Published in final edited form as:

Arthritis Rheumatol. 2016 November ; 68(11): 2612–2617. doi:10.1002/art.39761.

Risk for Gastrointestinal Perforation among Rheumatoid Arthritis Patients receiving Tofacitinib, Tocilizumab, or other Biologics

Fenglong Xie, MS¹, Huifeng Yun, PhD^{1,2}, Sasha Bernatsky, MD PhD³, and Jeffrey R Curtis, MD MS MPH^{1,2}

¹Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham

²Department of Epidemiology, University of Alabama at Birmingham

³McGill University, Montreal CA

Abstract

Objective—To evaluate gastrointestinal perforation (GIP) in rheumatoid arthritis (RA) patients receiving tofacitinib, tocilizumab or other biologics.

Methods—Using health plan data from 2006–2014, RA patients without prior GIP were identified. Those initiating tofacitinib or biologics were followed for incident GIP within hospitalization. Crude incidence rates were calculated by exposure. Adjusted Cox proportional hazards models evaluated the association between GIP and exposures.

Results—A cohort of 167,109 RA patients was analyzed. Among them, 4,755 initiated tofacitinib, 11,705 tocilizumab, 115,044 anti-tumor necrosis factor (TNFi), 31,214 abatacept, and 4,391 rituximab. Versus TNFi recipients, abatacept recipients were older, tofacitinib and rituximab were younger, and tocilizumab recipients were similar. All non-TNFi patients were more likely to have previously received biologics than the TNFi patients. Incidence of GIP per 1,000 person-years was 1.29 (tofacitinib), 1.55 (tocilizumab), 1.10 (abatacept), 0.73 (rituximab), and 0.84 (TNFi). Most perforations occurred in the lower GI. Incidence of lower tract GIP was 1.29 (tofacitinib), 1.26 (tocilizumab), 0.76 (abatacept), 0.73 (rituximab), and 0.46 (TNFi). Lower tract GIP risk was significantly elevated for both tocilizumab and tofacitinib patients versus TNFi. Adjusted hazard ratios (HRs) were 2.55, 95%CI 1.33–4.88 for tocilizumab, and 3.24, 95%CI 1.05–10.04 for tofacitinib. Older age (HRs=1.16 per 5 years, 95%CI 1.10–1.22), diverticulitis/other gastrointestinal conditions (HR=3.25, 95%CI 1.62–6.51), and prednisone use>7.5mg/day (HR=2.24, 95%CI 1.36–3.70) were predictors of lower-tract GIP. Incidence of upper-tract GIP was similar among all drug exposures.

Conclusion—We estimated that the risk for lower-tract gastrointestinal perforation associated with tocilizumab and tofacitinib was more than double that for TNFi.

Keywords

rheumatoid arthritis; gastrointestinal perforation; tocilizumab; tofacitinib; TNFi

Introduction

Gastrointestinal perforation (GIP) is an uncommon but serious adverse event. It has been reported that patients with rheumatoid arthritis (RA) may be at particular risk^{1–5}. Historically, RA patients most often suffered upper gastrointestinal tract perforations which have been associated with non-steroidal anti-inflammatory drug (NSAID) use^{1,5}. More recently, lower GIPs have been associated with tocilizumab^{2,6}, an interleukin-6 receptor antagonist approved for RA in the U.S. in 2010. Based on the initial clinical trial data from the tocilizumab development program, 26 cases were observed in patients receiving tocilizumab therapy, and none occurred in the placebo comparator group⁶. In contrast to the earlier experience in RA with NSAIDs where most perforations occurred in the upper GI tract, most perforations associated with tocilizumab occurred in the lower GI tract^{2,6}. However, given the early escape feature of the trials that permitted non-responders to cross over to active therapy as early as 16 weeks, only a small amount of placebo exposure was available. Thus neither a stable background rate, nor a comparator rate for patients receiving alternative RA agents, was available.

Recently, Janus kinase (JAK) drugs including tofacitinib have been studied in RA. Given the pleiotropic nature of this molecule and others select inhibitors of JAK1, JAK2, JAK3, or tyrosine-protein kinase 2, with some downstream effect on IL-6 signaling, the potential for an increased risk for GIP exists. Given that these molecules have been licensed in the U.S. relatively recently, there is limited real-world evidence, and almost no comparative evidence, on the risk for GIP associated with tocilizumab or tofacitinib. Therefore, we used a real-world dataset to examine risks for GIP, with a particular focus on perforations of the lower GI tract.

