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EXTENDED REPORT

Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs

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ABSTRACT

Objective To investigate the risk of developing lower intestinal perforations (LIPs) in patients with rheumatoid arthritis (RA) treated with tocilizumab (TCZ).

Methods In 13 310 patients with RA observed in the German biologics register *Rheumatoid Arthritis: Observation of Biologic Therapy*, 141 serious gastrointestinal events possibly associated with perforations were reported until 31 October 2015. All events were validated independently by two physicians, blinded for treatment exposure.

Results 37 LIPs (32 in the colon/sigma) were observed in 53 972 patient years (PYs). Only two patients had a history of diverticulitis (one in TCZ). Age, current/cumulative glucocorticoids and non-steroidal anti-inflammatory drugs were significantly associated with the risk of LIP. The crude incidence rate of LIP was significantly increased in TCZ (2.7/1000 PYs) as compared with all other treatments (0.2–0.6/1000 PYs). The adjusted HR (ref: conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs)) in TCZ was 4.48 (95% CI 2.0 to 10.0), in tumour necrosis factor- α inhibitor (TNFi) 1.04 (0.5 to 2.3) and in other biologic DMARDs 0.33 (0.1 to 1.4). 4/11 patients treated with TCZ presented without typical symptoms of LIP (acute abdomen, severe pain). Only one patient had highly elevated C reactive protein (CRP). One quarter of patients died within 30 days after LIP (9/37), 5/11 under TCZ, 2/13 under TNFi and 2/11 under csDMARD treatment.

Conclusions The incidence rates of LIP under TCZ found in this real world study are in line with those seen in randomised controlled trials of TCZ and higher than in all other DMARD treatments. To ensure safe use of TCZ in daily practice, physicians and patients should be aware that, under TCZ, LIP may occur with mild symptoms only and without CRP elevation.

INTRODUCTION

Lower intestinal perforations (LIPs) are rare in the general population with an incidence rate of about 0.04/1000 persons/year in the European population.¹ The incidence of LIP increases with age and is higher in women than in men. In most cases, perforations appear as a result of infected or inflamed diverticular disease. Lethality is high, with rates of around 30%² and increases with age.³

In patients with rheumatoid arthritis (RA), perforations of the gastrointestinal (GI) tract have been a concern for quite a long time. In the prebiologic era, GI complications were among the most common causes of death in patients with RA.⁴ At that time, concerns mainly referred to perforations of the upper GI tract, for which non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs) are the most important risk factors.⁵ However, in addition to risks for the upper GI tract, for the lower GI tract a higher risk for diverticular complications was found on NSAIDs in several case-control studies with ORs ranging from 1.8 to 11.2.^{6–8}

Similarly, GCs were found to be strongly associated with lower GI perforations^{9–11} with HRs in patients with RA of 2.8 (95% CI 1.3 to 6.1) compared with non-users⁹ or 4.7 (95% CI 1.9 to 12.0) when GCs and NSAIDs were used concomitantly.

Since the approval of the first biologics, the incidence of GI tract complications in RA was expected to decrease with the decreasing use of NSAIDs and high-dose GCs. However, this is only the case if concomitant GCs can be reduced by effective therapy. Curtis *et al* investigated the risk for GI tract complications on tumour necrosis factor- α inhibitors (TNFi) and found a higher incidence of hospitalised GI perforation with concomitant GCs (1.12 (95% CI 0.5 to 2.5)/1000 patient years (PYs)) than without (0.47 (95% CI 0.2 to 0.98)).⁹ The British Biologics Register (BSRBR)¹² compared the risk of GI perforations in patients treated with TNFi and those on conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs) only. While there was no statistically important elevation of the risk associated with TNFi with an incidence rate of lower GI perforations of 0.39/1000 PYs, concomitant GCs were the most important risk factor, conveying a 2.9 (95% CI 1.5 to 5.3) times higher risk, confined to lower GI perforations with a HR of 8.0 (95% CI 2.6 to 24.1).

