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ORIGINAL ARTICLE

Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review

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Abstract Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has recently been added to the therapeutic armamentarium against rheumatoid arthritis (RA). Despite its overall safety, concerns have been raised regarding diverticular perforation in patients receiving the drug. The aim of our research was to document the incidence of diverticular disease in RA patients treated in the pre-disease-modifying anti-rheumatic drug (DMARD) era, following treatment with conventional DMARDs, and subsequent to tocilizumab therapy. We performed a systematic literature review in MEDLINE, EMBASE, Conference Proceedings Citation Index–Science, Cochrane Central Register of Controlled Trials and Current Controlled Trials up to Nov. 2010. The publication titles and abstracts were independently assessed by two reviewers for relevance and quality, and the review was conducted following guidelines from the Centre for Reviews and Dissemination. In the pre-DMARD period of RA management, where patients were largely treated with NSAIDs and corticosteroids, gastrointestinal (GI) complications were a substantial cause of mortality with diverticulitis and colonic ulcers accounting for almost a third of GI-related deaths. In contrast, our search did not reveal any evidence of diverticular perforation in patients treated with conventional DMARDs. Eighteen cases of lower GI perforation (16 of whom had diverticulitis) have been documented in recent conference proceedings following tocilizumab treatment in clinical trials, with a lower GI perforation rate of 1.9 per 1,000 patient years (PY). This lies between the reported rate of GI perforations for corticosteroids and anti-TNF-α agents in the United Health Care database, with rates of 3.9 per 1,000 PY (95% CI 3.1–4.8) and 1.3 per 1,000 PY (95% CI 0.8–1.9), respectively. The majority of these patients were concurrently prescribed NSAIDs and/or long-term corticosteroids. Traditional DMARD therapy for RA appears not only to have modified the risk of lower GI perforation but prevented it. The risk of diverticular perforation may be slightly higher in patients treated with tocilizumab compared with conventional DMARDs or anti-TNF agents, but lower than that for corticosteroids. The mechanism of action of IL-6 antagonism in the pathophysiology of diverticular perforation has yet to be elucidated.

Keywords Biologics · Diverticular disease · DMARDs · Gastrointestinal perforation · Mortality · Rheumatoid arthritis · Tocilizumab

Introduction

Biologic disease-modifying anti-rheumatic drugs (DMARDs) have revolutionised the management of rheumatoid arthritis (RA). Substantial evidence exists supporting the role of these agents in controlling symptoms, abrogating radiographic progression, improving patient outcomes and reducing mortality [1, 2]. However, safety issues remain of chief concern, and hence, vigilance for side effects is of utmost importance

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[3]. Tocilizumab, a novel humanised monoclonal antibody targeting the IL-6 receptor, is a recent addition to our therapeutic compendium. Despite its efficacy in a number of clinical situations, concerns have been raised regarding diverticular perforation in patients receiving the drug [4]. We performed a systematic literature review therefore to document the incidence of diverticular disease in RA patients treated in the pre-DMARD era, following conventional DMARD therapy, and in patients receiving tocilizumab.

Methods

A systematic literature search was conducted in OVID MEDLINE (1966 to 27 October 2010), EMBASE (1949 to 10 November 2010), Conference Proceedings Citation Index–Science (Web of Science) (1990 to 10 November 2010), Cochrane Central Register of Controlled Trials (CENTRAL) (10 November 2010) and Current Controlled Trials (15 November 2010) using the terms 'diverticulitis', 'diverticular', 'gastrointestinal' and 'perforation' and combining them with 'rheumatoid arthritis', 'DMARDs' or 'tocilizumab' in the advanced search option without limitations. Individual DMARDs were also searched independently in combination with the above terms. The results were assessed by two independent reviewers to include those that mentioned safety with the use of these drugs on the basis of the title and abstract. Appropriate articles were further screened based on full text review to select only those reporting diverticular disease when used for a rheumatic indication. The review was conducted following criteria set out by the guidelines from the Centre for Reviews and Dissemination [5]. Furthermore, we manually reviewed the references of all the selected publications to complement our search including unpublished data from the manufacturer of tocilizumab (Roche). Identified articles were only included if they displayed a possible relationship between administration of the drug and diverticular disease, having excluded other potential causes or at least having failed to exclude drug-induced causality. For each case, relevant data, where available, were extracted to collect information regarding:

1. Year and type of study
2. Patient characteristics (number of patients, age, gender, location)
3. Treatment regime (duration, dose, use as monotherapy or in combination)
4. Clinical features (symptoms, signs, imaging findings, bedside and laboratory investigations)
5. Management (drug discontinuation, surgery, other)
6. Outcome (full recovery, partial recovery, deterioration, disease recurrence or death)

Results

Rheumatoid arthritis and diverticular perforation

During the pre-DMARD era of RA management, GI complications were one of the most common causes of death with the observed to expected mortality ratio (O/E) due to GI causes being 4.4 in early RA (<5 years duration) and 8.9 in established RA (>5 years) [6]. Diverticulitis and colonic ulcers were responsible for almost a third of this group. Allbeck et al. suggested that the relative risk of dying secondary to GI causes in patients with RA is more than sixfold as compared to age- and sex-matched cohorts [7]. In addition, diverticulitis was found to be an independent risk factor for GI perforation in RA patients with a third of these (32.4%) having a diagnosis of diverticulitis prior to or proximate to the hospitalisation with GI perforation [8]. Similarly, a diagnosis of rheumatic disease has been shown to be strongly associated with the development of sigmoid diverticular abscess perforation (odds ratio, OR, 3.5 (CI 1.9–6.7); $p<0.001$) [9].

NSAIDs, commonly prescribed for RA, have also been strongly associated with diverticular complications. In one series, up to 92% of patients presenting with diverticular bleeding were taking NSAIDs [10]. In another study, diverticula were found to be the most common source of bleeding in lower GI bleeds in NSAID users [11]. A recent review regarding NSAID-induced diverticular complications suggested an odds ratio of 1.5–11.2 [12].The relative risk of NSAID-related diverticular perforation has been calculated at 2.96 (CI 1.50–5.34, $p<0.01$) [13].

DMARDs and diverticular perforation

Our search did not reveal any reports of diverticular perforation in patients treated with commonly used traditional DMARDs (e.g. methotrexate, sulfasalazine, hydroxychloroquine and leflunomide). Several cases of gold-induced enterocolitis leading to colonic perforation have been described [14]. Diverticular disease following the use of TNF-α inhibitors has been reported; however, most of these patients were receiving concomitant NSAIDs and corticosteroids [15]. Curtis et al. suggested that the rate of hospitalisation for GI perforation among patients on biologics with concurrent steroids to be 1.12 (CI 0.5–2.49) per 1,000 patient years (PY) compared to 0.47 (0.22–0.98) per 1,000 patient years among those only on biologics [8].

In addition, corticosteroids are strongly associated with lower GI perforations. A case–control study calculated the OR of steroid-related perforated diverticular disease to be 28.3 (CI 4.8–165.7) [16]. Another study found an OR of 31.9 for sigmoid diverticular abscess perforations in patients with rheumatic conditions treated with steroids [9].

Tocilizumab and diverticular perforation

Eighteen cases of lower GI perforation have been documented in RA patients receiving tocilizumab in clinical trials. These phase III studies looking at the efficacy and safety of tocilizumab have found a GI perforation rate of 1.9 per 1,000 PY with tocilizumab therapy [17]. The majority of these patients were receiving NSAIDs and/or long-term corticosteroids.

Discussion

Diverticular disease is common in the general population with a substantial proportion of individuals being asymptomatic [18]. Acute perforation complicating colonic diverticular disease, however, has a mortality rate of up to 30% [19]. Hart et al. found the incidence of perforation to be 4/100,000/year, which increased with age and was more common in women (male to female, 5.8 v 3.1) [20]. In another study, Hernandez-Diaz et al. found overall GI perforations occurring at a rate of 0.1 per 1,000 person years (95% CI 0.04–0.23) [21] with the rate of diverticular perforation even lower [22]. A potential difficulty in reporting diverticular perforations both in trials and clinical practice is the lack of well-defined end points [23]. As a consequence, diverticular perforations almost certainly remain under-reported and are usually grouped with lower GI bleeding/complications. Studies which have estimated both bleeding and perforation have suggested that one case of GI perforation occurs for every 6–9 cases of GI bleeding [24].