Methods

Data Source & Cohort Eligibility

We used data from Medicare (2006–2013) and MarketScan (2010–2014) for this analysis. Medicare covers approximately 93% of patients over age 65 in the U.S., and younger patients with certain disabling conditions (including RA) can qualify. MarketScan is a longitudinal U.S. database of patient-level data for more than 143 million individuals and includes information regarding inpatient and outpatient encounters, labs, and pharmaceutical use. Data are contributed by large employers, hospitals, and other healthcare entities. Patients eligible for this analysis were required to be 18 years or older and to have 2 or more physician billing diagnoses for RA (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9–CM) 714.0, 714.2, 714.81). The validity of this approach has been previously shown to be high, with positive predictive value > 85% when combined with DMARD or biologic use⁷. Patients also had to have at least 6 months of medical and pharmacy coverage prior to follow-up which began at first use of tofacitinib or biologics for RA treatment. To increase certainty that all GIP were incident cases, patients were excluded if they had any prior diagnosis of GIP (inpatient or outpatient) using all available previous data (minimum of 6 months). Patients also were excluded if they had any diagnosis for inflammatory bowel disease, since that might have affected both choice of RA therapy and

risk of the outcome. For similar reasons, patients were excluded if they had any cancer diagnosis, other than non-melanoma skin cancer.

Exposure

Our main exposures were tofacitinib, tocilizumab and other biologics for RA treatment, including abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, and rituximab. Anti-tumor necrosis factor (TNFi) included adalimumab, certolizumab, etanercept, golimumab, and infliximab was used as reference group. Patients were considered currently exposed based upon the quantity dispensed of each filled prescription (for oral or injectable drugs) or the typical RA infusion intervals (56 days for infliximab, 30 days for tocilizumab and abatacept, and 183 days for rituximab) plus a 90 days extension. Patients must have had no prior use of each specific drug (using all available data).

Outcome

The primary outcome of interest was hospitalized GIP. We identified the outcomes based on specific hospital discharge diagnosis codes (Appendix Table). The validity of this definition in administrative data has been examined and has a positive prediction value of 94% (95% CI 86–98%)⁸. We also examined death as the terminus of the hospitalization for GIP, or within 90 days (only in Medicare; Marketscan does not capture out-of-hospital deaths). A sensitivity analysis examined an alternate GI outcome that included hospital discharge diagnosis codes for diverticulitis, diverticulosis or ischemic colitis (but where ‘perforation’ was not necessarily mentioned), also requiring a Current Procedural Terminology procedure codes (CPT) for surgery: suture, enterectomy, enterostomy or laparoscopy (Appendix table 1a and 1b).

Covariates

Potentially confounding or effect modifying covariates were selected based upon clinical interest and prior analyses include patients’ demographic (e.g. age, gender, race), co-morbidities and concurrent medications. Co-morbidities include diabetes, peptic ulcer disease, gastro-esophageal reflux disease, diverticulitis, and other gastrointestinal conditions. These conditions were assessed using ICD 9 diagnosis codes measured during baseline (Appendix table 2). These prior non-RA medication uses were identified using National Drug Codes (NDC) during the baseline period. Biologic use was assessed using NDC and Healthcare Common Procedure Coding System (HCPCS) codes using all available data prior to the index date.

Statistical analysis

Descriptive statistics were used to characterize drug exposure cohorts and standardized mean differences (SMDs) were used to estimate differences between exposure groups and the TNFi cohort for each characteristic SMDs >0.10 were considered imbalanced⁹. Follow-up began at the time of drug initiation of tofacitinib, tocilizumab or biologics and ended at the first occurrence of the outcome of interest, loss of medical and pharmacy coverage, death, end of data, or end of initiated drug exposure plus a 90 day extension. Patient was allowed to contribute at most one medication treatment episode for each biologic or tofacitinib.

Incidence rates of GIP were calculated for overall and by upper and lower tract. Exact Poisson distribution was used to calculate upper limit of 95% confidence interval if there were ≤ 5 events. After evaluating the proportional hazards assumption, we calculated the hazard ratio (HR) of the outcomes using Cox proportional hazards models. TNFi therapy was the referent category as it was the most commonly used biologic RA therapy and would provide stable effect estimates for comparisons. Standard errors were adjusted using robust sandwich estimate of Lin and Wei (1989) for the covariance matrix to reflect the clustering of treatment episodes within patients.

A sensitivity analysis examined an alternate outcome that included hospital discharge diagnosis codes for diverticulitis, diverticulosis or ischemic colitis and accompanied by a Current Procedural Terminology procedure codes (CPT) for surgery: suture, enterectomy, enteroenterostomy or laparoscopy (Appendix table 1a and 1b). All analyses were conducted using SAS 9.4. The university institutional review board approved the study protocol.

