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Risk of diverticulitis and gastrointestinal perforation in rheumatoid arthritis treated with tocilizumab compared to rituximab or abatacept

Claire Rempenault¹, Cédric Lukas¹, Bernard Combe¹, Astrid Herrero², Isabelle Pane³, Thierry Schaeffer⁴, Daniel Wendling⁵, Thao Pham⁶, Jacques-Eric Gottenberg⁷, Xavier Mariette⁸ and Jacques Morel¹; On behalf of the French Society of Rheumatology and the investigators participating in AIR-PR, ORA and REGATE registries

Abstract

Objective. To compare the risk of diverticulitis and gastrointestinal perforation (GIP) in RA treated with tocilizumab (TCZ) compared with rituximab (RTX) and abatacept (ABA).

Methods. We conducted a population-based study using three observational French registries on TCZ, RTX and ABA in RA. Using a propensity score approach, we compared the risk of diverticulitis or GIP in these patients.

Results. With inverse probability weighting, there was an increased risk of diverticulitis in TCZ-treated patients compared with RTX- or ABA-treated patients [hazard ratio (HR)=3.1 (95% CI: 1.5, 6.3), $P = 0.002$]. Moreover, patients treated with TCZ had also an increased risk of GIP due to diverticulitis compared with those treated with RTX or ABA [HR=3.8 (1.1–13.6), $P = 0.04$], resulting in an overall increased risk of GIP [HR=2.9 (1.1–7.8), $P = 0.03$], while no significant increased risk of GIP due to any other aetiology was found in TCZ treated patients. Diverticulitis and GIP occurred earlier with TCZ than other drugs after the last perfusion ($P = 0.01$), with atypical clinical presentation (slow transit in 30%, $P = 0.04$) and lower acute-phase reactants at the time of the event ($P = 0.005$).

Conclusion. TCZ for RA was associated with increased odds of diverticulitis as well as GIP due to diverticulitis as compared with RTX and ABA. Our study confirms the increased odds of GIP in patients receiving TCZ, which might be explained by an increased risk of diverticulitis with misleading clinical presentation.

Key words: rheumatoid arthritis, tocilizumab, diverticulitis, gastrointestinal perforation

Rheumatology key messages

- Tocilizumab is associated with an increased risk of diverticulitis.
- Tocilizumab is associated with an increased risk of gastrointestinal perforation, especially those due to diverticulitis.
- Gastrointestinal events including diverticulitis have misleading clinical presentations in RA treated with tocilizumab leading to gastrointestinal perforation.

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Introduction

Gastrointestinal (GI) perforation (GIP) is a rare but severe complication that occasionally occurs in patients with RA. The incidence of GIP in RA is estimated at 0.2–1.2/1000 person-years (PY) [1]. As compared with non-RA patients, RA patients seem at increased risk of GIP {hazard ratio [HR] = 1.5 [95% CI: 1.1, 1.9], with an increased risk of mortality [HR = 1.6 (1.1–2.2)]} [2]. Before the use of biologic agents, GIP occurred mainly in the upper GI tract, related to the use of NSAIDs [3, 4]. Nevertheless, in recent studies, nearly 80% of GIP occurred in the lower GI tract [1, 5]. Some risk factors for GIP in RA have been concordantly identified in multiple studies: age, comorbidities [estimated by the Charlson Comorbidity Index (CCI)], exposure to (or cumulative dose of) glucocorticoids or NSAIDs at the time of the event, and history of diverticulitis [5–7].

A clinical development program in RA revealed a potential risk of GIP in patients receiving at least 1 dose of intravenous (i.v.) tocilizumab (TCZ), a monoclonal antibody targeting IL-6 receptor (IL-6R). Pooled data from phase 2, 3 and 4 trials in this patient population found an estimated incidence of GIP of 2.0/1000 PY (95CI = 1.4–2.9) [8]. Two retrospective observational studies corroborated these findings [6, 7]. The analysis of the German RABBIT registry found an increased risk of lower GIP in RA patients receiving TCZ vs conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) [HR = 4.5 (2.0–10.0)] [6]. Additionally, an analysis of the Marketscan and Medicare databases, including 164 152 RA patients, found an increased risk of GIP in patients receiving TCZ vs TNF inhibitor (TNFi) agents [adjusted HR = 2.5 (1.3–4.9)] [7]. These results were confirmed in the Swedish registry ARTIS recently [9].

The aetiology of these GIP cases in patients with RA receiving TCZ has never been investigated in clinical studies. In the general population, lower GIP is frequently linked to diverticular disease [10]. Strangfeld *et al.* [6] showed that symptomatic diverticulitis was more likely complicated by GIP in patients receiving TCZ vs csDMARDs or TNFi agents (68.7% vs 32.5% or 35.1%). Nevertheless, to our knowledge, the risk of diverticulitis in patients receiving different biologic agents has never been explored.

Thus, we compared the risk of diverticulitis and GIP in RA treated with TCZ vs rituximab (RTX) and abatacept (ABA) for patients included in the registries of the French Society of Rheumatology by using a propensity score approach.

Materials and methods

Study data

We used data from three registries of the French Society of Rheumatology, [AutoImmunity and Rituximab (AIR), Orencia and RA (ORA) and REGistry-

RoAcTEmra (REGATE)] prospectively evaluating the efficacy and safety of RTX, ABA (i.v.) and TCZ (i.v.) in real-life patients with RA. These registries and their methodologies for data collection have been described previously [11–13]. In summary, standardized information about demographic, clinical and therapeutic characteristics as well as reported adverse events (AEs) were prospectively collected by trained staff at each site (at baseline, 3 and 6 months and every 6 months or at disease relapse afterwards) during 7 years for AIR and 5 years for ORA and REGATE. A systematic follow-up for safety reasons was performed even after drug discontinuation. In this study, data from the three registries were pooled. If a patient was included in several registries, all available data were taken into consideration. Informed patient consent was obtained. This cohort study was based on the guidelines of the STROBE statement

These studies were approved by the French authorities (Comité Consultatif sur le Traitement de l'information en matière de Recherche dans le domaine de la Santé (Advisory Committee on Information Processing in Health Research) and Commission Nationale de L'Informatique et des Libertés (the National Commission for Data Protection and Liberties)).