The clinical development programme of tocilizumab (TCZ) for the treatment of RA identified GI perforations as important risk. An integrated safety analysis of eight trials and long-term extension studies with TCZ reported that no GI perforation had occurred in the group treated with csDMARDs only, but 26 such cases were identified in patients of the group ever exposed to TCZ, resulting in an



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incidence rate of 2.8/1000 PYs.¹³ Eighteen of these perforations occurred in the colon. Due to the early escape design of the trials, only 825 PYs were available in the csDMARD group, limiting the significance of the finding.

Since there is little information on the overall incidence of LIP in patients with RA exposed to specific treatments, no robust comparisons of the incidence rate of GI perforations could be made between TCZ-treated patients and those on other therapies. Several other factors, such as diverticular disease, high disease activity or long-standing high-dose GC or NSAID use, could also have accounted for the higher incidence in TCZ-treated patients. Further, the few studies existing in this field differ considerably in study design, case definition and population studied, the latter impacting on the background risk.

Prospective observational cohort studies, such as the German biologics register Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT), have the advantage that all patients who start treatment with one of the approved biologic agents are eligible to be enrolled. In addition, a control group treated with csDMARDs only is observed under the same protocol. This design enables studying differences in incidence rates of adverse events occurring under different treatments. The aim of this study was to identify risk factors for LIP within the RABBIT register, taking concomitant (time varying) dosages of NSAIDs and GCs into account. We thereby aimed to examine the clinical signs and symptoms of LIP events to inform treating physicians how to advise their patients when starting a new treatment.

METHODS

Patients

We used data of the German biologics register RABBIT captured and validated until 31 October 2015.

RABBIT is an ongoing observational cohort study that started in May 2001. Since then, patients with RA are enrolled when starting a treatment with a biologic DMARD (bDMARD), or csDMARD after failure of at least one csDMARD. Once enrolled, patients are observed for at least 5 years regardless of treatment terminations and changes (with the option to extend observation for another 5 years, if the patient agrees).

The study protocol was approved in 2001 by the ethics committee of the Charité University School of Medicine, Berlin. Each patient participating in the study gave written informed consent before study entry.

Assessments and procedures

During follow-up, information from rheumatologists and patients is captured at regular intervals: at baseline, after 3 and 6 months, and thereafter every 6 months. Data collected include clinical status, disease activity (including disease activity score based on 28 joints (DAS28)), details on DMARD treatment (substance, dosage, application, start and stop dates, reasons for stopping) and concomitant treatments like NSAIDs (yes/no) and GCs (actual dose and mean dose since last questionnaire). At every time point of follow-up, all adverse events that occurred since last questionnaire are reported. At baseline and every 2 years, rheumatologists report comorbid conditions in predefined groups and in plain text. Patients report, among other items, physical function (using the Hannover Functional Status Questionnaire, FFbH).

Adherence to scheduled visits is monitored closely. Investigations of dropouts (defined as two missing follow-ups) are performed regularly. This includes inquiries to local administration offices regarding patient's vital status and, if the patient

had died, obtaining the causes of death from the health authorities. Complete details have been published.¹⁴

Outcomes

Primary outcome

Incidence of LIPs in patients exposed to TCZ, csDMARDs, TNFi, abatacept or rituximab.

Secondary outcomes

Clinical signs and symptoms of LIPs in these patients.

Thirty-day mortality after LIPs.

Outcome validation

To capture all LIPs, we first identified all events that might be associated with GI perforations (including also haemorrhages and bleedings of the intestinal tract) via a predefined group of MedDRA terms. These included all events of the standard MedDRA query (SMQ) 'GI perforation' plus 51 additional MedDRA codes (see online supplementary table S1). Based on medical records and specific queries to the treating rheumatologists, all events were validated first by the leading physician of RABBIT (AS). An additional external validation was done by the Head of the Department for Gastroenterology of the Charité University Medicine (BS). At time of validation, both reviewers were blinded for the patient's treatment exposure. Only events with a definite, non-iatrogenic and non-traumatic LIP were selected for the analysis. We only counted perforations localised below the duodenojejunal junction (ligament of Treitz) as lower GI perforation. The topmost localised perforation included in the analysis was in the terminal ileum.

