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Leading off

The Risk of Serious Infections Before and After Anti-TNF Therapy in Inflammatory Bowel Disease: A Retrospective Cohort Study

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Background: Serious infections have been observed in patients with inflammatory bowel disease (IBD) on anti-TNF use—but to what extent these infections are due to anti-TNF or the disease activity per se is hard to disentangle. We aimed to describe how the rates of serious infections change over time both before and after starting anti-TNF in IBD.

Methods: Inflammatory bowel disease patients naïve to anti-TNF treatment were identified at 5 centers participating in the Swedish IBD Quality Register, and their medical records examined in detail. Serious infections, defined as infections requiring in-patient care, the year before and after the start of anti-TNF treatment were evaluated.

Results: Among 980 patients who started their first anti-TNF therapy between 1999 and 2016, the incidence rate of serious infections was 2.19 (95% CI,1.43-3.36) per 100 person years the year before and 2.11 (95% CI, 1.33-3.34) per 100 person years 1 year after treatment start. This corresponded to an incidence rate ratio 1 year after anti-TNF treatment of 0.97 (95% CI, 0.51-1.84). Compared with before anti-TNF therapy, the incidence of serious infection was significantly decreased more than 1 year after treatment (incidence rate ratio 0.56; 95% CI, 0.33-0.95; $P = .03$).

Conclusions: In routine clinical practice in Sweden, the incidence rate of serious infection among IBD patients did not increase with anti-TNF therapy. Instead, serious infections seemed to decrease more than 1 year after initiation of anti-TNF treatment.

Lay Summary

The incidence rate of serious infection among inflammatory bowel disease patients did not increase with anti-TNF therapy compared with 1 year before treatment start. A decrease in incidence rate could be seen more than 1 year after initiation of anti-TNF.

Key Words: inflammatory bowel disease, anti-TNF, infections, biologics, real-world data

Introduction

Inflammatory bowel disease (IBD), consisting of Crohn´s disease (CD), ulcerative colitis (UC,) and inflammatory bowel disease unclassified (IBD-U), is a chronic inflammatory condition that affects the gastrointestinal tract.[1,2] Compared with the general population, IBD patients are at increased risk of serious infections.[3] Antitumor necrosis factor (anti-TNF) treatment has become standard treatment for moderate-severe flares and maintenance of remission in patients with IBD who fail conventional therapy.[4,5]

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Key Messages

What is already known?

- Serious infections have been observed in patients with inflammatory bowel disease treated with anti-TNF.

What is new here?

- The incidence rate of serious infection among inflammatory bowel disease patients did not increase with anti-TNF therapy and seemed to decrease more than 1 year after initiation of anti-TNF treatment.

How can this study help patient care?

- Healing the mucosa may outweigh the adverse immunosuppressive effect on the risk for infection and the findings are applicable when assessing the risk and benefits of therapies together with the patient.

Anti-TNF treatment interferes with the immune system, and both patients and physicians may have concerns with the risk of serious infections.

Earlier studies on the risk of infections related to anti-TNF use have shown varying results and data from randomized controlled trials (RCTs) and observational studies are conflicting. Although RCTs have rarely demonstrated any excess risks of infections, such risk increases have been reported in observational studies.[6–13] One of the reasons for the contrasting results may be that the untreated placebo group used in RCTs has a higher proportion of patients with active disease. The enrichment of severely sick (untreated) comparators makes it harder to demonstrate an increased risk of infection among treated patients. Observational studies more often have a longer follow-up and thereby greater statistical power to detect small differences and rare events. There are several other challenges in appropriately determining the risk of serious infection. In addition to anti-TNF and immunomodulating agents (azathioprine, 6-mercaptopurine, and methotrexate), disease activity, corticosteroid use, opioids, malnutrition, comorbidity, and age are all potential confounders potentially predisposing to infections.[14–17] Furthermore, the selection of relevant and appropriate comparison groups in treatment risk assessment trials is challenging. Whereas severely active placebo-treated patients are used as comparator in randomized control trials, anti-TNF-treated IBD patients were compared with IBD patients with or without other immunosuppressive agents or with healthy controls in most previous observational studies.[8,12,18] However in clinical practice, anti-TNF treatment is initiated when patients experience increasing disease activity and failure of conventional treatment, which in itself is known to increase the risk of infection.[14]

We aimed to describe how the rates of serious infections change before and after anti-TNF initiation in flaring IBD and thereby shed light on the role of anti-TNF (as opposed to that of disease activity) for the risk of infection. To do so, we performed a cohort study comparing incidence rates of serious infections before and after anti-TNF initiation.