Results

We identified 190,061 RA patients who met our inclusion criteria based on ICD9 codes and associated drug use. Among them, 1,164 (0.6%) of patients were excluded from analyses because they had prior evidence of GIP. An additional 24,745 (13.0%) of patients were excluded due to history of inflammatory bowel disease, cancer diagnosis, other than non-melanoma skin cancer, age younger than 18 or use of other biologic DMARDs not indicated for the treatment for RA. Mean (standard deviation) age was 63.7 (12.6) for patients enrolled in Medicare and 52.2 (12.6) for patients in MarketScan. The characteristics of RA patients included in the analysis were shown in Table 1 according to the therapy they received. Compared to patients on TNFi, abatacept patients were somewhat older; tofacitinib and rituximab are somewhat younger, tocilizumab patients were similar to TNFi patients in age. The prevalence of concomitant GI comorbidities such as diverticulitis was low (approximately 2%) and similar between exposure cohorts. All non-TNFi patients were more likely to be previously treated with biologics when compared to TNFi patients. Abatacept, rituximab and tocilizumab patients were less likely to use NSAIDs than TNFi patients. Rituximab and tocilizumab patients were more likely treated with higher dose glucocorticoid compared to TNFi patients. All other characteristics were similar among tofacitinib, tocilizumab and other biologic patients.

The overall incidence rate of hospitalized GIP was highest among patients receiving tocilizumab, 1.55 (0.95, 2.54) per 1000 patient years, based on 16 cases (Table 2, left). Three events occurred on tofacitinib (1.29 per 1000 person years, 95% CI 0.42–3.99). Based on 109 hospitalized events for GIP, the overall incidence rate of hospitalized GIP among TNFi users was 0.84 (95% CI: 0.69, 1.01) per 1000 patient years. Most perforation cases occurred in the lower GI tract (62% overall). Among all perforation events, the proportion occurring in the lower GI tract was higher for tocilizumab users (81%) than among the TNFi users (54%, $p = 0.04$). In declining order of incidence, the rate of lower tract GIP was 1.29 (tofacitinib), 1.26 (tocilizumab), 0.76 (abatacept), 0.73 (rituximab), and 0.46 (TNFi) per 1000 person-years (Table 2, left-middle). The incidence of upper tract GIP was similar among tofacitinib and all biologics (Table 2, left-right). After multivariable adjustment for

age, sex, diabetes, peptic ulcer disease, gastro esophageal reflux disease, diverticulitis and other gastrointestinal conditions, number of biologics used, NSAIDs, oral glucocorticoids, anticoagulants, and proton pump inhibitors (Figure), there was a significantly increased risk for lower tract GIP amongst the tocilizumab users (HR=2.55, 95% CI 1.16–3.73) and tofacitinib users (HR=3.24, 95% CI 1.05–10.04). Older age (HR=1.16 per 5 years, 95% CI 1.10–1.22), diverticulitis and other gastrointestinal conditions (HR=3.25, 95% CI 1.62–6.51), and prednisone use >7.5mg/day (HR=2.24, 95% CI 1.36–3.70) were associated with lower tract GIP. The proportional hazards assumption was not violated in any analysis. Among the 75 patients in Medicare who experienced a lower GIP, 16 (21.3 %) died in hospital, and an additional 18 (24.0 %) died within 90 days after hospital discharge (Appendix Table 3). Among 33 patients in the MarketScan data who experienced a lower GIP, 1 (3.0%) died in hospital. Among all 108 GIP events, 17 people died in hospital, yielding an overall mortality of 16%.

Using the alternate outcome, 215 events occurred in the TNFi users, and 26 occurred in the tocilizumab users. In these analyses, the rate of events per 1000 person-years was 1.65 (95% CI 1.44, 1.89) among TNFi users, which was significantly lower than in tocilizumab users (2.53 events per 1000 person-years, 95% CI 1.72, 3.71) (Table 2, right).

Discussion

In this analysis of real-world US data, we found more than a two-fold increased risk of hospital-related lower tract GIP amongst tocilizumab RA users compared to those receiving TNFi. The risk for lower GIP was approximate three-fold for tofacitinib and also significantly elevated compared to TNFi, albeit based on only 3 events. Despite these differences in relative risk, the absolute rate differences between treatments were small, in the range of approximately 1 per 1000 patient years. Still, even if uncommon, GIP is a costly, and potentially life-threatening adverse event. In this sample, 16% of patients died in-hospital following the GIP event.