Definition of DMARD exposure

Treatment was assigned using a risk window for exposure to bDMARDs: a patient was considered exposed to a certain bDMARD at the time of the event if he/she had received at least one dose of the drug within 3 months (rituximab 9 months) prior to the event. Patients unexposed to bDMARDs in this risk window were assigned to the csDMARD group.

All substances targeting TNF (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) were subsumed under TNFi since we had not seen any differences in incidence rates.

Statistical analysis

Multiple Cox regression was applied to compare the risks of LIPs between the treatment groups. Adjustment was made for age, sex, treatment with GCs and NSAIDs. We distinguished current (Cox regression 1) and cumulative (Cox regression 2) treatment with NSAIDs and GCs. For each patient, the portion of visits with new or ongoing NSAIDs treatment was used as a proxy for NSAID use (range: 0 to 1). Regarding cumulative treatment with GCs, we proceeded in a similar way, but considered each month with a dose of >5–10 mg/day with a weight of 0.5 and each month with a dose of >10 mg/day with a weight of 1. Further covariables (body mass index (BMI), number of bDMARD failures, DAS28) were additionally investigated in univariate Cox regression. We applied two sensitivity analyses: (a) we restricted the cohort to a subgroup of patients recruited after 2009 and (b) we repeated Cox regression 1 and 2 but restricted the reference group to biologic naïve patients. Exact Poisson and Clopper-Pearson binomial CIs were calculated for incidence rates and proportions. The uncertainty of HRs is shown in 95% CIs.

RESULTS

Patients

Until 31 October 2015, 13 310 patients had been enrolled in the RABBIT register. Patients in the csDMARD-treated biologic naïve control group were older and had shorter disease duration at inclusion than TNFi-treated patients. Patients starting treatment with non-TNFi biologics had the longest disease duration and the highest number of prior treatment failures (table 1). Most of them (66.1%) had prior TNFi treatment.

The prevalence of chronic GI disease at baseline was lowest in the csDMARD-treated group and highest in patients starting treatment with abatacept. Chronic diverticulosis was reported in 33 patients. In two patients, a history of diverticulitis was known to the rheumatologist, one of these patients had a perforated diverticulum before inclusion in the register. None of the patients with chronic GI disease at baseline developed an intestinal perforation during follow-up.

Incidence of GI perforations

In 53 972 PYs of follow-up, 141 adverse events possibly describing GI perforations were reported. After internal and external medical review, 44 GI perforations were identified (figure 1). Seven were localised in the upper GI tract: three under TNFi resulting in an incidence rate of 0.12 (95% CI 0.02 to 0.35)/1000 PYs and four under csDMARD (0.22 (95% CI 0.06 to 0.57)/1000 PYs).

Thirty-seven GI perforations were localised in the lower GI tract: 32 in the colon/sigma, 4 in the appendix, and 1 in the terminal ileum. Similar incidence rates were observed for patients

exposed to csDMARDs (0.6 (95% CI 0.3 to 1.1) /1000 PYs), TNFi (0.5 (95% CI 0.3 to 0.9)/1000 PYs), abatacept (0.5 (95% CI 0.01 to 2.8)/1000 PYs) and rituximab (0.2 (95% CI 0.01 to 1.1)/1000 PYs), whereas the incidence rate for patients exposed to TCZ was significantly higher (2.7 (95% CI 1.4 to 4.8)/1000 PYs) (figure 2). These crude incidence rates correspond to numbers needed to harm of 1647, 1911 and 371 in patients treated with csDMARDs, TNFi and TCZ, respectively. Sensitivity analysis (a) showed similar rates (see online supplementary figure S1).

Univariate and multivariate risk evaluation of LIP

Twenty-eight of the 37 patients who developed LIP had concomitant GCs, with a daily dose of ≥7.5 mg in 12 patients. Compared with those treated with TCZ, the average dose of GCs was higher in patients treated with TNFi and lower in csDMARD-treated patients (table 2). Further characteristics of patients who developed perforations did not differ significantly between the various treatment groups.