Materials and Methods

Study Design and Population

Patients were identified in the Swedish IBD Quality register, SWIBREG,[19] and data were captured through review of medical records. Recording of data and inclusion in this study occurred between January 20, 2016, and April 10, 2016, at the following hospitals: Skåne University Hospital, Norrland University Hospital in Umeå, Karlstad Central Hospital, Linköping University Hospital, and Örebro University Hospital.

Only IBD patients who had received their first anti-TNF treatment from 1999 to 2016 were included.

Data Collection

A case report form (CRF) was constructed to ensure identical data extraction at the different sites. Variables in the CRF included patient age, sex, smoking habits, subtype of IBD (UC/CD/IBDU), date of diagnosis, extent and behavior of disease, immunomodulating therapy, biological treatment, serious infections, and C-reactive protein (CRP) levels before and after initiation of biological treatment. The Montreal classification was used to classify IBD phenotypes.[4,20] Serious infection was defined as an infection that required hospital admission (inpatient care). The diagnosis of infection was assigned as a part of ordinary assessment routines (clinical examination, lab results, blood/stool cultures, and radiology) by the treating physician and documented in the medical records. Serious infections were classified into 10 categories: gastroenteritis/*Clostridioides difficile* infection, pneumonia, sepsis, cytomegalovirus (CMV) infection, other infection, urinary tract infection/pyelonephritis, Meningitis/meningoencephalitis, tuberculosis, necrotising fasciitis, and perianal/intra-abdominal abscess. Other infection was defined as infection-related hospitalization where no agent or no specific locus of infection was found. Only 1 infectious event per patient was registered the year before anti-TNF treatment and similarly after the commencement of anti-TNF treatment. If the patient had a diagnose of sepsis, we only registered sepsis and not the infection leading to sepsis. Perianal and intra-abdominal abscesses were considered a consequence and a complication to active disease; hence, this data are presented separately.

Statistical Methods

Baseline was defined as the initiation date of first anti-TNF treatment. All patients were followed from 1 year before anti-TNF treatment and were considered at risk for an infection until first serious infection or until baseline (ie, treatment start). After initiation of treatment, all patients were followed to first serious infectious event or until end of follow-up (April 10, 2016). Patients were considered exposed to anti-TNF and at risk for an infection from the first day of treatment and (a) 2 weeks after the last infusion/injection of adalimumab and certolizumab-pegol, (b) 4 weeks for golimumab, and (c) 8 weeks for infliximab. We accepted pretreatment CRP data when obtained ≤1 month before and up until ≤1 week after treatment initiation. C-reactive protein at follow-up was defined as samples measured 3 months after treatment initiation, obtained +/- 1 month.

Poisson regression was used to calculate incidence rates including 95% confidence intervals (CIs) before and during different time intervals after introduction of anti-TNF. Incidence

rate ratios including 95% CI comparing incidence before and after introduction of anti-TNF were also calculated using Poisson regression, using generalized estimating equation (GEE) and an unstructured covariance matrix to model the dependency in the data; SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for these analyses.

Wilcoxon signed-rank test was used to compare CRP levels. The χ^2 test was conducted to compare the occurrence of monotherapy (only anti-TNF) and combination therapy (anti-TNF and immunomodulators) at the time of infection, as well as to compare smoking habits. The SPSS program (SPSS Statistics for Windows, Version 25.0, IBM Corp.) was used for the analyses. Significance level was set to a $P < .05$ or a 95% CI not including 1.00.

Ethical Considerations

The study was approved by the ethical review board in Stockholm, Sweden (registration number: 2016/191-31/2). The data underlying this article will be shared on reasonable request to the corresponding author.

Results

Study Population

In total, we identified 980 patients with IBD previously naïve to anti-TNF starting treatment 1999 to 2016 (Supplementary Figure 1). Before start of anti-TNF treatment, the total follow-up was 959 person years, and patients in total were followed for 5608 person years after initiation of anti-TNF (average 5.7 years). The median disease duration at start of anti-TNF treatment was 5.3 years. At the time of infection, 33 patients (55.9%) were treated with infliximab and 24 (40.6%) with adalimumab (Supplementary Table 1).

In the study population, 61.0% of patients had CD (n = 598), 36.3% had UC (n = 356), and 2.7% had IBD-U (n = 26). Mean age at baseline was 36 years, and 117 individuals were younger than 20 years at their first anti-TNF treatment. Eighty-one individuals were older than 60 years. The most common location and behavior according to the Montreal classification for CD at diagnosis were ileocolonic (L3; 41.8%; n = 250) and nonstricturing/nonpenetrating (B1; 73.7%; n = 441). The most common extent of UC at the time of diagnosis was extensive colitis (E3), with 54.8% (n = 195). Some 11.5% (n = 113) were smokers (15.6% of CD, 5.9% of UC, and 0% of IBD-U; Table 1).