Eligibility criteria

Patients were recruited from 107 study sites (54 academic and 53 non-academic) in France from September 2005 to August 2013 for AIR and ORA and from January 2011 to June 2018 for REGATE. Inclusion criteria were diagnosis of RA according to the 1987 American College of Rheumatology criteria, age >18 years, and initiation of i.v. RTX, ABA and TCZ. A full list of patients receiving i.v. RTX, ABA or TCZ for each site was obtained from the pharmacist to avoid any inclusion bias.

Objectives

We assessed and compared the incidence of diverticulitis, GIP, diverticular GIP and GIP due to other aetiologies across RTX-, ABA- or TCZ-treated patients. Then we analysed risk factors for diverticulitis, GIP, diverticular GIP and GIP due to other aetiologies among all patients and specifically by treatment. Finally, we described and compared the clinical symptoms experiencing abdominal complications across RTX-, ABA- or TCZ-treated patients.

Outcomes and definition

The medical records of all patients with the events of interest were additionally analysed. Comorbidities were evaluated by age-adjusted CCI [14]. Exposure time to biologic DMARDs (bDMARDs) was defined as the time from the first infusion to 3 months after the last infusion of TCZ or ABA, and 6 months after the last infusion of

RTX. For each patient, mean Disease Activity Score in 28 joints (DAS28) and mean glucocorticoids dose were calculated as the mean of all recorded data during follow-up. The dose of NSAID used at the time of the AE was collected according to the Assessment of SpondyloArthritis International Society scoring [15]. History of diverticulosis, diverticulitis or GIP were only specifically collected in the TCZ registry, but when a patient presented an event, previous history was identified through medical records.

Outcome validation

To capture all diverticulitis and GIP cases among recorded AEs from the three registries, we used a methodology previously described [6]. A predefined list of MedDRA terms translated in French, including all events of the standard MedDRA query 'GI perforation' along with additional MedDRA codes was used to for the database search

. We excluded all events occurring after the exposure time (defined above). On the basis of medical records and specific questions (a standardized data collection form was sent to each site where a potential AE of interest was identified) completed by patient's physician. The diagnosis of diverticulitis was retained if the patient had a suggestive abdominal CT scan in adequation with the diagnosis or if the patient had received appropriate antibiotic treatment after a concordant clinical episode. All events were adjudicated by two investigators (C.R. and J.M.) with blinding to the allocated bDMARD. An additional external validation was provided by a gastrointestinal digestive surgeon (A.H.) with blinding to the allocated bDMARD

. When a patient presented an event (diverticulitis or GIP), the patient was censored. If a patient presented a second event in the course of treatment, it was notified as a recurrence but not analysed as a second event.

Definition of DMARD exposure

Patients with diverticulitis or GIP were considered exposed to the bDMARD if the AE occurred on treatment or within 3 months after the last infusion of TCZ or ABA or within 6 months after the last infusion of RTX.

Statistical analysis

Baseline characteristics and disease evolution are described with mean (s.d.) or frequency (%) as appropriate. The incidence rate of diverticulitis or GIP was calculated as the number of events over exposure time. We used a propensity score approach to account for factors that might affect both treatment assignment and outcome. Because we hypothesized an increased risk of diverticulitis or GIP associated with TCZ, the propensity score was defined as the probability of receiving TCZ. Covariate selection was done using a univariate analysis. Propensity was estimated

by using a logistic model with TCZ as the dependent variable and the following covariates as independent variables: age, sex, history of diabetes mellitus and neoplasia, CCI, number of previous csDMARDs, number of previous TNFi agents, daily dose of glucocorticoids at baseline, co-treatment with a csDMARD and duration of RA. The analysis was based on inverse probability weighting [IPW, i.e.: $1/\text{propensity score}$ in exposed patients (TCZ) and $1/(1 - \text{propensity score})$ in unexposed patients (RTX or ABA)] [16]. The covariate balance was checked after weighting by computing standardized differences. A standardized difference of $\geq 10\%$ is generally considered meaningful [17]. We first estimated the crude risk of diverticulitis or GIP with TCZ vs ABA or RTX, or ABA and RTX pooled, in the total cohort by a Cox regression analysis to estimate hazard ratios (HRs) and 95% CIs. Then patients were weighted using IPW to estimate the risk of diverticulitis or GIP with TCZ vs ABA or RTX, or ABA and RTX pooled, in the total cohort by a Cox regression analysis. Time was censored when a patient experienced a gastrointestinal event. In order not to overestimate statistical power, the weighting was accounted for in the calculation of *P*-values and confidence intervals through the robust standard error method. We identified risk factors for diverticulitis or GIP among the whole cohort and by each treatment by using univariate analysis (Student's *t* test for quantitative variables, χ^2 test for qualitative variables). Variables associated with diverticulitis or GIP with $P < 0.2$ on univariate analysis were included in a multivariate logistic regression analysis. As there were few events, we performed a sensitivity analysis restricted to the scientifically confirmed risk factors for these gastrointestinal events in the general population, namely: age, sex, tobacco exposure, daily dose of GCs and DAS28-CRP during follow-up. Finally, we compared the clinical and biological signs, evolution and treatment of diverticulitis or GIP among patients with TCZ vs ABA or RTX treatment by Fisher exact test for categorical data and Mann-Whitney *U* test for the numerical data. We also used subgroup analyses of GIP by aetiology of GIP: diverticular GIP or GIP due to another aetiology than diverticulitis. Statistical analyses involved using SPSS v15. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients and follow-up

Altogether, the REGATE, AIR and ORA registries included 4501 patients: 1496 receiving TCZ, 1986 RTX and 1019 ABA. There were more females in the TCZ and RTX registries than the ABA registry and more frequent history of neoplasia in the RTX than TCZ and ABA registries. Patients receiving TCZ had shorter RA duration and less frequently received glucocorticoids at baseline than those receiving RTX and ABA. Most of the