In the univariate analysis higher age, treatment with TCZ, current as well as cumulative GCs, and cumulative NSAIDs but none of the other risk factors (eg, sex, disease activity (DAS28), BMI and number of previous biologics) were significantly associated with LIP. In the multivariate analysis, higher age, current and cumulative use of GCs and NSAIDs were significantly associated with a higher risk of LIP, in addition to treatment with TCZ (table 3). Compared with csDMARDs, exposure to TCZ was associated with a 4.5 times higher risk for LIP (95% CI 2.01 to 9.99) (table 3, Cox regression 2), whereas no association was found for TNFi, abatacept or

Table 1 Patient characteristics at inclusion in the RABBIT register

Parameter	csDMARDs	TNFi	TCZ	ABA	RTX
N	4423	6711	877	371	928
Patient years, sum	18 113	24 851	4082	1976	4950
Age, years, mean (SD)	57.6 (12.3)	54.9 (12.6)	56.7 (12.8)	58.1 (12.9)	58.7 (12.1)
Female	3345 (75.6)	5113 (76.2)	685 (78.1)	282 (76.0)	719 (77.5)
Rheumatoid factor positive	2763 (62.6)	4983 (74.9)	608 (72.2)	267 (74.2)	764 (82.9)
No. of previous csDMARDs, mean (SD)	1.4 (0.9)	2.7 (1.4)	2.2 (1.1)	2.4 (1.3)	2.6 (1.2)
No. of previous bDMARDs, mean (SD)	0 (0.2)	0.2 (0.6)	1.0 (1.1)	1.4 (1.3)	1.4 (1.1)
NSAIDs	1497 (33.8)	2695 (40.2)	293 (33.4)	151 (40.7)	351 (37.8)
Glucocorticoids, not available	9 (0.2)	18 (0.3)	0	0	9 (1.0)
Glucocorticoids, <5 mg/day	1412 (31.9)	1682 (25.1)	240 (27.4)	80 (21.6)	215 (23.2)
Glucocorticoids, 5–10 mg/day	2057 (46.5)	3058 (45.6)	389 (44.4)	182 (49.1)	386 (41.6)
Glucocorticoids, ≥10 mg/day	945 (21.4)	1953 (29.1)	248 (28.3)	109 (29.4)	318 (34.3)
Disease duration, years, mean (SD)	7.2 (8.0)	10.7 (9.2)	10.6 (8.7)	12.0 (9.0)	13.8 (9.9)
DAS28, mean (SD)	4.7 (1.3)	5.4 (1.3)	5.2 (1.3)	5.4 (1.3)	5.3 (1.3)
CRP, mg/L, mean (SD)	14.1 (20.5)	21.2 (29.4)	18.0 (26.1)	19.6 (26.3)	18.3 (24.6)
FFbH, mean (SD)	69.4 (21.7)	61.4 (23.3)	62.6 (24.2)	58.6 (23.6)	55.9 (23.8)
BMI, mean (SD)	27.4 (5.3)	26.4 (5.3)	26.7 (5.4)	26.8 (5.8)	26.3 (5.1)
BMI ≥30 kg/m ²	1167 (26.4)	1412 (21.0)	218 (24.9)	81 (21.8)	181 (19.5)
Diabetes mellitus	436 (9.9)	668 (10.0)	102 (11.6)	46 (12.4)	111 (12.0)
Hyperlipoproteinemia	315 (7.1)	557 (8.3)	82 (9.4)	44 (11.9)	106 (11.4)
Diverticulosis/prior diverticulitis	12 (0.3)	11 (0.2)	3 (0.3)	4 (1.1)	5 (0.5)
Gastrointestinal diseases	159 (3.6)	339 (5.1)	43 (4.9)	26 (7.0)	59 (6.4)
Chronic renal disease	102 (2.3)	295 (4.4)	49 (5.6)	24 (6.5)	61 (6.6)

Values are numbers of patients (%) unless otherwise specified.

ABA, abatacept; bDMARDs, biologic disease-modifying anti-rheumatic drugs; BMI, body mass index; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; FFbH, Funktionsfragebogen Hannover (physical function in %); NSAIDs, non-steroidal anti-inflammatory drugs; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor-α inhibitor.

