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ORIGINAL ARTICLE

Anti-tumour necrosis factor agents reduce non-steroidal anti-inflammatory drug-induced small bowel injury in rheumatoid arthritis patients

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ABSTRACT

Objective The role of tumour necrosis factor α (TNFα) in the pathogenesis of non-steroidal anti-inflammatory drug (NSAID)-induced small intestinal damage remains unclear. We evaluated the preventive effect of anti-TNF therapy against NSAID-induced enteropathy in rheumatoid arthritis (RA) patients.

Design Capsule endoscopy was performed in 95 consecutive RA patients who received NSAID for more than 3 months, with or without anti-TNF therapy over a period of 3 months. The findings were scored from 0 to 4: 0, normal; 1, red spots; 2, one to four erosions; 3, more than four erosions; and 4, large erosions/ulcers. The relationship between the use of anti-TNF therapy and the risk of severe damage (scores 3 or 4) or the most severe damage (score 4) was assessed using multiple logistic regression analysis. Furthermore, a propensity score matching analysis was performed to reduce the effects of TNF selection bias.

Results By stratifying the patients on the basis of anti-TNF therapy, we obtained crude OR of 0.23 for severe damage (95% CI 0.09 to 0.65) and 0.37 for the most severe damage (95% CI 0.16 to 0.86). This protective effect of anti-TNF therapy remained robust to adjustments for baseline characteristics, with the adjusted OR for severe damage and the most severe damage ranging from 0.23 to 0.26 and 0.06 to 0.41, respectively. Propensity score matching yielded similar results and showed the protective effects of anti-TNF therapy against severe and most severe damage.

Conclusions Anti-TNF therapy may protect against NSAID-induced small intestinal damage in RA patients.

Significance of this study

What is already known on this subject?

- NSAID frequently injure the small intestine as well as the upper gastrointestinal tract.
- Experimental studies have demonstrated that TNFα plays an important role in the development of NSAID-induced damage to the small intestine.
- Anti-TNF biological agents are effective in the treatment of gastrointestinal lesions caused by several inflammatory disorders in which TNFα plays an important pathogenetic role.

What are the new findings?

- In the anti-TNF therapy-naive group, about half of the patients had NSAID-induced severe small intestinal damage.
- RA patients who received anti-TNF therapy had less severe NSAID-induced small bowel damage than those who did not receive such therapy.
- The protective effect of anti-TNF therapy against severe enteropathy remained robust to propensity score adjustment.

How might it impact on clinical practice in the foreseeable future?

- We demonstrate a pathogenic role of TNFα in NSAID-induced enteropathy in humans.
- Therapies targeting TNFα, and particularly anti-TNF biological therapy, could be a novel treatment for NSAID-induced severe small intestinal pathologies.

INTRODUCTION

Although disease-modifying antirheumatic drugs (DMARD) such as methotrexate have gained increasing importance in the treatment of rheumatoid arthritis (RA), patients with RA still frequently take non-steroidal anti-inflammatory drugs (NSAID) to reduce joint pain, stiffness and swelling. The most common and serious adverse effect of NSAID therapy is gastrointestinal toxicity that can cause ulceration, bleeding and perforation. Until quite recently, most studies had focused on NSAID-induced upper gastrointestinal complications. However, since the revolutionary advance in the detection of small bowel diseases that was brought about by the development of video capsule endoscopy (VCE)[1] in the beginning of the 21st century, NSAID-induced small bowel injury has received close attention. Several studies using VCE have demonstrated the high potential of NSAID to injure the small intestine, regardless of the length of NSAID therapy. It has been demonstrated that 40–90% of NSAID users have mucosal breaks (ulcers and/or erosions) in the small intestine.[2–5] A high prevalence of NSAID-induced enteropathy was also observed in our previous study, in which 81% of RA patients who received NSAID for more than 3 months had mucosal breaks in the small intestine.[6]

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Tumour necrosis factor α (TNFα) plays a key role in the pathogenesis of many inflammatory diseases, including RA, inflammatory bowel diseases and psoriasis. Therefore, anti-TNF agents have been used to treat these inflammatory pathologies.[7] In RA, anti-TNF biological therapies, which are used when conventional DMARD are unable to control RA synovitis, have been shown to be highly effective in reducing disease activity, disability and radiological damage.[8 9] Recent experimental studies have indicated that TNFα plays an important role in the development of NSAID-induced damage in the small intestine, similar to its role in the stomach.[10 11] In rats, the in-vivo blocking of TNFα by neutralising antibodies led to a significant reduction in indomethacin-induced small intestinal damage,[12] and TNFα knockout mice exhibited less severe damage, with reduction in neutrophil infiltration and epithelial cell apoptosis.[13] Therefore, we hypothesised that RA patients who chronically used NSAID and also received anti-TNF therapy would exhibit less severe enteropathy than those not receiving the therapy.