Our event rates, particularly those from the more sensitive definition of GIP (incidence rate of 2.53, 95% CI 1.72, 3.71) are comparable to that found in the tocilizumab trials and their uncontrolled long term extension studies where a perforation rate of 2.8 events per 1000 patient years was observed⁶. It is also consistent with the rate of 3.4 per 1000 patient years among tocilizumab users reported by Strangfeld et. al. from the German RABBIT registry¹⁰, based on 11 cases.

Similar to other US database studies of commercially insured RA patients receiving biologics, we noted glucocorticoids as an independent risk factor for GIP. In one study³ of RA patients on biologics (primarily TNFi) patients receiving systemic glucocorticoids had a higher rate of GIP (1.12 per 1000 patient years) than those not on systemic glucocorticoids (0.47 / 1000 patient years). In a separate study using a different database, findings were similar, and the overall GIP rate was 0.87 per 1000 patient years¹¹. These findings are consistent with the rate of GIPs observed in the certolizumab pegol trial program that found a rate of 0.7 per 1000 patient years, based on 6 cases¹². As we found, rates of perforation associated with tofacitinib, have been suggested to be higher than for TNFi therapy¹³. The

incidence of drug-associated upper GI tract complications is well recognized, at least with respect to NSAIDs, but lower GI tract complications are less well understood, although some evidence suggests drug-related toxicity may extend into the lower GI tract¹⁴. The mechanisms whereby DMARDs and biologics might lead to lower GI tract perforations may include impairments in host defenses.

The strengths of our study include use of two large health plan databases that allowed us to study this serious but rare safety event. Although cases could not be confirmed clinically, we did rely on a previously validated outcome definition with high positive predictive value (94%). We recognize the potential for residual confounding for factors that could not be measured in administrative claims data, such as RA severity and duration, over-the-counter NSAID use. However, given the known association of tocilizumab and tofacitinib with GIP, we think it likely that this would have conservatively biased our result as patients with the highest risk for GIP would have been less preferentially likely to be given tocilizumab and tofacitinib.

In conclusion, we found a more than two-fold risk of lower tract GIP among tocilizumab users and tofacitinib users compared to patients receiving TNFi. GIP is a costly, and potentially life-threatening adverse event, but the absolute rates of perforation were low, at 1–3 per 1000 patient years, and despite statistically significant differences, the rate differences between these RA treatments were relatively small, approximately 1 per 1000 patient years. This might suggest that the exposure risk is a concern primarily among a particular group of RA patients (including those with older age, co-morbidity like diabetes, and prednisone dose ≥ 7.5 mg per day). GIP risk is clearly only one consideration in evaluating the overall risk-benefit profile of choosing a specific therapy.

Acknowledgments

Disclosures: This project had no external funding. Dr. Curtis receives support from the Patient Centered Outcomes Research Institute (PCORI) and the National Institutes of Health (P60 AR064172).

- JRC: Research grants and/or consulting for unrelated work with Amgen, Abbvie, BMS, CORRONA, Crescendo, Janssen, Pfizer, Roche, UCB
- SB: Supported by the Drug Safety and Effectiveness Network, Canadian Institutes of Health Research
- Dr. Yun: research grants from Amgen

Appendix

Appendix table 1a

ICD-9 Codes used for Specific and Sensitive Case Definitions of Gastrointestinal Perforation

Position	ICD 9 CM diagnosis code	ICD 9 CM diagnosis code description	CPT code needed	Specific/sensitive definition
Upper GI	530.4x	Perforation of esophagus, rupture of esophagus	No	Yes/Yes
	531.10	Gastric ulcer, acute w/perforation, w/o mention of obstruction	No	Yes/Yes

