Drug Saf (2013) 36:329–334
DOI 10.1007/s40264-013-0041-y

SHORT COMMUNICATION

Ischaemic Colitis in Rheumatoid Arthritis Patients Receiving Tumour Necrosis Factor-α Inhibitors: An Analysis of Reports to the US FDA Adverse Event Reporting System

Allison Salk · Derrick J. Stobaugh · Parakkal Deepak · Eli D. Ehrenpreis

Published online: 12 April 2013

Abstract
Background Tumour necrosis factor-α (TNF-α) inhibitors are immunosuppressants, approved for the treatment and maintenance of rheumatoid arthritis (RA). Immunosuppression has been shown to induce ischaemic colitis (IC) in an animal model; however, a relationship between TNF inhibitors and IC has rarely been reported in the published literature.
Objective The aim of this study was to better characterize the association between TNF-α inhibitors with IC in RA patients, by analysing adverse event reports submitted to the US FDA Adverse Event Reporting System (AERS) and the published literature.
Methods The FDA AERS database was searched and we identified all reports between January 2003 and June 2011. The search was limited to an indication of RA, a 'primary suspect' drug of TNF-α inhibitors and a reaction of IC. Full-length reports were obtained and analysed utilizing the Freedom of Information Act. The cases were organized by age, sex, type of TNF-α inhibitor, concomitant drugs and medical co-morbidities. Cases were labelled as definite, probable, possible or doubtful drug-induced adverse events based on the Naranjo Scale. A PubMed search was performed to obtain published literature documenting events of anti-TNF-associated IC.
Results Twelve cases were eliminated because of more likely causes for IC. Thirty-five primary suspect reports of TNF-α inhibitors associated with IC in RA patients were identified in the FDA AERS. Thirteen cases were reported with infliximab, 12 with adalimumab, 7 with etanercept and 3 with certolizumab. The majority of the cases were in females (29/35) and those between the ages of 50 and 65 years (18/35). Use of the Naranjo Scale revealed 17 probable and 18 possible cases of anti-TNF-induced IC. In the literature, one report of IC associated with adalimumab was identified.
Conclusion TNF-α inhibitors may be initiating factors or co-factors in the development of IC in RA patients, and further research to determine the mechanism of this association is warranted.

1 Background

Tumour necrosis factors (TNFs) are primary cytokines related to immune function, cell differentiation, proliferation, energy metabolism and apoptosis [1]. TNF-α is the principal cytokine in the initiation of the inflammatory response, playing a critical role in our immune systems. However, excess production of TNF-α may lead to chronic inflammation and tissue damage, as seen in many rheumatic and inflammatory disorders [2]. In rheumatoid arthritis (RA), TNF-α plays an important role in both inflammation and joint destruction [3].

TNF-α inhibitors have been designed to bind to TNF-α and reduce the immune system response leading to symptoms in diseases such as RA [4, 5]. First licensed for clinical use in 1998, there are now five anti-TNF

A. Salk · D. J. Stobaugh · P. Deepak · E. D. Ehrenpreis (✉)
Center for the Study of Complex Diseases, Research Institute, North Shore University Health System, 1001 University Place, Evanston, IL 60201, USA
e-mail: ehrenpreis@gipharm.net

A. Salk
University of Michigan, Ann Arbor, MI, USA

D. J. Stobaugh · P. Deepak · E. D. Ehrenpreis
Gastroenterology Department, North Shore University Health System, Highland Park, IL, USA

medications approved for the treatment of RA: infliximab, adalimumab, etanercept, certolizumab pegol and golimumab, with RA being the disease indication where all five are approved for use [6].