TABLE 1 Baseline and follow-up characteristics of patients with RA who received tocilizumab (TCZ), rituximab (RTX) or abatacept (ABA)

Registry (n)	All patients (4501)	TCZ (1496)	RTX (1986)	ABA (1019)
Female, n (%)	3465 (77.0)	1196 (79.9)	1563 (78.7)	706 (69.3)
Age, mean (s.d.)	57.5 (13.2)	56.6 (13.6)	58.0 (12.7)	58.1 (13.6)
History of diabetes mellitus, n (%)	470 (10.4)	156 (10.4)	196 (9.9)	118 (11.6)
History of neoplasia, n (%)	378 (8.5)	81 (5.4)	238 (12.4)	59 (5.8)
Charlson index, mean (s.d.)	3.1 (1.7)	3.0 (1.5)	3.2 (1.8)	3.3 (1.9)
Tobacco exposure, n (%)	852 (18.9)	317 (21.2)	435 (21.9)	NR
RA duration, mean (s.d.) (months)	161.0 (116.6)	152.3 (120.2)	163.4 (114.7)	168.5 (114.5)
RF and/or ACPA positive, n (%)	3716 (87.3)	1193 (88.0)	1692 (85.6)	831 (86.9)
Number of prior csDMARDs, mean (s.d.)	2.7 (1.4)	2.2 (1.3)	3.0 (1.4)	2.8 (1.5)
Prior use of TNFi, n (%)	3573 (79.4)	1195 (79.9)	1545 (77.8)	833 (81.7)
Exposure time to the assigned bDMARD, mean (s.d.) (months)	37.7 (29.9)	35.0 (22.0)	42.6 (34.2)	32.0 (29.5)
Dose (/perfusion) of the assigned bDMARD, mean (s.d.) (mg)	NA	554.2 (127.3)	NR	688.7 (133.0)
Concomitant treatment with csDMARDs, n (%)	2742 (60.9)	892 (59.6)	1287 (64.8)	563 (55.3)
Concomitant treatment with GCs, n (%)	3329 (74.0)	1024 (68.4)	1544 (77.7)	761 (74.7)
Daily dose of GCs at baseline, mean (s.d.) (mg)	11.3 (8.9)	10.2 (7.3)	12.1 (9.9)	11.3 (8.4)
Daily dose of GCs during follow-up mean (s.d.) (mg)	6.9 (4.6)	7.5 (4.2)	6.8 (4.8)	6.4 (4.5)
DAS28 at inclusion, mean (s.d.)	5.3 (1.3)	5.1 (1.3)	5.6 (1.2)	5.3 (1.3)
DAS28 during follow-up, mean (s.d.)	3.9 (1.2)	3.3 (1.2)	4.3 (1.1)	4.0 (1.2)

ACPA: anti-citrullinated protein antibodies; bDMARDs: biologic DMARDs; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; DAS28: Disease Activity Score in 28 joints; GCs: glucocorticoids; NA: not applicable; NR: not reported.

patients (79.4%) had prior TNFi treatment (Table 1). History of diverticulosis, diverticulitis or GIP was recorded only in the TCZ registry [20.1% had a digestive history, including 3.0% diverticulosis (20% recorded as complicated) and 0.3% GIP].

Propensity weighted analysis

Because of missing data, propensity scores were calculated for 3823 patients. We observed no differences in these patients' characteristics compared with the whole cohort

Weights ranged from 1 to 38.0. The weighted groups were well balanced for recorded baseline and follow-up variables, with standardized differences ranging from 0% to 7.1%

Incidence and risk of diverticulitis or GIP with TCZ, RTX and ABA treatment

From 69 414 recorded AEs in the three registries, 49 diverticulitis or GIP were considered after internal and external adjudication (Fig. 1). Most of the time, GIP was linked to diverticulitis, but in the TCZ and RTX registries, some GIP cases were linked to other aetiologies such as appendicitis or peptic ulcer disease (Fig. 1). No patient experienced an event in two different registries.

In total, 21 cases of diverticulitis occurred with TCZ treatment (3989.7 PY), corresponding to an incidence rate (IR) of 5.26/1000 PY; 10 occurred with RTX (6321.8 PY), corresponding to an incidence of 1.58/1000 PY; and 10 occurred with ABA (2389.1 PY), corresponding to an incidence of 4.19/1000 PY (Table 2). In the crude

analysis, we found an increased risk of diverticulitis with TCZ vs pooled RTX or ABA [HR 2.1 (95% CI: 1.1, 3.8), $P = 0.02$] and vs RTX [HR 2.8 (1.3–6.0), $P = 0.007$] but not when compared with ABA (Table 2). In the propensity-weighted analysis, risk of diverticulitis remained increased with TCZ vs pooled RTX or ABA [HR 3.1 (1.5–6.3), $P = 0.002 < 0.0001$] and vs RTX [HR 4.0 (1.7–9.6), $P < 0.0001$] but not vs ABA (Table 2).