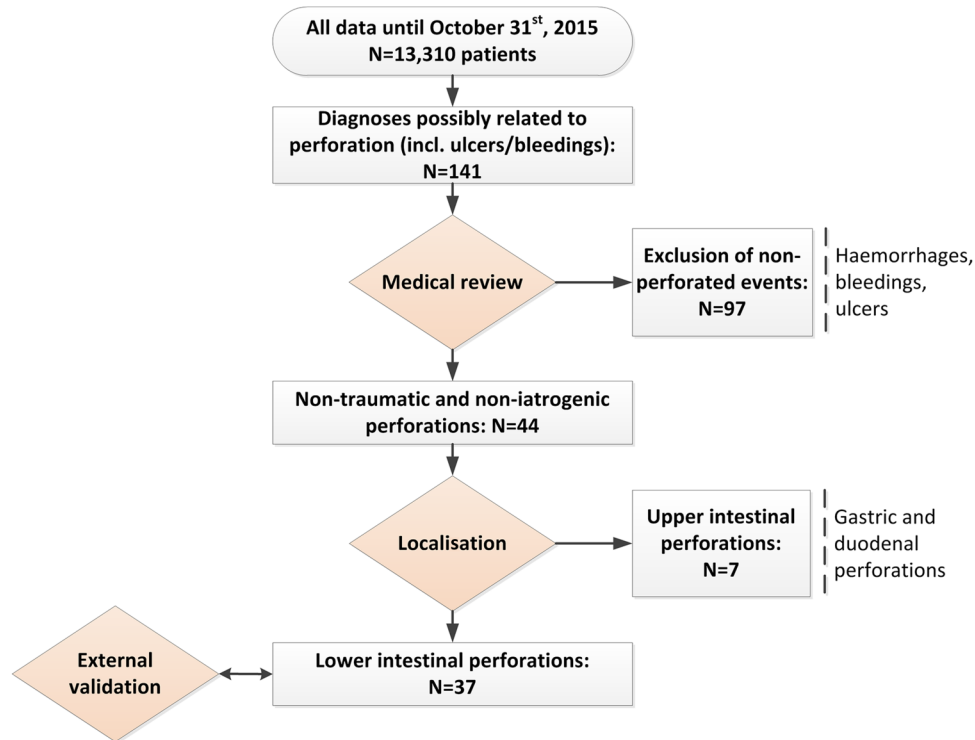


Figure 1 Flowchart of case selection and validation process.

rituximab. Sensitivity analyses (b) did not show different results (see online supplementary table S3).

Clinical signs and outcome of LIPs

While 90% of the patients with csDMARD and 60% of those on TNFi reported acute abdominal pain, this was only the case for 27% (three cases) on TCZ. The majority of patients treated with csDMARDs or other bDMARDs had very high C reactive protein (CRP) values (above 100 mg/L). In contrast, this was the case in only one patient treated with TCZ.

Online supplementary table S2 shows demographics, CRP values, features of clinical presentation and comedication with GC of each patient who developed LIP on TCZ.

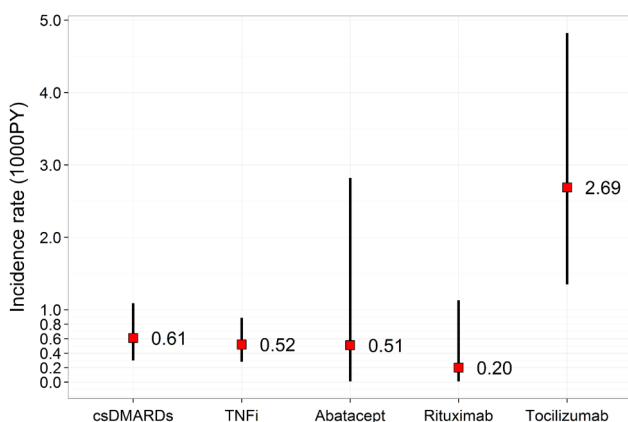


Figure 2 Incidence rates of lower intestinal perforation stratified by DMARDs. Events/patient years (PYs): csDMARDs=11/18 113; TNFi=13/24 851 (adalimumab=6, etanercept=6, infliximab=1); Abatacept=1/1976; Rituximab=1/4950; Tocilizumab=11/4082. csDMARD, conventional synthetic DMARD; TNFi, tumour necrosis factor- α .