Anti-TNF Treatment and Serious Infections

Incidence during follow-up

The annual incidence of serious infections during follow-up is presented in Figure 1. During the year before anti-TNF treatment, there were 21 (2.0%) serious infections during 958 person years (2.19 per 100 person years). This compares with 59 (6.0%) serious infections during 4213 person years after anti-TNF exposure (1.40 per 100 person years) and a reduction in incidence beyond 1 year of anti-TNF treatment (1.22 per 100 person years). The incidence of serious infection beyond 1 year of anti-TNF treatment was hence 44% lower than the year leading up to anti-TNF-treatment (incidence rate ratio 0.56; 95% CI, 0.33-0.95; P = .030). We observed no change in the incidence rate of serious infections the first year after treatment compared with the year before treatment (incidence rate ratio 0.97; 95% CI, 0.51-1.84; P = .915; Table 2). The median time from start of anti-TNF treatment to the first serious infection was 1.9 years, (IQR1-IQR3, 0.8-4.4). Out of the 59 patients with a serious infection during treatment, only 2 (3.4%) had had a serious infection the year before starting treatment.

Types of infections

Pneumonia was, followed by gastroenteritis and sepsis, the most common serious infection before anti-TNF initiation, with slightly lower incidence after compared with before anti-TNF. After the introduction of anti-TNF, there was a numerical increase in CMV infections, urinary tract infections, meningitis, tuberculosis, and necrotising fasciitis (Figures 2 and 3).

Concomitant immunomodulating treatment

Before treatment with anti-TNF, 56.1% (550 of 980) of the patients were treated with immunomodulating agents. This proportion was stable throughout the follow-up period with 61.0% (598 of 980) of the patients treated with immunomodulating agents 1 year after initiation of anti-TNF and 59.3% (527 of 889) of the patients beyond 1 year after treatment start. Among patients with a serious infection after the initiation of anti-TNF treatment, 45 of 59 (76.3%) patients were at the time of infection treated with a combination therapy with an immunomodulator. Among these patients, the total exposure time of immunomodulators was 154 years, with a mean of 5 years per patients (Table 1). The proportion of patients who did not acquire an infection and were at any time treated with a combination therapy was 67.0%, (617 of 921 patients). Among anti-TNF treated patients, the addition of combination therapy was not linked to risk of serious infection (P = .14).

Age

The highest incidence of serious infections before treatment was in patients aged younger than 20 years at the initiation of anti-TNF. In this age group, the incidence of infections was significantly reduced after onset of anti-TNF. Incidence rate 3.55 (95% CI, 1.33-9.45) per 100 person years before compared with 0.39 (95% CI, 0.10–1.57) beyond 1 year after anti-TNF treatment and an incidence rate ratio of 0.11 (95% CI, 0.02-0.60; P = .01). In patients aged 60 years and older at anti-TNF initiation, the incidence of serious infection was not significantly different after vs before treatment (incidence rate ratio 0.38; 95% CI, 0.05-2.73; P = .34). The incidence rate ratio between patients 60 years and older compared with younger peers after anti-TNF treatment start was 0.73 (95% CI, 0.29-2.33; P = .483; Table 2).

Smoking habits

There was no difference in smoking status among patients with an infection compared with the entire cohort (P = .15; Table 1).

C-reactive protein levels

C-reactive protein levels before and after start of treatment were available in 69.1% (n = 677) of the patients. Mean CRP level before anti-TNF was 18.1 mg/L (95% CI,16.0-20.2) and after start of treatment 6.5 mg/L (95% CI, 5.4-7.7), representing a 64.1% reduction in the CRP level compared with the CRP level before treatment initiation (P < .001; Figure 4).

Table 1. Patients with inflammatory bowel disease undergoing anti-TNF treatment. Patient characteristics before and after anti-TNF initiation.