METHODS

Patients

Between January 2008 and December 2011, 103 consecutive RA patients (19 men and 84 women; mean age 61 years; age range 24–80 years) who received NSAID for more than 3 months, with or without anti-TNF therapy over a period of 3 months, were enrolled in this study. The main exclusion criteria included swallowing disorders, active malignancy, pregnancy; history of abdominal surgery and any serious central nervous system, psychiatric, cardiovascular, respiratory, or intestinal disease. Patients on misoprostol were excluded from the study because of the preventive effects of this drug on NSAID-induced damage to the small intestine that were confirmed by a VCE study.[5] As we specifically focused on the effects of long-term anti-TNF biological administration on NSAID-induced enteropathy in the present study, we excluded patients who received anti-TNF therapy for less than 3 months or patients who received biological agents targeting molecules other than TNFα, such as tocilizumab and abatacept. Written informed consent was obtained from all the patients. The protocol for the study was approved by the ethics committee of the Osaka City University Graduate School of Medicine.

VCE procedure and data interpretation

VCE was performed using a PillCam SB1 or SB2 (Given Imaging, Ltd, Yoqneam, Israel). Patients fasted for 12 h before swallowing the capsule. Fluids were allowed 2 h later, followed by a light meal after another 2 h. Data were collected for up to 8 h after capsule ingestion. After 8 h, the sensor array and recording device were removed.

The VCE digital image stream was reviewed and interpreted independently by two endoscopists (YN and SS) who were blind to the treatments of the patients. Capsule endoscopic findings of NSAID-induced enteropathy were scored according to the following method of Graham *et al*:[14] 0, normal; 1, red spots; 2, one to four small erosions; 3, more than four small erosions; and 4, large erosions/ulcers. A red spot was defined as a mucosal disruption that was denuded of villi, with red areas but no clear mucosal breaks. A small erosion was defined as a circumscribed area of mucosal disruption that was denuded of villi, with or without exudates or red colour and that involved, at most, a diameter that was equivalent to those of valvulae conniventes. Large erosions were defined as circumscribed breaks in the mucosa that were larger than the equivalent diameter of valvulae conniventes. Ulcers were defined as large erosions with a central area with exudates. Typical examples of small bowel pathologies are shown in figure 1. Endoscopic scores of 3 and 4 indicated severe damage.[14] If the endoscopic findings were different between the two interpreters, the findings were reviewed together by both blinded interpreters to reach a consensus.

Statistical analysis

Data are presented as mean±SD for continuous variables and as numbers (percentages) for categorical variables. For categorical data, comparisons between groups were performed using the χ^2 test (or Fisher's exact test when necessary because of small sample sizes), whereas continuous data were compared using Student's t test. The relationship between the use of anti-TNF therapy and the risk of severe damage (endoscopic scores 3 or 4) or the most severe damage (endoscopic score 4) was estimated by calculating OR and 95% CI by using multiple logistic regression.

Furthermore, a propensity score matching analysis was performed to reduce the effects of TNF selection bias and potential confounding factors. The propensity score matching method was proposed to evaluate statistically causal effects free from confounding effects, by mathematically refashioning an observational study into a randomised study; therefore, studies using the propensity score approach are occasionally considered pseudo-randomised studies.[15] We created a propensity score matched cohort by attempting to match each RA patient receiving anti-TNF therapy with a patient not receiving anti-TNF therapy (a 1:1 match) without replacement by using an optimal matching technique. A total of 11 variables that could possibly influence the outcomes (severe or most severe damage) was used to generate a propensity score ranging from 0 to 1 by logistic regression.[16] These variables included age, gender, history of peptic ulcers, drinking and smoking habits, dose of NSAID, type of NSAID (non-selective cyclooxygenase (COX) inhibitor or selective COX-2 inhibitor (celecoxib)), concomitant use of salazosulfapyridine, bisphosphonate, and acid suppressants (proton pump inhibitors (PPI) or histamine-2-receptor

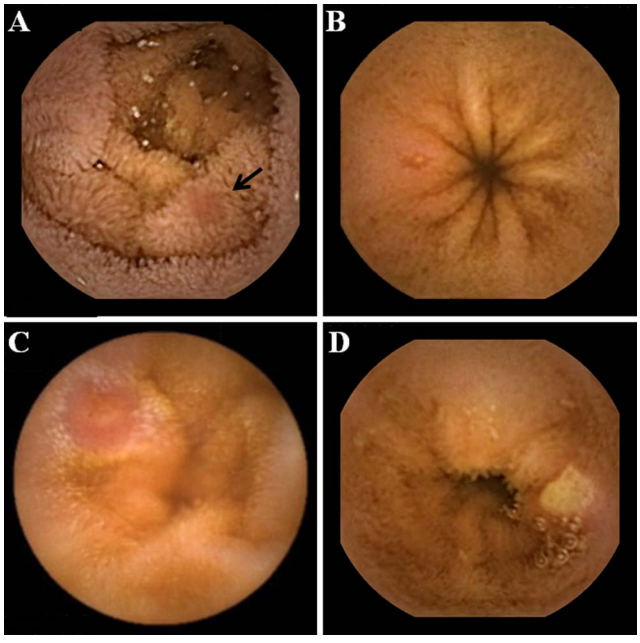

Figure 1 Capsule endoscopic images of small bowel pathologies induced by non-steroidal anti-inflammatory drugs. (A) red spot (arrow), (B) small erosion, (C) large erosion, (D) ulcer.