Ischaemic colitis (IC) is the most common form of intestinal ischaemia resulting from a decrease in blood flow to the colon, resulting in inflammation [7]. The condition is characterized by abdominal pain, bloody stools and diarrhoea, and may present with varying severity. A variety of medications and medical conditions can lead to IC [8]. Almost 50 drugs and drug classes are known to cause IC, including NSAIDs [9], alosetron [10], oral contraceptives [11], triptans [12] and pseudoephedrine [13]. The various mechanisms of drug-induced IC include local vasospastic effect, systemic hypotension, vasculitis, thrombotic lesion induction, increased intracolonic pressure and other undetermined mechanisms. Immunosuppressive agents have also been shown to induce IC in an animal model [14]. Additionally, TNF-α has also been identified as a mediator of inflammation in post-ischaemic injury in human colonic cells [15]. An increase in circulating, soluble TNF (sTNF) levels have been reported after the use of etanercept and infliximab [16]. However, an association between TNF-α inhibitors and IC has not been evaluated using a pharmacovigilance database.

We sought to explore and better characterize this association in RA patients by analysing adverse event reports submitted to the US FDA Adverse Event Reporting System (AERS), as well as published literature.

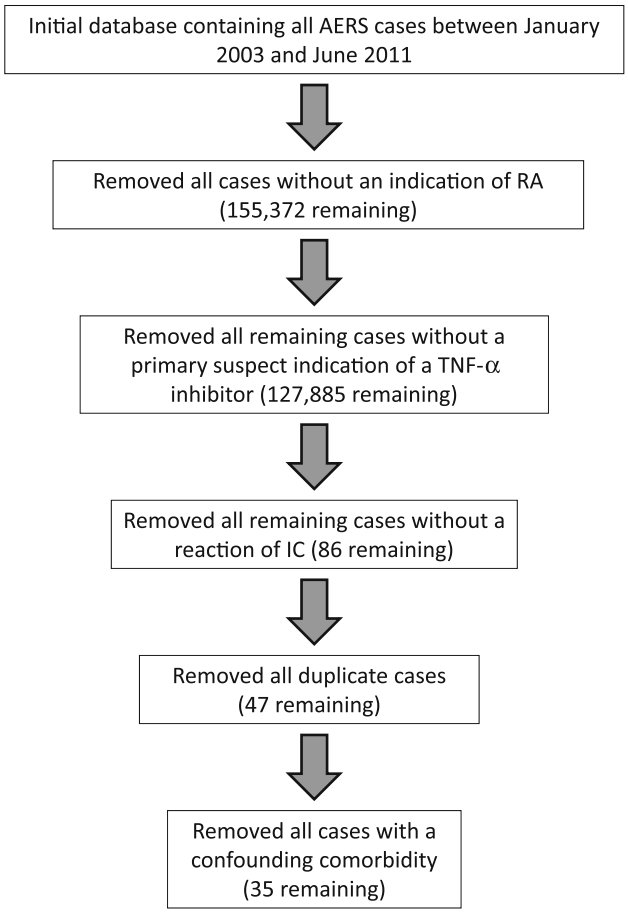

Fig. 1 Depiction of the selection of cases included in the analysis. *AERS* Adverse Event Reporting System, *IC* ischaemic colitis, *RA* rheumatoid arthritis, *TNF*-α tumour necrosis factor-α

2 Methods

AERS is a publicly available database based on voluntary reporting for post-marketing surveillance of all FDA-approved drugs. There were a total of 2,562,390 reports of adverse events between January 2003 and June 2011, which were downloaded from the FDA AERS and analysed using SPSS 20 (IBM Co. Armonk, NY, USA). We queried reports with an indication of 'rheumatoid arthritis' for all five approved TNF-α inhibitors (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab), using both trade and generic names. As only 'colitis ischaemic' and 'ischaemic colitis' are indicative of IC in the Medical Dictionary for Regulatory Activities (MedDRA®), they were the only search terms used for the reaction column. Index cases were further limited to those listed as 'primary suspect' drug role for one of the TNF-α inhibitors. The process of selecting cases can be seen in Fig. 1. Furthermore, we also gathered a control drug as well as control reactions for a basis of comparison. We selected sulfasalazine (both trade and generic names) as primary suspect control drugs, and a variety of mental disorders as control reactions: alcohol abuse, appetite disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, delusional disorder (erotomanic type), delusional disorder (unspecified type), delusion of grandeur, fear of disease, hallucination (auditory), intentional drug misuse, logorrhoea, major depression, persecutory delusion, self-injurious behaviour, self-medication, stress symptoms, suicidal behaviour. A Fisher's exact test, in a two-by-two contingency table, was used to compare the two drugs using SPSS 20.