According to classifications of colonic diseases, LIPs are considered as complicated diverticulitis (in contrast to diverticulitis without perforation). In total, 92 events of diverticulitis were reported during follow-up. The proportion of patients who developed a perforation was higher in patients treated with TCZ than in all other treatment groups (see table 4).

The 30-day mortality after perforation was 24% in all groups (9/37 patients). The mortality in patients on TCZ (46%) was considerably elevated, although not statistically significant ($p=0.09$, Fisher's exact test) (table 4).

DISCUSSION

Our objective was to evaluate the risk for LIP under various treatments by using the data of a large German RA cohort. We observed a significantly elevated risk for LIP in patients treated with TCZ compared with patients treated with csDMARD and also as compared with patients treated with TNFi or other biologics. LIPs are uncommon events that occurred in patients exposed to TCZ with an incidence of 2.7 per 1000 PYs only, but were associated with a 30-day mortality of 46%.

In patients treated with TCZ, symptomatic diverticulitis was more often associated with perforation than in other treatments. In these patients, the clinical presentation tended to be milder than in other patients. This might explain the finding from van Vollenhoven *et al*¹⁵ that in the majority of patients in the TCZ clinical development programme who had a perforation, the diverticulitis was recognised only after the perforation had occurred.

The incidence rate of LIP in patients treated with TCZ in our cohort was comparable to that reported from randomised controlled trials with TCZ, postmarketing surveillance studies, spontaneous reports or US-based healthcare data in which per 1000 PYs 2.8, 2.4 and 2–2.3 LIPs, respectively, were observed.^{13 16 17} Observational cohort studies reported lower incidence rates in patients with RA not treated with TCZ: in the

Table 2 Clinical characteristics during follow-up of patients who developed LIP

Parameter	csDMARDs	TNFi	TCZ	ABA	RTX
N	11	13	11	1	1
Age at LIP, years, mean (SD)	66.8 (4.8)	67.3 (8.3)	69.2 (7.6)	[73]	[61]
Female	7 (63.6)	7 (53.8)	9 (81.8)	[1 (100)]	[1 (100)]
Rheumatoid factor positive	11 (100)	12 (92.3)	6 (54.5)	[1 (100)]	[1 (100)]
No. of previous bDMARDs, mean (SD)	0.7 (1.3)	1.8 (0.8)	3.3 (1.6)	[4]	[4]
Cumulative NSAID treatment*, mean (SD)	0.4 (0.4)	0.4 (0.3)	0.3 (0.4)	[1]	[0.5]
Disease duration at LIP, years, mean (SD)	13.2 (9.1)	13.0 (7.5)	15.7 (8.4)	[13]	[12]
DAS28 prior to LIP					
≤6 months, mean (SD)	3.8 (0.7)	4.0 (1.7)	3.5 (2.1)	[5.0]	[5.4]
≤12 months, mean (SD)	3.8 (0.7)	4.0 (1.6)	3.7 (2.0)	[5.0]	[5.5]
CRP (mg/L) prior to LIP					
≤6 months, mean (SD)	8.1 (7.9)	25.8 (33.4)	11.5 (17.6)	[0.7]	[3.8]
≤12 months, mean (SD)	10.6 (8.5)	28.3 (33.0)	16.0 (21.5)	[0.7]	[4.2]
ESR (mm/hour) prior to LIP					
≤6 months, mean (SD)	19.4 (11.6)	36.0 (27.6)	14.8 (15.8)	[12.0]	[12.0]
≤12 months, mean (SD)	18.8 (11.3)	36.0 (27.1)	16.3 (13.9)	[12.0]	[13.7]
Glucocorticoids prior to LIP					
Average over 6 months, mean (SD)	5.6 (3.8)	9.7 (9.3)	7.5 (7.5)	[5.0]	[10.0]
Average over 12 months, mean (SD)	5.6 (3.4)	9.6 (9.0)	8.1 (7.3)	[5.0]	[10.0]

*Cumulative treatment with NSAID (range: 0 to 1) was calculated for each patient as: no. of follow-ups with concomitant NSAID use divided by the total no. of follow-ups. ABA, abatacept; bDMARDs, biologic disease-modifying anti-rheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; LIP, lower intestinal perforation; NSAID, non-steroidal anti-inflammatory drug; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor- α inhibitor.