		All patients, *n* (%]	Patients with infection *before* onset of anti-TNF treatment, *n* (%)	Patients with infection *after* onset of anti-TNF treatment, *n* (%)
Total		980	21 (100)	59 (100)
Phenotype	CD	598 (61)	16 (76)	34 (58)
Location	L1	126 (21)		
	L2	198 (33)		
	L3	250 (42)		
	L4	13 (2)		
	Unknown	11 (2)		
Behavior	B1	441 (74)		
	B2	114 (19)		
	B3	28 (5)		
	Unknown	15 (3)		
Phenotype	UC	356 (36)	4 (19)	24 (41)
Extent	E1	64 (18)		
	E2	90 (25)		
	E3	195 (55)		
	Unknown	6 (2)		
	IBD-U	26 (3)	1 (5)	1 (2)
Sex	Male	530 (54)	12 (57)	34 (58)
	Female	450 (46)	9 (43)	25 (42)
Age[a]	<20	117 (12)	4 (19)	4 (7)
Min 6	20–39	485 (50)	12 (57)	30 (51)
Max 87	40–59	297 (30)	3 (14)	20 (34)
	≥60	81 (8)	2 (10)	5 (5)
Smoking habits	Never smoked	518 (53)	14 (67)	32 (54)
	Former smoker	261 (27)	4 (19)	21 (36)
	Current smoker	113 (12)	1 (5)	4 (7)
	Unknown	88 (9)	2 (10)	2 (3)
Exposure time (days), anti-TNF treatment	Mean	1333	-	1302
	Min	28	-	35
	Max	6119	-	6119
Exposure time (days), immunomodulating treatment	Mean	1117	180	1870
	Min	14	10	33
	Max	7589	365	4311

[a]Age and Montreal classification at baseline (start of anti-TNF) for all patients.

Perianal and intra-abdominal abscesses

We observed 8 (0.8%) patients with perianal and intra-abdominal abscesses before treatment start of anti-TNF and 8 (0.8%) patients after the start of anti-TNF. A 72.0% reduction in the incidence rate of perianal abscesses and intra-abdominal abscesses during treatment with anti-TNF was found compared with before treatment. We found an incidence rate of 0.83 (95% CI, 0.36-1.64) per 100 person years compared with 0.23 (95% CI, 0.10-0.45) per 100 person years after start of treatment, with an incidence rate ratio of 0.28 (95% CI, 0.10-0.74; P = .006; Figure 5).

Discussion

In the current study, we did not observe an increasing incidence of serious infections after initiation of anti-TNF among patients with IBD. In fact, compared with baseline, a significantly reduced incidence rate was seen after more than 1 year of anti-TNF treatment. To the best of our knowledge, this is the first study to describe rates of serious infections both before and after initiation of anti-TNF in flaring IBD patients in routine medical practice.

Previous studies on the risk of serious infections during immunosuppressive treatment have presented inconsistent results. The divergent results can be explained by differences in the studied populations, comparators, and the varying definitions of infection. Several meta-analyses based on RCTs with highly selected patient groups have failed to detect an increased risk of serious infections.[6–8,21] Out of 10 meta-analyses based on RCTs in an umbrella review from 2018, 8 found no evidence of an increased risk of infections when biological therapies were used in patients with IBD or when

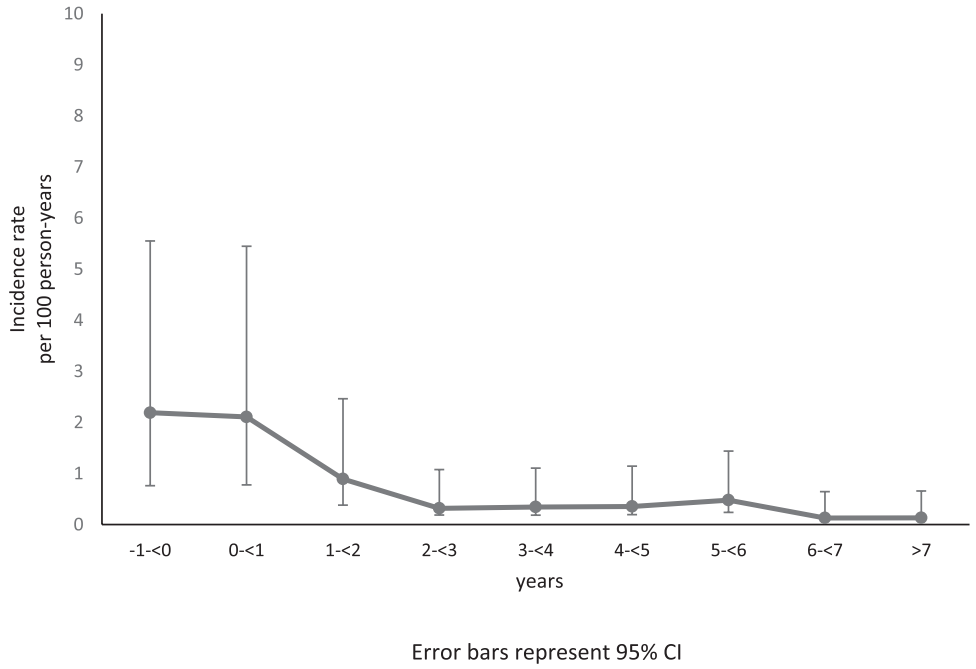

Figure 1. The annual incidence rate of serious infections among IBD patients the year before start of anti-TNF treatment (-1 to <0) and during anti-TNF treatment (0 to <1, 1 to <2 etc.). A decline in the incidence rate can first be seen beyond 1 year of treatment with anti-TNF, with an incidence rate of 1.22 (95% CI, 0.90-1.66) events per 100 person year compared with 2.19 (95% CI, 1.43-3.36) events per 100 person year the year before treatment. This is a significant reduction of infections, with an incidence rate ratio of 0.56 (95% CI, 0.33-0.95; $P = .030$).