Position	ICD 9 CM diagnosis code	ICD 9 CM diagnosis code description	CPT code needed	Specific/sensitive definition
	531.11	Gastric ulcer, acute w/ perforation, w/ obstruction	No	Yes/Yes
	531.20	Gastric ulcer, acute w/ hemorrhage and perforation, w/o mention of obstruction	No	Yes/Yes
	531.21	Gastric ulcer, acute w/ hemorrhage and perforation, w/ obstruction	No	Yes/Yes
	531.50	Gastric ulcer, chronic or unspecfd w/ perforation, w/o mention of obstruction	No	Yes/Yes
	531.51	Gastric ulcer, chronic or unspecfd w/ perforation, w/ obstruction	No	Yes/Yes
	531.60	Gastric ulcer, chronic or unspecfd w/ hemorrh & perf, w/o mention of obstruction	No	Yes/Yes
	531.61	Gastric ulcer, chronic or unspecfd w/ hemorrhage and perforation, w/ obstruction	No	Yes/Yes
	532.10	Duodenal ulcer, acute w/ perforation, w/o mention of obstruction	No	Yes/Yes
	532.11	Duodenal ulcer, acute w/ perforation, w/ obstruction	No	Yes/Yes
	532.20	Duodenal ulcer, acute w/ hemorrhage and perforation, w/o mention of obstruction	No	Yes/Yes
	532.21	Duodenal ulcer, acute w/ hemorrhage and perforation, w/ obstruction	No	Yes/Yes
	532.50	Duodenal ulcer, chronic or unspecfd w/ perforation, w/o mention of obstruction	No	Yes/Yes
	532.51	Duodenal ulcer, chronic or unspecfd w/ perforation, w/ obstruction	No	Yes/Yes
	532.60	Duodenal ulcer, chronic or unspecfd w/ hemorrh & perf, w/o mention of obstruction	No	Yes/Yes
	532.61	Duodenal ulcer, chronic or unspecfd w/ hemorrhage and perforation, w/ obstruction	No	Yes/Yes
	533.10	Peptic ulcer, acute w/ perforation, w/o mention of obstruction	No	Yes/Yes
	533.11	Peptic ulcer, acute w/ perforation, w/ obstruction	No	Yes/Yes
	533.20	Peptic ulcer, acute w/ hemorrhage and perforation, w/o mention of obstruction	No	Yes/Yes
	533.21	Peptic ulcer, acute w/ hemorrhage and perforation, w/ obstruction	No	Yes/Yes
	533.50	Peptic ulcer, chronic or unspecfd w/ perforation, w/o mention of obstruction	No	Yes/Yes
	533.51	Peptic ulcer, chronic or unspecfd w/ perforation, w/ obstruction	No	Yes/Yes

Position	ICD 9 CM diagnosis code	ICD 9 CM diagnosis code description	CPT code needed	Specific/sensitive definition
	533.60	Peptic ulcer, chronic or unspcfd w/ hemorrh & perf, w/o mention of obstruction	No	Yes/Yes
	533.61	Peptic ulcer, chronic or unspcfd w/ hemorrhage and perforation, w/ obstruction	No	Yes/Yes
Lower GI	534.10	Gastrojejunal ulcer, acute w/ perforation, w/o mention of obstruction	No	Yes/Yes
	534.11	Gastrojejunal ulcer, acute w/ perforation, w/ obstruction	No	Yes/Yes
	534.20	Gastrojejunal ulcer, acute w/ hemorrh & perf, w/o mention of obstruction	No	Yes/Yes
	534.21	Gastrojejunal ulcer, acute w/ hemorrhage and perforation, w/ obstruction	No	Yes/Yes
	534.50	Gastrojejunal ulcer, chronic or unspcfd w/ perf, w/o mention of obstruction	No	Yes/Yes
	534.51	Gastrojejunal ulcer, chronic or unspcfd w/ perforation, w/ obstruction	No	Yes/Yes
	534.60	Gastrojejunal ulcer, chronic or unspcfd w/ hemorrh & perf, w/o mention of obstruction	No	Yes/Yes
	534.61	Gastrojejunal ulcer, chronic or unspcfd w/ hemorrh & perf, w/ obstruction	No	Yes/Yes
	540.0x	Acute appendicitis, w/ perforation, peritonitis(generalized), rupture	No	No /Yes
	562.00	Diverticulosis of small intestine (w/o mention of hemorrhage)	Set 1	No /Yes
	562.02	Diverticulosis of small intestine (w hemorrhage)	Set 1	No /Yes
	562.01	Diverticulitis of small intestine (w/o mention of hemorrhage)	Set 1	No /Yes
	562.03	Diverticulitis of small intestine (w hemorrhage)	Set 1	No /Yes
	562.10	Diverticulosis of colon (w/o mention of hemorrhage)	Set 2	No /Yes
	562.12	Diverticulosis of colon (w hemorrhage)	Set 2	No /Yes
	562.11	Diverticulitis of colon (w/o mention of hemorrhage)	Set 2	No /Yes
	562.13	Diverticulitis of colon (w hemorrhage)	Set 2	No /Yes
	557.xx	Vascular insufficiency of intestine	Set 2	No/Yes
	568.93	Un-specified perforation of intestine	No	Yes/Yes

CPT: Current Procedure Terminology

Appendix table 1b**CPT Codes used for Sensitive Case Definitions of Gastrointestinal Perforation**