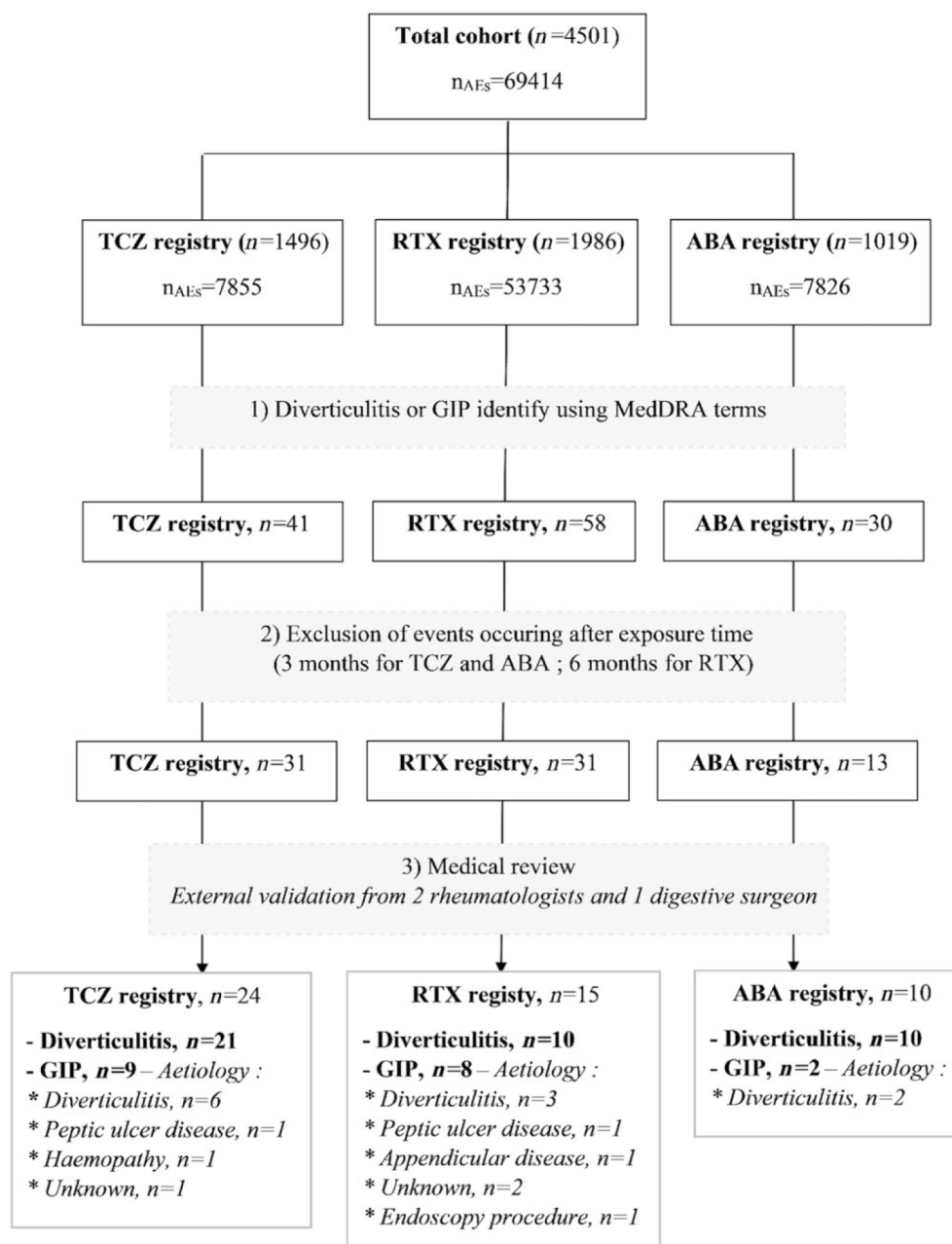
Regarding GIP, nine cases occurred with TCZ (IR = 2.3/1000 PY), eight cases occurred with RTX (IR = 1.3/1000 PY) and two cases occurred with ABA (IR = 0.8/1000 PY). The crude analysis failed to demonstrate an increased risk of GIP in the TCZ-treated patients compared with RTX- or ABA-treated patients. However, in the propensity-weighted analysis, we found an increased risk of GIP with TCZ vs pooled RTX or ABA [HR 2.9 (1.1–7.8), $P = 0.03$] and with a trend compared with RTX [HR 2.6 (0.9–7.6), $P = 0.07$] or to ABA [HR 3.9 (0.8–18.6), $P = 0.09$] (Table 2). Consistently with the previous demonstrated increased risk of diverticulitis, this increased risk of GIP remained significant

Risk factors for diverticulitis and GIP with TCZ, RTX and ABA treatment

On univariate analysis

), older age, low number of prior csDMARDs, concomitant treatment with methotrexate and TCZ treatment were associated with diverticulitis overall and higher DAS28–CRP at baseline and during follow-up in the TCZ group. On multivariate analysis (Table 3), only older age and TCZ remained

Fig. 1 Flowchart of case selection and validation process



ABA: abatacept; AEs: adverse events for diverticular GIP but not for GIP due to another aetiology (Table 2); GIP: gastrointestinal perforation; n: number; RTX: rituximab; TCZ: tocilizumab.

associated with diverticulitis; nevertheless, a higher daily dose of GCs during the follow-up seemed to be associated with diverticulitis. Similar results were found in the sensitivity analysis available

On univariate analysis

, GIP overall was associated with only older age, but with TCZ treatment, it was associated with history of cancer and glucocorticoids at baseline and with RTX, older age, male sex, tobacco exposure and shorter RA duration. Of note, history of diverticulosis,

diverticulitis or GIP was not associated with diverticulitis or GIP in the TCZ group. On multivariate analysis (Table 4), only older age remained associated with GIP. Nevertheless, patients experiencing GIP had also a higher daily dose of glucocorticoids during follow-up although not significantly ($P = 0.08$). Specifically, in the TCZ group, a history of cancer was associated with GIP ($P = 0.03$) and only older age and tobacco exposure remained associated with GIP in the RTX group. Similar results were found in the sensitivity analysis

TABLE 2 Incidence and risk of diverticulitis or gastrointestinal perforation (GIP) with TCZ, RTX or ABA treatment