Table 2. The incidence rate of infection *before* and *after* start of anti-TNF treatment (events/100/person year) and incidence rate ratio.

	Age, y	Number of events	Years at risk[a] (person years)	Incidence in observed group	(95% CI) in observed group	Incidence rate ratio[b]	95% CI
The year before treatment start	<20	4	112	3.55	1.33–9.45		
	20–39	12	472	2.54	1.44–4.47		
	40–59	3	294	1.02	0.33–3.16		
	≥60	2	79	2.53	0.63–10.12		
	Total	21	958	2.19	1.43–3.36		
First year after treatment start	<20	2	107	1.69	0.43–6.87		
	20–39	8	430	1.86	0.83–3.33		
	40–59	5	249	2.00	1.36–5.46		
	≥60	3	66	4.53	0.61–9.78		
	Total	18	854	2.11	1.33–3.34	0.97	0.51–1.84
More than 1 year after treatment start	<20	2	511	0.39	0.1–1.57		
	20–39	22	1608	1.37	0.90–2.08		
	40–59	15	1034	1.45	0.88–2.41		
	≥60	2	205	0.98	0.24–3.90		
	Total	41	3359	1.22	0.90–1.66	0.56	0.33–0.95

[a]Years at risk before treatment is observation time. Years at risk after treatment is anti-TNF exposure time.
[b]Compared with 1 year before treatment.

restricting the analyses to UC only.[22] However, a recent meta-analysis in which only observational studies with ≥500 person years of observation time were included showed an increased risk of serious infections among patients with IBD treated with combination therapies including anti-TNF or anti-TNF single therapy compared with immunomodulating agents only.[10] A large population-based study from France included in the previously mentioned meta-analysis also provided evidence of an increased risk of serious infections with anti-TNF monotherapy compared with thiopurine monotherapy (hazard ratio [HR], 1.71). In the same study, an increased risk of serious infections and opportunistic infections with combination therapy compared with anti-TNF monotherapy (HRs 1.23 and 1.96, respectively) was demonstrated.[9]

Gastrointestinal disease activity has been recognized as a major risk factor for infections in IBD.[14,16] Patients with

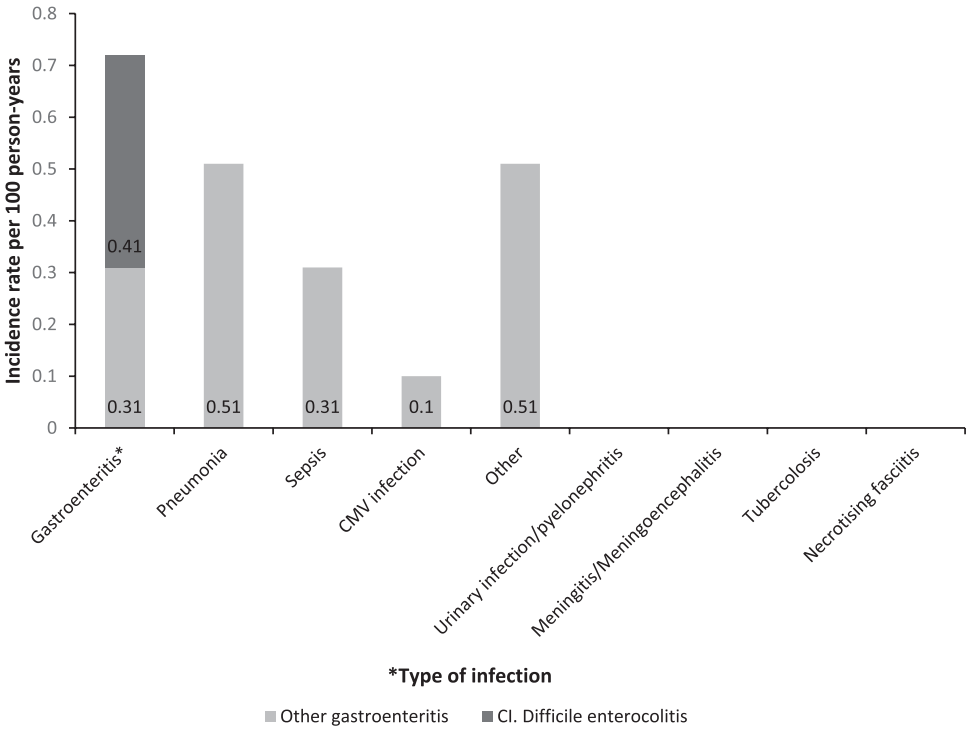

Figure 2. Incidence rate of different types of serious infections (ie, infections requiring hospital admission the year before treatment start of anti-TNF).