The Freedom of Information Act was used to obtain paper charts of all relevant case reports. These were reviewed and analysed to establish authenticity, and duplicate cases were identified and eliminated to avoid repetition. All cases with active medical disease, which are more likely causes for IC as such, were eliminated from analysis (namely those with sepsis, a serious cardiovascular condition, coagulation disorder or chronic IC). A case was defined as any AERS report with a unique individual safety report (ISR) number and a unique case number, with an indication of RA, on a primary suspect TNF-α inhibitor, with a reaction of IC and without an aforementioned active

medical disease. Using the Naranjo Scale, all relevant cases were defined as definite, probable, possible or doubtful for causing the drug-induced adverse event [17]. The cases were organized by age, sex, type of TNF-α inhibitor, concomitant drugs and significant medical co-morbidities.

A review of the literature was additionally performed to analyse published literature regarding TNF-α inhibitor-associated IC. A PubMed search was performed using the Medical Subject Heading terms: 'anti-TNF' or 'tumor necrosis factor inhibitor' or 'TNF-alpha' or 'ischemic colitis' separated by the Boolean operator 'AND' between any one of the first three terms and the last term.

3 Results

3.1 US FDA Adverse Event Reporting System Case Review

A total of 47 primary suspect cases with TNF-α inhibitors were initially identified in RA patients. In 12 cases, the presence of other active diseases that were more likely risk factors for IC led to elimination from the analysis: six patients had sepsis, two had vasculitis, one had an acute myocardial infarction, one had an intra-atrial thrombus, one had a known procoagulant disorder (anti-phospholipid antibody syndrome) and one had chronic IC. After the elimination of these patients, a Fisher's exact test was performed. TNF-α inhibitors significantly increased the risk of developing IC compared with sulfasalazine (odds ratio 20.12; 95 % CI 1.16–348.59; $p = 0.0016$).

Among the 35 primary suspect reports without other likely causes, the majority of cases were in those over the age of 60 years (Table 1), with a median age of 62 years (range 36–83). The median time to develop IC was 344 days (range 22–3629 days). Sixteen patients did not have any reported significant co-morbidities or concomitant medications that could increase the risk of IC. The number of cases in females outnumbered those in males by a ratio of almost 5 to 1. Five cases were rechallenged, although none produced a positive result. Adalimumab, etanercept, infliximab and certolizumab pegol were identified as primary suspect TNF-α inhibitors for the event of drug-induced IC. The median age was highest with infliximab, and there were more deaths reported in cases associated with infliximab. Seventeen patients discontinued use of the TNF-α inhibitor they were receiving, while 13 continued use and 5 were unknown. Overall, there were two deaths directly related to IC while the other three were from all-cause mortality.

After applying the Naranjo scale [17], 18 out of the 35 cases were defined as possible cases of anti-TNF-induced IC. Seven cases were reported with infliximab, seven with adalimumab, two with etanercept and two with certolizumab. The majority of cases were in females (83.3 %) and those between the ages of 50 and 70 years (55.6 %). Evidence of a colonoscopy, biopsy or other documented medical confirmation for IC was present in ten cases. Significant co-morbidities were present in four cases: one patient had coronary artery disease and three had diabetes mellitus. In 15 cases, concomitant medications were reported that may increase the risks for IC: nine patients were receiving NSAIDs, two were receiving ACE inhibitors, two each were receiving estrogen, lisinopril, amlodipine and β-blockers, and one each were receiving benidipine, olmesartan and simvastatin. Three patients did not have any significant co-morbidities or concomitant medications that could increase the risk of IC. On follow-up reports, ten patients recovered, five expired, the episode is ongoing in one patient, while information is unavailable for two of the cases.