	AE (n)		IR (/1000 PY)		Crude analysis		IPW analysis	
					HR [95% CI]	P	HR [95% CI]	P
TCZ vs other bDMARDs	TCZ (ref)		RTX & ABA					
Exposure (PY)	3 989.7 PY		8 710.9 PY					
Diverticulitis	21	5.26	20	2.30	2.1 [1.1, 3.8]	0.02	3.1 [1.5, 6.3]	0.002
GIP	9	2.26	10	1.15	1.9 [0.7, 4.7]	0.17	2.9 [1.1, 7.8]	0.03
*Diverticular GIP	6	1.50	5	0.57	2.3 [0.7, 7.6]	0.17	3.8 [1.1, 13.6]	0.04
*GIP due to another aetiology	3	0.75	5	0.57	1.4 [0.3, 6.2]	0.66	2.1 [0.5, 10.0]	0.33
TCZ vs RTX	TCZ (ref)		RTX					
	3989.7 PY		6321.8 PY					
Diverticulitis	21	5.26	10	1.58	2.8 [1.3, 6.0]	0.007	4.0 [1.7, 9.6]	0.002
GIP	9	2.26	8	1.26	1.7 [0.6, 4.5]	0.29	2.6 [0.9, 7.6]	0.07
*Diverticular GIP	6	1.50	3	0.47	2.6 [0.7, 10.6]	0.17	4.6 [1.1, 19.6]	0.04
*GIP due to another aetiology	3	0.75	5	0.79	1.00 [0.2, 4.5]	1.00	1.7 [0.3, 8.1]	0.51
TCZ vs ABA	TCZ (ref)		ABA					
	3989.7 PY		2389.1 PY					
Diverticulitis	21	5.26	10	4.19	1.2 [0.6, 2.7]	0.6	1.7 [0.7, 4.1]	0.22
GIP	9	2.26	2	0.84	2.6 [0.5, 11.9]	0.23	3.9 [0.8, 18.6]	0.09
*Diverticular GIP	3	0.75	2	0.84	1.8 [0.4, 9.0]	0.46	2.6 [0.5, 14.1]	0.26

HR: hazard ratio; IPW: inverse probability weighting; IR: incidence rate; PY: person-years; ref.: reference. Significant values have been highlighted in bold.

TABLE 3 Risk factors for diverticulitis in multivariate analysis

Group (n)	All patients (3737) ^a		TCZ (993) ^b		RTX (1763) ^c		ABA (939) ^d	
	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P
Age at time of the event	1.03 [1.0, 1.1]	0.02	1.01 [0.9, 1.1]	0.75	1.1 [1.0, 1.2]	0.09	1.1 [1.0, 1.1]	0.11
Female	0.7 [0.3, 1.6]	0.43	0.8 [0.2, 3.0]	0.73	0.3 [0.8, 1.5]	0.15	2.1 [0.4, 11.5]	0.37
Tobacco exposure	NA	NA	0.31 [0.04, 2.5]	0.27	6.1 [1.3, 27.8]	0.02	NA	NA
History of neoplasia	1.1 [0.4, 3.3]	0.84	2.1 [0.4, 10.7]	0.36	0.5 [0.1, 5.0]	0.57	0.7 [0.2, 15.7]	0.62
History of diverticulitis	NA	NA	0 [0, 0]	0.99	NA	NA	NA	NA
Exposure time to bDMARD	1.01 [0.9, 1.02]	0.07	1.01 [0.98, 1.04]	0.51	1.0 [0.9, 1.1]	0.83	1.04 [1.0, 1.1]	0.002
RA duration, per months	0.99 [0.9, 1.0]	0.33	0.99 [0.9, 1.0]	0.27	0.99 [0.9, 1.0]	0.45	0.99 [0.9, 1.0]	0.64
Number of prior csDMARDs	0.98 [0.7, 1.3]	0.90	1.1 [0.7, 1.8]	0.63	0.8 [0.4, 1.5]	0.46	0.94 [0.5, 1.5]	0.79
Number of prior bDMARDs	1.06 [0.8, 1.4]	0.69	1.2 [0.7, 1.9]	0.47	0.6 [0.3, 1.2]	0.17	0.9 [0.5, 1.8]	0.88
Treatment with csDMARDs	1.7 [0.8, 3.6]	0.18	1.1 [0.3, 3.5]	0.85	1.8 [0.3, 9.5]	0.49	2.0 [0.5, 8.5]	0.35
Treatment with TCZ	2.4 [1.1, 4.8]	0.02	NA	NA	NA	NA	NA	NA
Daily dose of GCs – baseline	0.96 [0.9, 1.0]	0.17	0.97 [0.9, 1.1]	0.49	0.9 [0.8, 1.1]	0.22	0.98 [0.9, 1.1]	0.75
Daily dose of GCs – follow-up	1.08 [1.0, 1.2]	0.06	1.06 [0.9, 1.2]	0.41	0.98 [0.7, 1.3]	0.87	1.2 [1.1, 1.4]	0.02
DAS28-CRP – follow-up	1.0 [0.9, 1.0]	0.71	1.6 [0.9, 3.0]	0.11	0.8 [0.4, 1.5]	0.48	0.99 [0.9, 1.1]	0.70

bDMARDs: biologic DMARDs; csDMARDs: conventional synthetic DMARDs; DMARDs: disease modifying anti rheumatic drugs; GCs: glucocorticoids; NA: not adapted; OR: odds ratios. Significant values have been highlighted in bold. Parameters included in the logistic regression model. ^aAge, sex, history of neoplasia, exposure time to the assigned bDMARDs, RA duration, number of prior csDMARDs and bDMARDs, treatment with TCZ, daily dose of GCs at baseline and during follow-up, DAS28-CRP during follow-up. ^bAge, sex, tobacco exposure, history of neoplasia, history of diverticulitis, exposure time to the assigned bDMARDs, RA duration, number of prior csDMARDs and bDMARDs, daily dose of GCs at baseline and during follow-up, DAS28-CRP during follow-up. ^cAge, sex, tobacco exposure history of neoplasia, exposure time to the assigned bDMARDs, RA duration, number of prior csDMARDs and bDMARDs, daily dose of GCs at baseline and during follow-up, DAS28-CRP during follow-up. ^dAge, sex, history of neoplasia, exposure time to the assigned bDMARDs, RA duration, number of prior csDMARDs and bDMARDs, daily dose of GCs at baseline and during follow-up, DAS28-CRP during follow-up.