Table 3 Univariate HRs and results of multiple Cox regression

	Univariate		Multiple Cox regression 1		Multiple Cox regression 2	
	HR	95% CI	HR	95% CI	HR	95% CI
Age at event (by 5 years)	1.48	(1.25 to 1.75)	1.55	(1.30 to 1.84)	1.57	(1.32 to 1.87)
Male	1.68	(0.84 to 3.34)	1.58	(0.79 to 3.20)	1.45	(0.72 to 2.90)
BMI	1.00	(0.94 to 1.06)				
bDMARD failures (reference: 0)						
1 bDMARD	1.54	(0.67 to 3.52)				
≥2 bDMARDs	0.71	(0.17 to 3.00)				
DAS28 (current)	1.14	(0.92 to 1.42)				
DAS28 (average last 12 months)	1.16	(0.91 to 1.48)				
DMARD (reference: csDMARDs)						
TNFi	0.84	(0.39 to 1.80)	1.00	(0.46 to 2.20)	1.04	(0.48 to 2.26)
Other bDMARDs	0.40	(0.09 to 1.78)	0.41	(0.09 to 1.84)	0.33	(0.08 to 1.44)
Tocilizumab	4.17	(1.87 to 9.27)	5.11	(2.31 to 11.3)	4.48	(2.01 to 9.99)
GCs						
Current GC (by 5 mg)	1.22	(1.13 to 1.31)	1.28	(1.18 to 1.38)		
Cumulative GCs*	1.81	(1.47 to 2.22)			1.87	(1.50 to 2.33)
NSAIDs						
Current NSAID	1.80	(0.92 to 3.53)	2.18	(1.11 to 4.31)		
Cumulative NSAIDs†	2.71	(1.20 to 6.12)			3.00	(1.33 to 6.82)

In Cox regression 1, we adjusted for current doses of GCs and NSAIDs, whereas in Cox regression 2 for cumulative doses.

*Concomitant GC use (range: 0 to 1) was calculated for each patient as the area under curve of follow-up month with medium doses (>5 to 10 mg/day, weight of 0.5) plus follow-up month with high doses (>10 mg/day, weight of 1) and then divided by total no. of follow-up months.

†Cumulative treatment with NSAIDs (range: 0 to 1) was calculated for each patient as: no. of follow-ups with concomitant NSAIDs use divided by the total no. of follow-ups.

bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; GC, glucocorticoid; NSAIDs, non-steroidal anti-inflammatory drugs; other bDMARDs, abatacept and rituximab; TNFi, tumour necrosis factor- α inhibitor.

Rochester cohort, a rate of 1.3/1000 PYs¹⁸ in 813 patients diagnosed with RA between 1980 to 2008 (and followed until 2009) was observed. Only 17% of the patients had ever been exposed to bDMARDs and 77% had concomitant GCs. From

US claims data,¹⁹ a rate of 0.87/1000 PYs in patients with RA was reported. In the British Biologics Register, an incidence of LIP of 0.39/1000 PYs in patients on TNFi treatment and of 0.15/1000 PYs in biologic naïve csDMARD-treated patients was

Table 4 Incident diverticulitis, perforations and lethal perforations

	PYs	Total no. of diverticulitis		
		(Incidence rate/1000 PYs (95% CI))	Thereof: no. of LIP (proportion, (95% CI*))	No. of patients died within 30 days after LIP (proportion, (95% CI*))
csDMARDs	18 113	34 (1.9 (1.3 to 2.6))	11 (32.4 (17.4 to 50.5))	1 (9.1 (0.0 to 41.3))
TNFi	24 851	37 (1.5 (1.1 to 2.1))	13 (35.1 (20.2 to 52.5))	3 (23.1 (5.0 to 53.8))
Tocilizumab	4082	16 (3.9 (2.2 to 6.4))	11 (68.7 (41.3 to 89.0))	5 (45.5 (16.8 to 76.6))
Abatacept	1976	1 (0.5 (0.0 to 2.8))	1 (100 (2.5 to 100))	0 (0 (0 to 97.5))
Rituximab	4950	4 (0.8 (0.2 to 2.1))	1 (25.0 (0 to 80.6))	0 (0 (0 to 97.5))
Total	53 972	92 (1.7 (1.4 to 2.1))	37 (40.2 (30.1 to 31.0))	9 (24.3 (11.8 to 41.2))