Set	CPT Code	CPT code description
1	44202	Laparoscopy, surgical; enterectomy, resection of small intestine, single resection and anastomosis
	44203	Laparoscopy, surgical; each additional small intestine resection and anastomosis
	44120	Enterectomy, resection of small intestine; single resection and anastomosis
	44121	Enterectomy, resection of small intestine; each additional resection and anastomosis
	44125	Enterectomy, resection of small intestine, with enterostomy
	44130	Enterectomy, resection of small intestine, with or without cutaneous enterostomy
	44602	Suture of the small intestine (enter orrhaphy) for perforation ulcer, diverticulum, wound, injury or rupture
	44603	Suture of the small intestine (enter orrhaphy) for perforation ulcer, diverticulum, wound, injury or rupture
2	44204	Laparoscopy, surgical; colectomy, partial, with anastomosis
	44205	Laparoscopy, surgical; colectomy, partial, with removal of terminal ileum with ileocolostomy
	44140	Colectomy, partial; with anastomosis
	44145	Colectomy, partial; with coloproctostomy (low pelvic anastomosis)
	44604	Suture of the large intestine (colorrhaphy) for perforated ulcer, diverticulum, wound, injury or rupture, with or
	44605	Without colostomy

Appendix table 2**ICD-9 and CPT Codes* used for Definitions for co-morbidities**

Co-morbidity	ICD-9 diagnosis code	CPT code
Diabetes	250.0–250.7 inpatient or outpatient physician visit	
Peptic ulcer disease	531–534.9x outpatient physician visit only	
Gastro esophageal reflux disease	530.81(inpatient or outpatient physician visit)	
Diverticulitis and other gastrointestinal conditions	540.0x from outpatient physician visit 562.00–562.03 from outpatient physician visit or inpatient discharge without corresponding CPT code in right column	44120, 44121, 44125, 44130, 44202, 44203, 44602, 44603, but without diagnosis from left column**
	562.10–562.13, 557.xx from outpatient physician visit or inpatient discharge without corresponding CPT code in right column	44140, 44145, 44204, 44205, 44604, 44605 but without diagnosis from left column**

CPT: Current Procedure Terminology

* see Appendix Table 1 for textual descriptions of diagnosis and procedure codes

* patients who had both one of these diagnosis listed plus the surgery were excluded from the cohort at baseline

Appendix Table 3

Mortality after lower gastrointestinal perforation, by data source

	Medicare			Market Scan	
	Total lower GIP cases, N	In-hospital death N (%)	Died after discharge, within 90 days N (%)	Total lower GIP case N	In-hospital death N (%)
Any TNFi	44	10 (22.7)	9 (20.5)	15	0 (0.0)
Selected TNFi					
Adalimumab	9	0 (0)	3 (33.3)	8	0 (0.0)
Etanercept	15	6 (40)	3 (20.0)	3	0 (0.0)
Infliximab	17	3 (17.7)	2 (11.8)	3	0 (0.0)
Golimumab or Certolizumab	3	1 (33.3)	1 (33.3)	1	0 (0.0)
Abatacept	25	5 (20)	8 (32.0)	5	0 (0.0)
Rituximab	0	0 (NA)	0 (NA)	3	1 (33.3)
Tocilizumab	6	1 (16.7)	1 (16.7)	7	0 (0.0)
Tofacitinib	0	NA	NA	3	0 (0.0)
Total	75	16 (21.3)	18 (24.0)	33	1 (3.0)

TNFi=Tumor necrosis factor inhibitor; GIP= Gastrointestinal perforation

¹ Enrollment ended within 90 days after hospital discharge (no out-of hospital death date was available in Marketscan).

References

1. Lanas A, Carrera-Lasfuentes P, Arguedas Y, et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. May; 2015 13(5):906–912 e902. [PubMed: 25460554]
2. Gout T, Ostor AJ, Nisar MK. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. *Clinical rheumatology*. Nov; 2011 30(11):1471–1474. [PubMed: 21833686]
3. Curtis JR, Xie F, Chen L, et al. The incidence of gastrointestinal perforations among rheumatoid arthritis patients. *Arthritis and rheumatism*. Feb; 2011 63(2):346–351. [PubMed: 20967860]
4. Laine L, Connors LG, Reicin A, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. *Gastroenterology*. Feb; 2003 124(2):288–292. [PubMed: 12557133]
5. Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut*. Dec; 2006 55(12):1731–1738. [PubMed: 16687434]
6. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. *Arthritis research & therapy*. 2011; 13(5):R141. [PubMed: 21884601]
7. Kim SY, Servi A, Polinski JM, et al. Validation of rheumatoid arthritis diagnoses in health care utilization data. *Arthritis Res Ther*. 2011; 13(1):R32. [PubMed: 21345216]
8. Curtis JR, Chen SY, Werther W, John A, Johnson DA. Validation of ICD-9-CM codes to identify gastrointestinal perforation events in administrative claims data among hospitalized rheumatoid arthritis patients. *Pharmacoepidemiology and drug safety*. Nov; 2011 20(11):1150–1158. [PubMed: 22020901]