TABLE 4 Risk factors for gastrointestinal perforation (GIP) in multivariate analysis

Group (n)	All patients (3737) ^a		TCZ (993) ^b		RTX (1763) ^c	
	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P
Age at time of the event	1.04 [1.0, 1.1]	0.04	1.01 [0.9, 1.1]	0.79	1.1 [1.0, 1.2]	0.04
Female	0.66 [0.2, 1.8]	0.66	1.0 [1.0, 1.0]	0.99	0.6 [0.1, 3.0]	0.56
Tobacco exposure	NA	NA	0 [0, 0]	0.99	5.5 [1.1, 28.1]	0.04
History of neoplasia	0.98 [0.2, 4.5]	0.98	7.1 [1.2, 41.6]	0.03	0 [0, 0]	0.99
History of diverticulitis	NA	NA	0 [0, 0]	0.99	NA	NA
Exposure time to bDMARD	1.00 [1.0, 1.1]	0.83	1.1 [0.9, 1.1]	0.78	1.01 [0.9, 1.1]	0.42
RA duration, per months	1.0 [0.9, 1.0]	0.51	1.0 [0.9, 1.1]	0.47	0.98 [0.9, 1.0]	0.06
Number of prior csDMARDs	0.9 [0.6, 1.3]	0.46	1.0 [0.5, 1.9]	0.95	0.99 [0.5, 1.9]	0.99
Number of prior bDMARDs	1.03 [0.7, 1.5]	0.88	1.3 [0.7, 2.6]	0.43	0.9 [0.4, 1.8]	0.77
Treatment with csDMARDs	1.1 [0.4, 3.1]	0.78	2.6 [0.5, 14.4]	0.28	0.3 [0.1, 1.6]	0.18
Treatment with TCZ	1.9 [0.7, 5.0]	0.21	NA	NA	NA	NA
Daily dose of GCs – baseline	0.97 [0.9, 1.1]	0.47	1.0 [0.9, 1.1]	0.96	0.9 [0.8, 1.0]	0.19
Daily dose of GCs – follow-up	1.08 [1.0, 1.2]	0.08	1.1 [0.9, 1.3]	0.53	1.1 [0.9, 1.3]	0.26
DAS28-CRP – follow-up	1.0 [0.9, 1.0]	0.56	0.9 [0.4, 2.2]	0.90	0.99 [0.9, 1.1]	0.81

bDMARDs: biologic DMARDs; csDMARDs: conventional synthetic DMARDs; DMARDs: disease modifying anti rheumatic drugs; GCs: glucocorticoids; NA: not adapted; OR: odds ratios. Significant values have been highlighted in bold. Parameters included in the logistic regression model. ^aAge, sex, history of neoplasia, exposure time to the assigned bDMARDs, RA duration, number of prior csDMARDs and bDMARDs, treatment with TCZ, daily dose of GCs at baseline and during follow-up, DAS28-CRP during follow-up. ^bAge, sex, tobacco exposure history of neoplasia, history of diverticulitis, exposure time to the assigned bDMARDs, RA duration, number of prior csDMARDs and bDMARDs, daily dose of GCs at baseline and during follow-up, DAS28-CRP during follow-up. ^cAge, sex, tobacco exposure history of neoplasia, exposure time to the assigned bDMARDs, RA duration, number of prior csDMARDs and bDMARDs, daily dose of GCs at baseline and during follow-up, DAS28-CRP during follow-up.

Clinical signs and outcomes of patients with diverticulitis or GIP

Ten of 49 (20.4%) diverticulitis or GIP cases occurred in patients with a history of diverticulosis, diverticulitis or GIP, with no difference among treatments. As compared with RTX and ABA treatment, with TCZ, diverticulitis and GIP occurred earlier after the last perfusion [24.5 (18.4) vs 58.6 (49.2) days, $P = 0.01$] and in patients with lower disease activity [DAS28 at the time of the event 3.1 (1.5) vs 4.5 (1.6), $P = 0.008$]. Clinically, patients more frequently showed atypical presentation [body temperature 37.4 (1.1) vs 38.6 (0.6), $P = 0.04$; and sub-occlusive syndrome in 30% vs 0, $P = 0.04$]. Moreover, these patients had lower objective signs of inflammation at the time of the event [haemoglobin level 13.9 (1.9) vs 10.6 (2.8) g/dl, $P = 0.01$; platelet count 251 583 (5976) vs 371 500 (68 066)/mm³, $P = 0.04$; and CRP level 31.2 (58.4) vs 88.2 (89.6) mg/l, $P = 0.005$] (Table 5). Recurrence occurred in 16.7% patients with TCZ treatment. As compared with uncomplicated diverticulitis, GIP occurred in patients with a higher dose of glucocorticoids at the time of the event although not significantly [median (range)=10 (2.5–12.5) vs 6.5 (0–24) mg/dl, $P = 0.06$]. Mortality within 30 days after the events did not differ among TCZ, RTX or ABA treatment

Only one death occurred in the TCZ group (accounting for 11.1% of patients experiencing a GIP), occurring after GIP due to peptic ulcer disease, and one

death in the RTX group (12.5% of patients experiencing a GIP), occurring after an undetermined rectal perforation. Both deaths occurred in older patients with multiple comorbidities.

Discussion

Our study confirms an increased risk of GIP with TCZ treatment for RA but also highlights an increased risk of diverticulitis due to TCZ, with disconcerting clinical and biological presentation. Apart from the bDMARD, age was the only risk factor associated with diverticulitis and GIP in our whole cohort.

Even if the comparator is different, our observed risk of GIP (HR =2.9 vs RTX or ABA in our study) was similar to that reported by Strangfeld *et al.* (HR =4.5 vs csDMARDs) [6], Xie *et al.* [7], (HR =2.5 vs TNFi) and Barbulescu *et al.* (HR =2.2 vs TNFi), except when TCZ was compared exclusively to ABA or RTX, probably due to a limited number of events and thus a lack of power [9]. Our results were also consistent with those by Strangfeld *et al.* [6] regarding the reduced symptomatic events (clinical presentation and laboratory parameters) in the TCZ group. However, mortality rate among TCZ-treated patients with GIP was lower in our study than that observed in the above studies (11.1% vs 15.4% to 46%) [6, 7]. This finding could be explained by the sensitization of the French rheumatologists to the increased risk already described in these two studies [6, 7].