Seventeen of the cases were defined as probable IC associated with anti-TNF exposure. Six of these were with infliximab, five with adalimumab, five with etanercept and one with certolizumab. The majority of the cases were in females (82.4 %) and those between the ages of 50 and 70 years (70.6 %). Evidence of a colonoscopy, biopsy or other documented medical confirmation for IC was present in ten cases. One patient had diabetes mellitus and in three cases concomitant medications were reported that may increase the risk of IC: one patient each was receiving estrogen, NSAIDs and an ACE inhibitor. Thirteen patients did not have any significant co-morbidities or concomitant medications that could increase the risk of IC. Follow-up information was unavailable for one report while the remaining 16 patients recovered.

3.2 PubMed Literature Review

In the literature review, one report of IC associated with adalimumab was identified. [18] This report documents a 60-year-old male with no concomitant medications or risk factors. An exploratory laparotomy revealed his IC, a right colectomy was performed and the patient recovered shortly after hospitalization.

4 Discussion

In our analysis of the FDA AERS, we identified 35 cases of IC associated with an exposure to TNF-α inhibitors. There were no cases reported with golimumab and only three with certolizumab, which likely reflects the later approval of these two agents and that these might have been prescribed fewer times than infliximab, etanercept and adalimumab. [19] Of those with a probable cause of drug-

Table 1 Case characteristics by type of tumour necrosis factor-α inhibitor reported for both probable and possible cases as defined by the Naranjo scale [17]

Drug name	Infliximab ($n = 13$)	Adalimumab ($n = 12$)	Etanercept ($n = 7$)	Certolizumab pegol ($n = 3$)	Total ($n = 35$)
Male : Female ratio	2 : 11	3 : 9	1 : 6	0 : 3	6 : 29
Median age [years (range)]	68 (55–83)	58.5 (36–79)	64 (58–80)	51 (51–55)	62 (36–83)
No. of cases with no known significant co-morbidities or concomitant medication	7	4	4	1	16
No. of cases with concomitant medications	3 with NSAID; 1 with NSAID, ACE inhibitor and lisinopril; 1 with NSAID and estrogen; 1 with β-blocker; 7 with none	1 with amlodipine; 1 with ACE inhibitor and lisinopril; 1 with estrogen, NSAID and olmesartan; 1 with NSAID; 1 with estrogen; 1 with NSAID and simvastatin; 1 with ACE inhibitor; 1 with benidipine; 4 with none	1 with amlodipine; 1 with β-blocker; 5 with none	2 with NSAID; 1 with none	2 with amlodipine; 1 with ACE inhibitor and lisinopril; 1 with estrogen, NSAID and olmesartan; 6 with NSAID; 1 with estrogen; 1 with NSAID and simvastatin; 1 with NSAID and estrogen; 1 with NSAID, ACE inhibitor and lisinopril; 1 with ACE inhibitor; 1 with benidipine 2 with β-blocker; 17 with none
Cases with significant co-morbidities	None	None	2 diabetes mellitus 1 heart disease	2 diabetes mellitus	4 diabetes mellitus 1 heart disease
Confirmation of ischaemic colitis	3 biopsy; 3 colonoscopy; 2 biopsy and colonoscopy;	1 biopsy; 7 colonoscopy	1 biopsy; 2 computerized tomography	1 sigmoidoscopy	5 biopsy; 10 colonoscopy; 2 biopsy and colonoscopy; 2 computerized tomography; 1 sigmoidoscopy
Outcome	9 recovered 3 death 1 unknown	10 recovered 1 unknown 1 death	6 recovered 1 death	2 recovered 1 unknown	27 recovered 5 died 3 unknown

induced IC per the Naranjo scale [17], most recovered shortly after hospitalization. This is consistent with published literature because most patients with drug-induced IC recovered shortly after the diagnosis, similar to our findings [9]. Although RA has been associated with vasculitis [20] and congestive heart failure [21], both known causes of IC, none of the 35 patients were reported to have either of these conditions.