It is evident that in the pre-DMARD era, RA-related mortality was high, with GI complications being one of the chief contributors [25]. Over the last two decades, multiple case reports and series of lower GI perforations have been reported in patients with RA. Various possible mechanisms have been suggested including GI perforation being an extra-articular manifestation of RA, GI vasculitis complicating RA or co-existing autoinflammatory conditions [26–28]. Amyloidosis has also been suggested as a cause in several cases [29]. However, the widespread use of NSAIDs and corticosteroids remains the most likely explanation. Evidence exists that while the incidence of NSAID-related upper GI complications has decreased in recent years, that of lower GI complications is increasing [24]. One explanation might be the increasing use of traditional NSAIDs and a proton pump inhibitor (PPI) combination as PPIs only protect the upper bowel. As a consequence, this may have led to increased reporting of lower GI events. Both steroids and NSAIDs have been shown to be strongly associated with severe complications of diverticular disease [22].

The modern management of RA with the early use of non-biologic DMARDs has not only improved patient outcomes but seemingly prevented lower GI complications. Since the routine use of traditional DMARDs, accounts of lower GI bleeding and perforation in RA have been rare with most patients also receiving steroids. Gold therapy was associated with enterocolitis; however, it is rarely used now to manage RA. Interestingly, 5-aminosalicylate derivatives have been used to treat mild cases of diverticulitis [30]. This may indicate a potential advantage of sulfasalazine as the DMARD of choice in certain circumstances such as in patients with known diverticular disease who need to be treated with a biologic agent.

It appears that there has been a re-emergence of lower GI complications, especially diverticular perforation following the introduction of biologic therapy for RA. This risk appears slightly higher in patients treated with tocilizumab (1.9 per 1,000 PY) compared with conventional DMARDs or anti-TNF agents (1.3 per 1,000 PY; 95% CI 0.8–1.9) but much lower than that for corticosteroids (3.9 per 1,000 PY; 95% CI 3.1–4.8) [17]. Although the numbers are low and considering the aforementioned methodological flaws with reporting such events, awareness among clinicians is critical due to the high morbidity and mortality associated with GI perforation. National biologics registers incorporating data from drug regulatory authorities and manufacturers will be of great benefit in further documenting this complication. An initial screening history for diverticular disease, patient education regarding symptoms of colonic disease and assessment of compounding risk factors for infection or perforation have been recommended [31].

The mechanism of action of tocilizumab in the pathophysiology of diverticular perforation has yet to be elucidated. Th17 cells have a vital role in innate and adaptive immune response to infections at mucosal surfaces [32]. Their differentiation and maintenance is promoted in part by IL-6. Whether inhibition of IL-6 breaks this mucosal barrier in the colonic diverticula leading to perforation is a possibility.

Recent interest in the variable effect of anti-TNF agents on transmembrane TNF-α-expressing cells, versus the seemingly singular effect on soluble TNF-α, may hopefully stimulate similar interest in tocilizumab [33]. This may elucidate differences in soluble IL-6 receptor versus membrane-bound IL-6 receptor-signalling mechanisms of action both in the pathophysiology of rheumatoid arthritis and the pharmacodynamics of tocilizumab. Current interest in specifically blocking trans-signalling (soluble IL-6 receptor) has shown promise in experimental models and may overcome the associated infection risks of complete IL-6 blockade [34].

Conclusion

Diverticular perforation is a serious and potentially life-threatening condition. The risk of this appears to be elevated in RA patients prescribed biologic agents especially tocilizumab. We therefore caution the use of tocilizumab in patients with symptomatic diverticular disease. Furthermore, immediate investigation of anyone with lower GI symptoms receiving a biologic agent for RA is critical.

Conflict of interest Andrew Östör has received support from (including attendance at conferences), undertakes clinical trials for and acts as a consultant to Roche, Chugai, Schering–Plough/MSD, Abbott, Wyeth, BMS, GSK, MerckSorono and UCB. Other authors have no conflict of interest.

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