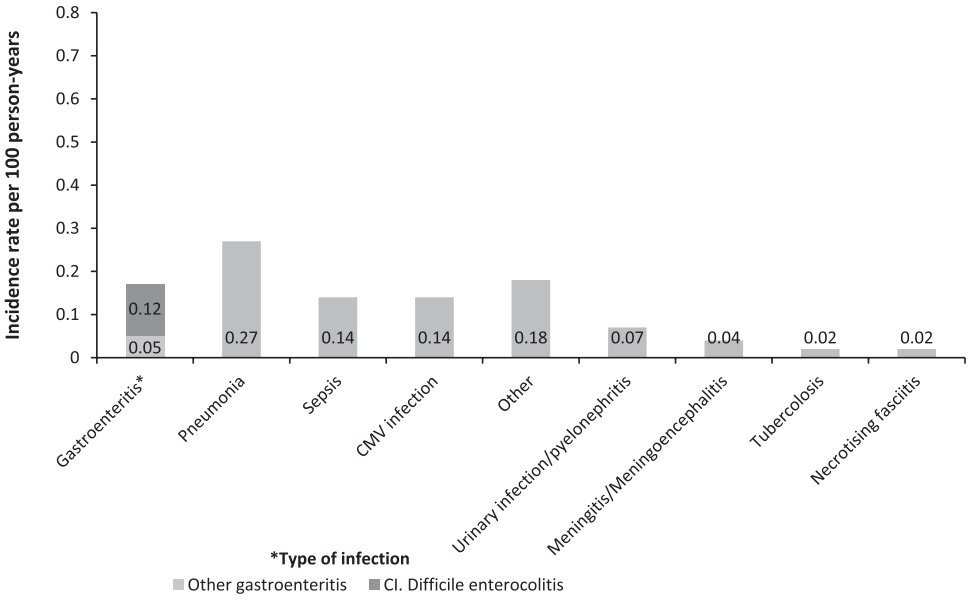

Figure 3. Incidence rate of different types of serious infections (ie, infections requiring hospital admission) after treatment start of anti-TNF. Compared with the year before treatment start, a numerical decrease in gastroenteritis, pneumonia and sepsis was seen. Incidence rate of CMV infection, meningitis/meningoencephalitis, tuberculosis, and necrotising fasciitis increased.

IBD who were selected to receive biological treatment already suffer from an active disease that has not responded adequately to the previously given therapy. Hence, patients considered for anti-TNF treatment may be at an increased risk of infections even before the onset of therapy. In the French study, Kirchgesner et al tried to adjust for this using exposure to corticosteroids, IBD-related surgery, and hospitalization; but these measures could be too blunt to accurately reflect the correct disease activity. In the current study, by comparing the same IBD population before and after commencement of anti-TNF, patients with active disease before treatment acted as their own control when comparing the patient during anti-TNF treatment. The significant decrease in incidence rate of serious infections beyond 1 year after start of treatment in our study may be explained by decreased disease activity among patients responding to anti-TNF. The decline in the incidence of perianal and intra-abdominal abscesses and the significant reduction of CRP levels after start of anti-TNF treatment in