*Exact Clopper-Pearson 95% CI for the proportion.

csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; IR, incidence rate per 1000 PYs; LIP, lower intestinal perforations; PYs, patient years; TNFi, tumour necrosis factor- α inhibitor.

found.¹² GCs were the most important risk factor for LIP in this study.

Comparable to other studies, we also observed a higher risk for patients who were older, male or treated with GCs in higher dosages or NSAIDs in higher frequency. Minor differences in the distribution of these risk factors between the treatment groups did, however, not explain the higher incidence of LIPs in TCZ-treated patients. Adjustment for these factors did not decrease the HR for developing a LIP under TCZ.

Biological mechanisms may also support the increased risk of LIP in patients treated with TCZ: the interleukin 6 (IL-6) receptor targeted by TCZ seems to have an important function of the intestinal barrier. It is hypothesised that locally accumulated fat tissue may cover inflamed diverticula, similar to creeping fat in Crohn's disease which covers inflamed intestinal segments and where IL-6 is predominantly found.^{20 21} Creeping fat may limit the transmural intestinal inflammation to the intestine.^{22 23}

Our study has strengths and limitations. An important risk factor of LIP is previous diverticulitis that was likely underreported at enrolment into RABBIT. Adjustment for this risk factor was not possible since none of the patients with a history of diverticulitis, diverticulosis or another chronic GI disease developed a LIP. However, patients with prior diverticulitis are unlikely to be overrepresented in patients treated with TCZ since first clinical trials of TCZ reported a higher risk of LIP and the German Society for Rheumatology recommended not using TCZ in patients with a history of diverticulitis (<http://dgrh.de/rheumatocilizumab.html>). This may have caused a lower reporting threshold for LIP under TCZ treatment. Nevertheless, we do not assume different reporting behaviour for LIPs due to the severity of the events requiring hospitalisation and possibly leading to severe sequelae. An underreporting of LIPs is therefore not likely under any treatment. The rather constant reporting rates over time support this assumption. In addition, all LIPs were diagnosed by treating gastroenterologists or surgeons of general hospitals and not the rheumatologists participating in RABBIT.

The low numbers of LIPs observed in the register were another limitation which restricted the number of covariables in the Cox regression to adjust for confounding by indication. In addition, the risk conveyed by cumulative NSAID use could only be considered by a proxy since exact doses and start/stop dates of NSAIDs as well as the exposure prior to enrolment in RABBIT are not comprised in our data. The effect of long-term NSAID use in high doses might therefore be inadequately estimated.

The strengths of our study are the prospective design, the comprehensive case validation with independent external

validation, the availability of clinical information on the course and outcome of LIP and the long-term follow-up of patients exposed to different treatments including treatment switches which allows comparative analyses.

CONCLUSION

This is the first comparative analysis of real-life data on the risk of LIP, covering all DMARDs available in Germany for the treatment of RA. In agreement with the results from the TCZ clinical development programme which qualified LIP as important identified risk, we found a rate of 2.7/1000 PYs in patients treated with TCZ. This rate was significantly higher than in other biologic agents or csDMARDs. It is of clinical importance that the majority of patients who experienced a LIP on TCZ did not have a history of diverticulitis. Further, some patients with LIP presented with relatively mild symptoms. In combination with the suppressed values of CRP under TCZ treatment, this may lead to a delayed diagnosis by non-specialised physicians not familiar with TCZ. Rheumatologists should be aware that IL-6 inhibition can be associated with an increased risk of LIP in patients with prior diverticulitis. Patients should be advised to observe signs and symptoms of LIP carefully and to inform non-specialised doctors that CRP, in their case, cannot be interpreted as a marker of diverticular inflammation. This could contribute to reduce a rare but serious risk in daily care.

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