgery. However, there is a risk that not all of these events were excluded, due to lack of documentation of the causes of prescriptions and diagnostic testing in the medical records. This could increase the event rate among patients with a more aggressive disease and, consequently, receiving more aggressive medical treatment.

Unfortunately, the number of patients who received monotherapy with anti-TNF in our study was too low to be analyzed in regard of risk for infection, so we were not able to compare IM to anti-TNF.

The treatment strategy could also impact the vigilance to signs of infection among both professionals and patients, leading to increased use of diagnostic tests and antimicrobials in patients with assumed immunocompromising treatments.

This study only focused on infectious events which lead to an intervention from the medical care system and we did not measure self-limited infectious events such as common cold and other common virus infections. Furthermore, we lack information of vaccinations in the patients in our study and one can assume that the proportion of patient who had vaccinations to influenza and pneumococcus is probably higher in the patient treated with IM and biologics.

Finally, the data on the infectious events for each patient in our study could be influenced by variations in the time of exposure to, compliance to and doses of the different treatments.

In conclusion, the overall frequency of infectious events in patients with IBD in our study was low and most of infectious events was not associated with immunosuppressive treatment. Patients who receive IM therapy or combination therapy (IM+ anti TNF) have significant higher risk for an infectious event than patients with no immunosuppressive treatment. However, in our study there was no significant difference in risk between patient on IM and combination therapy.

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