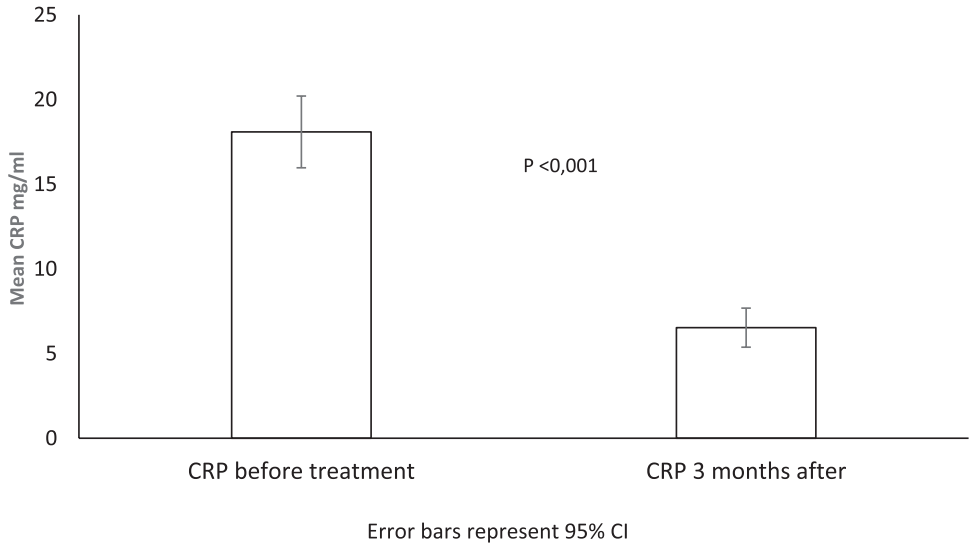

Figure 4. Mean CRP level before and 3 months after start of anti-TNF treatment among IBD patients. After the start of anti-TNF treatment there was a 65% reduction in the CRP level compared with the CRP level before treatment initiation, $P < .001$.

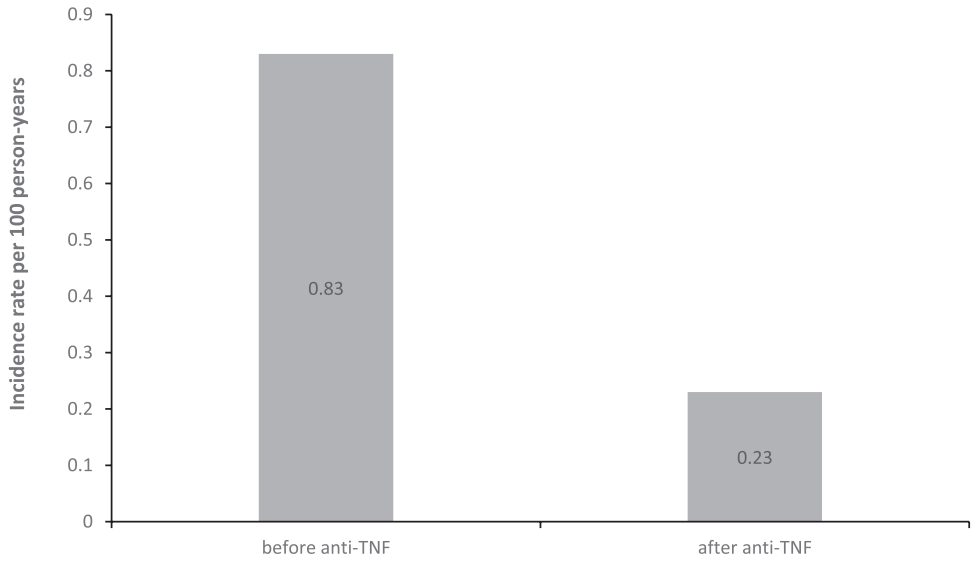

Figure 5. The incidence rate of perianal and intra-abdominal abscess before and after onset of anti-TNF treatment. A reduction of 72% in the incidence rate was seen after start of anti-TNF treatment, incidence rate ratio 0.28 (95% CI, 0.10-0.74; $P = .006$).

our study may indicate a decrease in disease activity which in turn reduces the risk of infections.[23]

Contrary to the result in our study, Zabana et al showed that patients with IBD had an increased risk for serious infection after starting immunosuppressive treatment compared with before treatment (median follow-up 3 years before and 5 years after). Although their methodology is similar to ours, the discrepancy in the result may be explained by selection bias. We included all patients starting anti-TNF treatment. However, Zabana et al included only patients who suffered from infections during immunosuppressive treatment and retrospectively examined the risk of infection before start of treatment.[24]

Younger patients with IBD tend to have more active disease.[25] Earlier data suggest that children with IBD are less likely to have infections during anti-TNF treatment than during steroid treatment.[26] Furthermore, results from a nationwide cohort study among pediatric IBD patients from Denmark showed that pediatric IBD patients do not have an increased risk of infection during anti-TNF treatment.[27] In the current study, patients younger than 20 years old experienced a substantial decrease of infection incidence rate ratio (0.11) with the introduction of anti-TNF treatment. The results could be explained by the fact that young patients have a more active disease with increased risk of infection before treatment with anti-TNF. In the present study, 81 out of 980 patients were older than 60 years. There were few infections among them, and no significant difference in incidence after treatment with anti-TNF compared with before and compared with the total cohort. High age is in itself a risk factor for infections.[28–31] However, previous studies have shown that when adjusting for comorbidity and activity of the IBD, the risk of an infection during anti-TNF treatment is similar between younger and older patients.[9,15] In the beginning of the biological era,

clinicians may have been reluctant to treat fragile, elderly patients with anti-TNF, and this may have biased our result. Because serious infection is a rare event, age-stratified analyses had limited statistical power.