TABLE 5 Clinical signs and outcomes of patients with diverticulitis or GIP

	TCZ (n = 24)	Other bDMARDs		P
		RTX (n = 15)	ABA (n = 10)	
Incident tobacco exposure, n (%)	2 (8.3)	2 (13.3)	1 (10)	1.00
History of diverticulosis, n (%)	4 (16.7)	0 0	2 (20)	0.67
History of diverticulitis, n (%)	1 (4.2)	0 0	2 (20)	0.6
History of GIP, n (%)	1 (4.2)	0 0	0 0	1.00
Time since last perfusion (days), mean (s.d.)	24.5 (18.4)	78.1 (51.5)	31.3 (30.7)	0.01
Time since first symptoms to diagnosis (days), mean (s.d.)	11.7 (10.6)	3.2 (3.9)	18.5 (32.2)	0.25
Incident GCs use, n (%)	17 (70.8)	9 (60)	7 (70)	0.76
Daily incident GCs dose (mg), mean (s.d.)	7.3 (5.2)	9.2 (3.0)	7.2 (4.4)	0.15
Incident NSAIDs use, n (%)	7 (29.2)	3 (20)	2 (20)	0.52
ASAS score, mean (s.d.)	95.0 (11.2)	83.3 (57.7)	50.0	0.24
Incident use of GCs plus NSAIDs, n (%)	6 (25)	2 (13.3)	1 (10)	0.28
Incident DAS28, mean (s.d.)	3.1 (1.5)	5.1 (1.7)	3.9 (1.1)	0.008
Body temperature (°C), mean (s.d.)	37.4 (1.1)	38.4 (0.8)	38.7 (0.6)	0.04
Presentation with unusual abdominal pain, n (%)	19 (79.2)	6 (40)	9 (90)	0.21
Presentation with diarrhea, n (%)	2 (8.3)	1 (6.7)	2 (20)	0.65
Presentation with constipation or sub-occlusive syndrome, n (%)	7 (29.2)	0 0	0 0	0.008
Incident haemoglobin level (g/dl), mean (s.d.)	13.9 (1.9)	7.1 (1.0)	11.9 (1.7)	0.01
Incident leucocyte count (/mm ³), mean (s.d.)	10 772 (4687)	13 085 (12 466)	12 323 (2878)	0.74
Incident platelet count (/mm ³), mean (s.d.)	251 583 (5976)	368 000 (117 380)	375 000 (8485)	0.04
Incident CRP level (mg/L), mean (s.d.)	31.2 (58.4)	172.5 (99.2)	40.0 (31.9)	0.005
Evolution into recurrence, n (%)	4 (16.7)	0 0	0 0	0.11
Permanent stop of the assigned bDMARDs, n (%)	17 (70.8)	6 (40)	1 (10)	0.03

ASAS, Assessment of SpondyloArthritis International Society; bDMARDs: biologic DMARDs; CsDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; DAS28: Disease Activity Score in 28 joints; GCs: glucocorticoids.

Indeed, the lack of abdominal pain was associated with increased risk of mortality with GIP in patients with autoimmune diseases [18]. In our study, abdominal pain was noticed in all GIP patients, whereas only a few of those treated with TCZ had abdominal pain in the RABBIT registry [6]. Due to this increased risk of mortality, prophylactic elective sigmoid colectomy might be considered within immunosuppressed patients after recovery from acute diverticulitis according to international recommendations if a switch is not possible [19, 20].

The underlying mechanism of action behind the increased risk of GIP in RA patients receiving TCZ remains unknown. *In vitro* studies demonstrated that IL-6 is required to maintain small intestinal crypt homeostasis [21], to enhance intestinal epithelial cell proliferation and renewal following an injury [22], and to protect against inappropriate apoptosis [23]. It has also been demonstrated that IL-6 mediates colonic contraction [24, 25]. Therefore, we hypothesize that in susceptible RA patients, neutralization of IL-6 might favor diverticulitis (owing to the change in colonic contraction) with an atypical inflamed presentation. The digestive epithelium would not repair the primary lesion and this diverticulitis might result in GIP. Nevertheless, despite limited tolerance data, only a few GIP have been reported with sarilumab, a new anti-IL-6R monoclonal antibody [26, 27]. Moreover, Xie *et al.* also showed an increased risk of GIP in patients receiving JAK inhibitor vs TNFi agents

[adjusted HR = 3.2 (1.1–10.0)] [7], suggesting that neutralization of IL-6 is not sufficient to explain the development of GIP.

While risk factors for GIP are well known in RA (i.e. age, glucocorticoids, NSAIDs, CCI, and a history of diverticulitis) [5–7], only older age was identified as risk factor of GIP in our overall population. Because NSAID exposure and history of diverticulitis were not systematically collected in the three registries (nor other risk factors for GIP in the general population such as body mass index), it was unfeasible and inaccurate to analyse them, which constitutes an important bias. Nevertheless, regarding glucocorticoids, we found a trend for receiving a higher mean daily dose during follow-up in patients with GIP and also a higher daily dose, although not significantly, in patients with GIP vs uncomplicated diverticulitis. This finding could be explained by a lower statistical power owing to the low number of events observed in these registries. Another limitation could be the study design resulting in missing data, lack of randomization and a possible channeling bias. Because of missing data, we could not calculate the propensity score for the whole cohort, and some confounding factors (not collected in the registries) might have not been included in this score. Finally, adverse events were spontaneous reports of adverse drug reactions from physicians at participating sites. Consequently, vigilance regarding gastrointestinal events such as diverticulitis might be increased in patients

receiving tocilizumab, resulting in an overestimated risk of diverticulitis due to a declaration bias.

The strengths of our study are the prospective design, multi-centric setting and large sample size; exhaustive collection of medical data to characterize and adjudicate AEs to be included in the analyses; and mitigation of the indication bias with a propensity score approach and therefore mimicking a pseudo-randomization design. Using the same approach in the same registries, we previously reported that drug retention differed between the three drugs [13]. Moreover, to our knowledge, this is the first study suggesting that the increased risk of GIP among TCZ-treated patients was linked to an increased risk of diverticulitis among those patients.