9. Yang DS, Dalton JE. A unified approach to measuring the effect size between two groups using SAS®. SAS Global Forum 2012. 2012 paper. 335–2012.
10. Strangfeld A, Richter A, Herzer P, Rockwitz K, Demary W, Aringer M, Zink A, Listing J. Risk for Lower Intestinal Perforations in RA Patients Treated with Tocilizumab in Comparison to Treatment with TNF Inhibitors, Rituximab, Abatacept or Conventional Synthetic Dmards. American College of Rheumatology Meeting Abstract #2051. 2015
11. 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. The Journal of rheumatology. Jul; 2012 39(7): 1355–1362. [PubMed: 22467929]
12. Fleischmann R, Rubbert-Roth A, Combe B, VanLunen B, Andrews4 P, De Longueville M. Gastrointestinal perforation with certolizumab pegol. Ann Rheum Dis 2012. 2012; 71(Suppl3)
13. Lee EB, Curtis JR, Riese R, Connell CA, Chew R, Boy MG, Maller E, Su C, Wang L. Tofacitinib, An Oral Janus Kinase Inhibitor: Analysis Of Gastrointestinal Adverse Events Across The Rheumatoid Arthritis Clinical Program. ACR abstract #34071. 2013; 1
14. Chan FK, Cryer B, Goldstein JL, et al. A novel composite endpoint to evaluate the gastrointestinal (GI) effects of nonsteroidal antiinflammatory drugs through the entire GI tract. The Journal of rheumatology. Jan; 2010 37(1):167–174. [PubMed: 19884267]

Figure. Incidence rates and adjusted hazard Ratio of lower gastrointestinal Perforation associated with RA therapies

Footnote for figure: IR=incidence rate; HR=Hazard ratio; CI=confidence interval.

Table 1

Characteristics of RA patients initiating TNFi therapy, Abatacept, Rituximab, Tocilizumab, and Tofacitinib

	Any TNFi n=115,044 (n=45,950/69,097) [/]	Selected TNFi			ABA n=31,214 (n=9,042/22,712) [/]	RIT n=4,391 (n=3,930/461) [/]	TOC n=11,705 (N=5,017/6,688) [/]	TOF n=4,755 (n=3,148/1,607) [/]
		ADA n=34,787 (N=16,205/18,582) [/]	ETA n=35,076 (N=16,221/18,855) [/]	INF n=28,722 (N=5,755/22,967)				
Age, mean ± SD	58.7 ± 13.9	57.0 ± 13.7	57.2 ± 13.8	63.7 ± 12.9	62.2 ± 13.5 [*]	55.2 ± 12.8 [*]	59.5 ± 13.5	56.6 ± 12.4 [*]
Female, %	80.2	80.1	80.1	80.8	82.6	82.3	83.5	83.2
Co-morbid conditions ² , %								
Diabetes	17.5	16.6	16.9	19.4	19.0	15.3	17.3	14.7
Peptic Ulcer Disease	1.1	1.0	1.1	1.2	1.2	0.7	0.9	0.8
Gastro esophageal reflux disease	12.5	12.2	12.2	14.2	14.5	11.6	13.4	11.6
Diverticulitis and other gastrointestinal conditions	2.1	2.0	1.9	2.4	2.5	2.3	2.1	1.7
Medications %								
Number of biologics used								
None	61.8	58.7	66.4	58.7	42.0 [*]	37.5 [*]	23.5 [*]	23.4 [*]
1	29.0	33.3	26.2	30.8	40.5 [*]	33.8	40.9 [*]	33.1
2	9.2	8.1	7.5	10.5	17.5 [*]	28.7 [*]	35.6 [*]	43.5 [*]

	Any TNFi n=115,044 (n=45,950/69,097) [/]	Selected TNFi			ABA n=31,214 (9,042/22,712) [/]	RIT n=4,391 (3,930/461) [/]	TOC n=11,705 (5,017/6,688) [/]	TOF n=4,755 (3,148/1,607) [/]
		ADA n=34,787 (16,205/18,582) [/]	ETA n=35,076 (16,221/18,855) [/]	INF n=28,722 (5,755/22,967)				ADA n=34,787 (16,205/18,582)

Medications³

NSAIDs	41.3	42.2	41.9	38.3	37.2 [*]	35.2 [*]	37.2 [*]	39.7
Oral glucocorticoids	38.7	39.1	38.0	37.2	36.8	35.3	35.0	36.0
None								