Older individuals have a higher risk of developing IC, with over 90 % of the IC cases diagnosed in those over the age of 60 years [22]. In our study, five patients were younger than 50 years and nine were between the ages of 51 and 60 years (40 % were aged 60 years and under). This age distribution suggests that TNF-α inhibitor-induced IC targets a younger population than seen with typical IC.

Although RA is 2.5-fold more likely to develop in women than in men [23], in our study women were almost five times more likely to develop TNF-α inhibitor-induced IC than men. This sex difference may be accounted for due to estrogen being a risk factor for IC and IC being more common in the female population. Also, it has been reported that women are 1.5- to 1.7-fold more likely than men to experience adverse drug reactions, which may influence the high prevalence of females as well [24]. Lastly, this difference may be merely a chance finding.

Immunosuppression has been shown to cause IC in an animal model. Possible mechanisms include a deleterious effect exerted on the gastrointestinal system, increased vulnerability of the gastrointestinal connective tissue and decreased intestinal resistance to bacterial invasion [14]. It is foreseeable, that one or more of these factors could cause TNF-α inhibitors to induce IC since TNF-α inhibitors suppress immune function. Additional mechanisms could include a paradoxical increase in circulating sTNF levels during treatment with TNF-α inhibitors [16]. TNF-α has been shown to play a central role in the inflammatory cascade of post-ischaemic injury in human colonic cells [15]. Similar paradoxical adverse events of new-onset inflammatory bowel disease during the treatment of rheumatologic diseases with TNF-α inhibitors have been reported [25].

The Bradford Hill criteria provides valuable insight into the context of the results and the study [26]. The strength of our association is based on a significant p-value from the Fisher's exact test performed, and although the confidence intervals are wide, they are still significant with a large odds ratio. Our study analyses the FDA database, which, although a national database, does include some international cases (from Canada, Latin America, Europe and Asia), giving a wide variety of patients to bolster the consistency of the data used. The choice of using IC alone focuses on the point of specificity along with the suggestions that have been given for the mechanism of action. Temporally, we only took cases in which the occurrence of the adverse event occurred after the drug was taken. In part, this led us to excluding a case of a patient with chronic IC. The aforementioned mechanisms for IC with TNF-α inhibitors lends credence to the plausibility of these findings, and they lend credence to the coherence this finding has with what is currently known in the field of medicine. Finally, we suggest that our findings are analogous to the previous finding, which has shown an increased development of IC with immunomodulators [14].

There are limitations to research conducted with the AERS database. Reports are spontaneously submitted to the FDA from consumers, healthcare professionals and lawyers. Reporting biases may also occur in databases such as the AERS, including under- and over-reporting of drug events. Furthermore, unrecorded co-morbidities and medications may exist, particularly with unrecorded over-the-counter NSAIDs. Thus, this analysis should not be interpreted as a comparison of medications and their relative risks. This study does not prove causality, but rather suggests a correlation. These 35 case reports complement animal studies and the minor amount of literature available.

5 Conclusions

We are presenting 18 possible and 17 probable cases of IC associated with TNF-α inhibitor administration in RA patients. TNF-α inhibitors may be initiating factors or co-factors in the development of IC in RA patients. As a voluntary reporting system, AERS cannot assess the true incidence of IC due to TNF-α inhibitors nor establish causation.

Acknowledgements The authors wish to acknowledge and thank the Keyser Family Research Fund and the Center for the Study of Complex Diseases for their benevolent support. We also acknowledge Harold Stepper, for his timely response in sending case reports from the US FDA.

Funding No sources of funding were used to conduct this study or prepare this manuscript.

Conflicts of interest The authors declare no conflicts of interest and their work was independent of financial support. The views expressed are those of the authors and do not necessarily represent the views of the FDA.