To conclude, using a propensity score approach, TCZ treatment for RA was associated with an increased risk of diverticulitis as compared with RTX and ABA treatment. Regarding GIP, only those related to diverticular disease were increased by TCZ. Moreover, patients receiving TCZ and experiencing these gastrointestinal complications might have disconcerting clinical presentation.

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Data availability statement

Additional data are available on reasonable request to the scientific committee of the registries. C.R., the corresponding author, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References

- 1 Curtis JR, Xie F, Chen L *et al*. The incidence of gastrointestinal perforations among rheumatoid arthritis patients. *Arthritis Rheum* 2011;63:346–51.
- 2 Myasoedova E, Matteson EL, Talley NJ, Crowson CS. Increased incidence and impact of upper and lower gastrointestinal events in patients with rheumatoid arthritis in Olmsted County, Minnesota: a longitudinal population-based study. *J Rheumatol* 2012;39: 1355–62.
- 3 Lanas A, Boers M, Nuevo J. Gastrointestinal events in at-risk patients starting non-steroidal anti-inflammatory drugs (NSAIDs) for rheumatic diseases: the EVIDENCE study of European routine practice. *Ann Rheum Dis* 2015;74:675–81.
- 4 Lanas A, Perez-Aisa MA, Feu F *et al*. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with

- nonsteroidal antiinflammatory drug use. *Am J Gastroenterol* 2005;100:1685–93.
- 5 Curtis JR, Lanas A, John A, Johnson DA, Schulman KL. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. *Arthritis Care Res* 2012;64:1819–28.
 - 6 Strangfeld A, Richter A, Siegmund B *et al.* Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. *Ann Rheum Dis* 2017;76:504–10.
 - 7 Xie F, Yun H, Bernatsky S, Curtis JR. Risk for gastrointestinal perforation among rheumatoid arthritis patients receiving tofacitinib, tocilizumab, or other biologics: gastrointestinal perforation in RA. *Arthritis Rheumatol* 2016;68:2612–7.
 - 8 Genovese M, Rubbert-Roth A, Smolen J. Longterm Safety and Efficacy of Tocilizumab in Patients with Rheumatoid Arthritis: A Cumulative Analysis of Up to 4.6 Years of Exposure. *Rheumatology* 2013;40:768–80.
 - 9 Barbulescu A, Delcoigne B, Askling J, Frisell T. Gastrointestinal perforations in patients with rheumatoid arthritis treated with biological disease-modifying anti-rheumatic drugs in Sweden: a nationwide cohort study. *RMD Open* 2020;6:e001201.
 - 10 Ross JT, Matthay MA, Harris HW. Secondary peritonitis: principles of diagnosis and intervention. *BMJ* 2018;361:k1407.
 - 11 Mariette X, Gottenberg J-E, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology* 2011;50:222–9.
 - 12 Salmon J-H, Perotin J-M, Morel J *et al.* Serious infusion-related reaction after rituximab, abatacept and tocilizumab in rheumatoid arthritis: prospective registry data. *Rheumatology* 2018;57:134–9.
 - 13 Gottenberg J-E, Morel J, Perrodeau E *et al.* Comparative effectiveness of rituximab, abatacept, and tocilizumab in adults with rheumatoid arthritis and inadequate response to TNF inhibitors: prospective cohort study. *BMJ* 2019;364:l67.
 - 14 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
 - 15 Dougados M, Simon P, Braun J *et al.* ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. *Ann Rheum Dis* 2011;70:249–51.
 - 16 Rosenbaum PR. Model-based direct adjustment. *J Am Stat Assoc* 1987;82:387–94.
 - 17 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;34:3661–79.
 - 18 Endo Y, Abe Y, Kawano S *et al.* The association between absence of abdominal pain and mortality in lower intestinal perforation in patients with autoimmune rheumatic diseases. *Biomed Res Int* 2019;2019:5381453–8.
 - 19 Rafferty J, Shellito P, Hyman NH, Buie WD, Standards Committee of American Society of Colon and Rectal Surgeons. Practice parameters for sigmoid diverticulitis. *Dis Colon Rectum* 2006;49:939–44.
 - 20 Andersen JC, Bundgaard L, Elbrønd H *et al.* Danish national guidelines for treatment of diverticular disease. *Dan Med J* 2012;59:C4453.
 - 21 Jeffery V, Goldson AJ, Dainty JR, Chieppa M, Sobolewski A. IL-6 signaling regulates small intestinal crypt homeostasis. *J Immunol Baltim Md* 1950 2017;199:304–11.
 - 22 Kuhn KA, Manieri NA, Liu T-C, Stappenbeck TS. IL-6 stimulates intestinal epithelial proliferation and repair after injury. *PLoS One* 2014;9:e114195.
 - 23 Dann SM, Spehlmann ME, Hammond DC *et al.* IL-6-dependent mucosal protection prevents establishment of a microbial niche for attaching/effacing lesion-forming enteric bacterial pathogens. *J Immunol* 2008;180:6816–26.
 - 24 Chang X-W, Qin Y, Jin Z *et al.* Interleukin-6 (IL-6) mediated the increased contraction of distal colon in streptozotocin-induced diabetes in rats via IL-6 receptor pathway. *Int J Clin Exp Pathol* 2015;8:4514–24.
 - 25 Zhang L, Hu L, Chen M, Yu B. Exogenous interleukin-6 facilitated the contraction of the colon in a depression rat model. *Dig Dis Sci* 2013;58:2187–96.
 - 26 Fleischmann R, Genovese MC, Lin Y *et al.* Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years' follow-up. *Rheumatology* 2020;59:292–302.
 - 27 Genovese MC, van der Heijde D, Lin Y *et al.* Long-term safety and efficacy of sarilumab plus methotrexate on disease activity, physical function and radiographic progression: 5 years of sarilumab plus methotrexate treatment. *RMD Open* 2019;5:e000887.