	Any TNFi n=115,044 (n=45,950/69,097) ¹	Selected TNFi	ADA n=34,787 (16,205/18,582) ¹	ETA n=35,076 (16,221/18,855) ¹	INF n=28,722 (5,755/22,967) ¹	ABA n=31,214 (9,042/22,172) ¹	RIT n=4,391 (3,930/461) ¹	TOC n=11,705 (5,017/6,688) ¹	TOF n=4,755 (3,148/1,607) ¹
0 < < 7.5 mg/day	44.7	44.9	44.9	45.2	44.5	45.2	43.2	44.2	43.9
7.5 mg/day	16.6	16.0	16.0	16.8	18.4	18.0	21.5*	20.8*	20.1
Anticoagulants	4.9	4.4	4.4	4.6	6.4	6.6	5.7	6.0	4.5
Proton pump inhibitors	34.3	33.6	33.6	33.7	35.9	36.9	34.6	36.7	33.3
Any Hospitalization, %	33.7	36.8	36.8	37.6	24.8	30.3	68.9	36.7	46.3
Physician visits, mean ± SD	9.2 ± 6.8	8.6 ± 6.5	8.6 ± 6.5	9.0 ± 6.8	9.9 ± 6.7	10.3 ± 7.4*	9.5 ± 7.7	9.9 ± 6.9*	8.5 ± 6.2

All data shown as % except as listed

NSAIDs=non-steroidal anti-inflammatory drugs; TNFi=Tumor necrosis factor inhibitor Included adalimumab, certolizumab, etanercept, golimumab and infliximab. ABA=abatacept; ADA=adalimumab; ETA=etanercept; INF=infliximab; RIT=rituximab; TOC=tocilizumab; TOF=tofacitinib.

¹Numbers in parentheses refer to the number of patients contributing to the analysis from MarketScan/Medicare.

²Co-morbidities were assessed using baseline data.

³All medication use but biologics were assessed using baseline data, biologic use was assessed using all available data.

* SMD > 0.10 compared to TNFi use

Table 2

Incidence rate of hospitalized gastrointestinal perforation, by RA therapy

Current Biologics	Specific definition for GIP						Alternate (more sensitive) definition of GIP			
	Person-years	Cases	All GIP IR (95%CI)	Cases	Lower GIP IR (95%CI)	Cases	Upper GIP IR (95%CI)	Person-years	Cases	IR (95%CI)
Any TNFi	13,0323.8	109	0.84(0.69, 1.01)	59	0.46 (0.35, 0.58)	50	0.38(0.29, 0.51)	130,250.7	215	1.65 (1.44, 1.89)
Selected TNFi										
ADALIMUMAB	35,139.5	34	0.97 (0.69, 1.35)	17	0.48 (0.30, 0.78)	17	0.48 (0.30, 0.78)	35,124.5	58	1.65 (1.28, 2.14)
ETANERCEPT	37,928.9	28	0.74 (0.51, 1.07)	18	0.47 (0.30, 0.75)	10	0.26 (0.14, 0.49)	37,909.1	54	1.42 (1.09, 1.86)
INFLIXIMAB	43,379.3	38	0.88 (0.64, 1.20)	20	0.46 (0.30, 0.71)	18	0.41 (0.26, 0.66)	43,345.9	87	2.01 (1.63, 2.48)
ABATACEPT	39,227.2	43	1.10(0.81, 1.48)	30	0.76 (0.53, 1.09)	13	0.33(0.19, 0.57)	39,203.3	71	1.81 (1.44, 2.29)
RITUXIMAB	4,133.8	3	0.73 (0.17, 2.29) [/]	3	0.73 (0.17, 2.29) [/]	0	0.00 (0.00, 0.89) [/]	4,131.2	8	1.94 (0.97, 3.87)
TOCILIZUMAB	10,292.7	16	1.55 (0.95, 2.54)	13	1.26 (0.73, 2.18)	3	0.29 (0.07, 1.24) [/]	10,288.9	26	2.53 (1.72, 3.71)
TOFACITINIB	23,28.8	3	1.29 (0.27, 4.06) [/]	3	1.29 (0.27, 4.06) [/]	0	0.00 (0.00, 1.58) [/]	2,328.8	3	1.29 (0.27, 4.069) [/]

GIP= Gastrointestinal perforation

IR=Incidence rate, cases/ 1000 person-years

CI=Confidence interval

TNFi=Tumor necrosis factor inhibitor Included adalimumab, certolizumab, etanercept, golimumab and infliximab.

[/] Confidence intervals were calculated based on exact Poisson distribution for event 5.