References

1. Cawthorn W, Sethi J. TNF-α and adipocyte biology. FEBS Lett. 2008;582(1):117–31.
2. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol. 1996;14:397–440.
3. Matsuno H, Yudoh K, Katayama R, et al. The role of TNF-alpha in the pathogenesis of inflammation and joint destruction in

rheumatoid arthritis (RA): a study using a human RA/SCID mouse chimera. Rheumatology (Oxford). 2002;41(3):329–37.
4. Elliott MJ, Maini RN, Feldmann M, et al. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. Arthritis Rheum. 1993;36(12):1681–90.
5. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet. 1994;344(8930):1105–10.
6. Segal B, Rhodus N, Patel K. Tumor necrosis factor (TNF) inhibitor therapy for rheumatoid arthritis. Oral Surg Oral Med Oral Pathol. 2008;106(6):276–84.
7. Brandt L, Boley S. AGA technical review on intestinal ischemia. Gastroenterology. 2000;118(5):954–68.
8. Lewis JH. The risk of ischaemic colitis in irritable bowel syndrome patients treated with serotonergic therapies. Drug Saf. 2011;34(7):545–65.
9. Sherid M, Ehrenpreis E. Types of colitis based on histology. Dis Mon. 2011;57(9):457–89.
10. Chang L, Tong K, Ameen V. Ischemic colitis and complications of constipation association with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. Am J Gastroenterol. 2010;105(3):866–75.
11. Rasmussen D, Segars L. Case of ischemic colitis in a young adolescent associated with triphasic hormonal contraceptive therapy: a case report and review of the literature. W VA Med J. 2011;107(5):22–5.
12. Westgeest H, Akol H, Schreuder T. Pure naratriptan-induced ischemic colitis: a case report. Turk J Gastroenterol. 2010; 21(1):42–4.
13. Dowd J, Bailey D, Moussa K, et al. Ischemic colitis associated with pseudoephedrine: four cases. Am J Gastroenterol. 1999;94(9):2430–4.
14. Gomella L, Gehrken G, Hagihara P, et al. Ischemic colitis and immunosuppression: an experimental model. Dis Colon Rectum. 1986;29(2):99–101.
15. Jarry A, Bach-Ngohou K, Masson D, et al. Human colonic myocytes are involved in postischemic inflammation through ADAM17-dependent TNFalpha production. Br J Pharmacol. 2006;147(1):64–72.
16. Kast RE, Altschuler EL. Both etanercept and infliximab can elevate tumor necrosis factor (TNF)-alpha and be the cause of treatment related new onset disease: the need to measure circulating TNF-alpha [letter]. J Rheumatol. 2008;35(8):1679 (author reply 1679–80).
17. Naranjo C, Busto U, Sellers E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(20):239–45.
18. Gopalswamy S, Dindyal S, Arumugam P. A rare cause of ischemic colitis and review of literature. Internet J Gastroenterol. 2010;9(1):10.
19. Simsek I. TNF inhibitors: new and old agents for rheumatoid arthritis. Bull NYU Hosp Jt Dis. 2010;68(3):204–10.
20. Genta M, Genta R, Gabay C. Systemic rheumatoid vasculitis: a review. Semin Arthritis Rheum. 2006;36(2):88–98.
21. Nicola P, Maradit-Kremers H, Roger V, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 2005;52(2):412–20.
22. Brandt LJ, Feuerstadt P. Intestinal ischemia. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia: Saunders; 2010. p. 2038.
23. Tehlirian C, Bathon J. Rheumatoid arthritis. In: Stone JH, Crofford LJ, White PH, editors. Primer on the rheumatic diseases. New York: Springer Science + Business Media; 2008. p. 114–41.
24. Gandhi M, Aweeka F, Greenblatt R, et al. Sex differences in pharmacokinetics and pharmacodynamics. Annu Rev Pharmacol Toxicol. 2004;44:499–523.
25. Song IH, Appel H, Haibel H, et al. New onset of Crohn's disease during treatment of active ankylosing spondylitis with etanercept. J Rheumatol. 2008;35:532–6.
26. Shakir SA, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria. Drug Saf. 2002;25(6):467–71.