We did not see any difference in the incidence of serious infections among patients with combination therapy, immunomodulators in addition to anti-TNF, compared with monotherapy with anti-TNF. This result contrasts to earlier studies in which the risks of both serious and opportunistic infections have been shown to increase with a combination of more than 1 immunosuppressive drug.[9,32–34] Once again, there is conflicting evidence with findings from the ENCORE registry where no significant increase of risk was found when combination therapy was compared with single treatment with anti-TNF.[35] Since the population studied comprised only 59 out of 980 patients that developed infection after treatment, further analyses are difficult to pursue in our study, and we were not able to risk stratify the different treatment groups, which may have influenced our results.

The most common type of infection after anti-TNF treatment was pneumonia. The high incidence of pneumonia confirms earlier data.[9,36,37]

One other potential explanation as to why anti-TNF treatment did not increase the incidence of serious infection in the current study could be a better control of disease activity and hence a decreased risk of infections. Consequently, the need for corticosteroids should decrease, and thus patients would have fewer infections.[34,38–41] Furthermore, a better nutritional status as an effect of IBD in remission due to anti-TNF may also decrease the risk of infections.[17,42–45] We also did not find that an infection the year before the start of treatment increased the risk of infection after onset of treatment.

A limitation to our study is that corticosteroid utilization and malnutrition were not captured. The activity of the disease was not well enough documented in the medical records; instead we used the CRP level as a marker of the disease activity. The significant reduction of perianal and intra-abdominal abscesses after treatment start with anti-TNF may also indicate a reduction in disease activity. Serious infections are rare events, and we cannot rule out that larger studies are needed to capture minor increases in serious infection rates during the first year with anti-TNF treatment. Despite 980 patients included in the current study, the size did not allow for subgroup analysis based on type of infection. The lack of power for such analysis is another limitation to the study. Although all infection-related hospitalizations were captured from the 5 participating centers, we cannot preclude that a small number of patients sought health care elsewhere. However, such misclassification may have occurred both before and after anti-TNF treatment and is unlikely to have more than marginal effect on our risk estimates. Another limitation is that the patients were only followed until the first infectious event. Any additional infections will not have been accounted for. Patients susceptible to infections can hypothetically have suffered from additional infections after the first infectious event. This may well have contributed to the decreasing incidence through time. The patients were followed in the same way even before treatment start, and this should minimize the risk of selection bias.

Conclusion

In this real-world study from 5 Swedish centers caring for both urban and rural areas, the rate of serious infections in IBD patients was equally high the year before and the year after start of anti-TNF treatment and significantly lower beyond the first year of anti-TNF treatment. Healing the mucosa may outweigh the adverse immunosuppressive effect on the risk for infection and emphasize the importance of treating the underlying disease. The findings are applicable when assessing the risk and benefits of therapies together with the patient.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Appendix 1

The SWIBREG Study Group consists of the following collaborators: Malin Olsson[1], Jonas Bengtsson[2], Hans Strid[3], Marie Andersson[3], Susanna Jäghult[4], Michael Eberhardson[5], Caroline Nordenvall[6,7], Jan Björk[8,9], Ulrika L. Fagerberg[10,11,12], Martin Rejler[13,14], Mattias Block[2,15], Eva Angenete[2,15], Per M. Hellström[16]

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Author Contribution

O.G. and J.H.O. planned the conception and the design of the study. A.F. and I.V. performed the data collection. J.H.O. and A.F. performed the data analyses. J.H.O. and O.G. interpreted the data. J.O.H., A.F., J.H., O.O., J.F.L., P.M., and O.G. drafted the manuscript. All authors revised and approved the final version of the article that was submitted.

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Conflicts of Interest

J.H.O. has received lecture fees from Takeda and served as a consultant for Janssen.

J.H. has served as a speaker and/or advisory board member for AbbVie, Celgene, Celltrion, Ferring, Hospira, Janssen, MEDA, Medivir, MSD, Olink Proteomics, Pfizer, Prometheus Laboratories, Sandoz/Novartis, Shire, Takeda, Thermo Fisher scientific, Tillotts, Vifor, and UCB. He has also received grant support from Janssen, MSD, and Takeda.

H.H. has received lecture fees from Takeda, AbbVie, Tillotts, and Ferring and has served as a consultant for Takeda, Janssen, AbbVie, Vifor, Tillotts, and Pfizer.

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