antagonists (H_2RA)) and disease activity score in 28 joints (DAS28, a disease activity index for RA). After matching, crude comparisons of the matched cohorts were performed using the McNemar's test and paired t tests; OR with 95% CI were calculated using conditional logistic regression. The propensity score matched sets were then used in logistic regression models to evaluate the relationship between the use of anti-TNF therapy and the risk of severe damage or the most severe damage. Absolute standardised differences (ASD) were computed to evaluate matching effectiveness. Statistical analyses were performed using SPSS version software 11.0 for Windows and the R statistical package (free download from http://www.r-project.org) V.2.13.0. All statistical tests were two-sided, and p values less than 0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics of patients

Comparative data were analysed for 95 patients; eight patients (all women; mean age 58 years) were excluded because the entire small bowel could not be visualised. A total of 65 patients received the standard doses of NSAID, 30 patients were being treated with lower doses of NSAID, and no patients received higher doses of NSAID. Of the 95 patients, 59 patients did not receive anti-TNF therapy, while 36 patients received anti-TNF therapy (etanercept (n=19), infliximab (n=15) and adalimumab (n=2)).

Table 1 shows the baseline demographic information, as well as the clinical variables. Compared to the patients not receiving anti-TNF therapy, the patients receiving anti-TNF therapy had a higher rate of concomitant use of methotrexate, with a tendency to be younger and to use selective COX-2 inhibitors more frequently. The two treatment groups were similar with respect to gender, history of peptic ulcers, drinking and smoking habits, NSAID doses, rates of concomitant use of steroids, salazosulfapyridine, bisphosphonate and acid suppressants, and DAS28 score.

After propensity score matching, there were 36 matched pairs of patients who did or did not receive anti-TNF therapy. The baseline characteristics of the two groups were comparable. The C statistic, which is equivalent to the receiver operating characteristic curve, was 0.72 for the propensity model. The ASD values ranged from 6% to 35%.

Effect of anti-TNF therapy on NSAID-induced severe small intestinal damage

Of the 59 patients in the anti-TNF therapy-naive group, 27 (45.8%) had severe damage (score of 3 (n=9) or 4 (n=18)), while the remaining 32 patients had non-severe (score<3) damage (scores of 1 (n=20) and 2 (n=12)). Of the 36 patients in the anti-TNF therapy group, six (16.7%) had severe damage (score of 3 (n=5) or 4 (n=1)), while the remaining 30 patients had non-severe damage (scores of 0 (n=6), 1 (n=15) and 2 (n=9)).

By categorising the patients on the basis of anti-TNF therapy, we obtained OR of 0.23 for severe damage (95% CI 0.09 to 0.65) and 0.37 for the most severe damage (95% CI 0.16 to 0.86). This effect of anti-TNF therapy on NSAID-induced enteropathy remained robust to adjustments for age, drinking and smoking habits, use of salazosulfapyridine, bisphosphonate, or acid suppressants, and DAS28 score, with the adjusted OR for severe damage and the most severe damage ranging from 0.23 to 0.26 and 0.06 to 0.41, respectively (table 2).

Propensity score matching yielded similar results in terms of the protective effects of anti-TNF therapy, with the adjusted OR for severe damage and the most severe damage ranging from 0.23 to 0.33 and 0.09 to 0.11, respectively (table 2).

DISCUSSION

In this study, we demonstrated that RA patients who received anti-TNF therapy had less severe NSAID-induced small bowel damage than those who did not receive such therapy. Given that the observed association between the use of anti-TNF biological agents and the risk of severe or most severe NSAID-induced enteropathy could be affected by confounding factors such as gender, age, dose of NSAID and clinical activity of RA, we conducted a sensitivity analysis by using the propensity score matching method. The results of this analysis showed a similar reduction in the risk of NSAID-induced severe damage to the small intestine in RA patients who received anti-TNF therapy. These results strongly suggest that anti-TNF biological agents

Table 1 Baseline characteristics and propensity score matched baseline characteristics

	Baseline			Propensity score matched baseline			
	TNF− (n=59)	TNF+ (n=36)	p Value	TNF− (n=36)	TNF+ (n=36)	p Value	ASD (%)
Age (years)*							
Mean (SD)	63 (10)	59 (12)	0.09	60 (11)	59 (13)	0.56	9
Female,* n (%)	46 (78.0)	30 (83.3)	0.6	34 (94.4)	30 (83.3)	0.29	35
History of peptic ulcer,* n (%)	20 (3.9)	12 (33.3)	1.00	11 (30.6)	12 (33.3)	1.00	6
Alcohol intake,* n (%)	8 (13.6)	5 (13.9)	1.00	4 (11.1)	5 (13.9)	1.00	8
Smoker,* n (%)	8 (13.6)	6 (16.7)	0.77	5 (13.9)	6 (16.7)	1.00	8
Standard dose of NSAID,* n (%)	38 (64.4)	27 (75.0)	0.36	23 (63.9)	27 (75.0)	0.45	24
Selective COX-2 inhibitors,* n (%)	9 (15.3)	12 (33.3)	0.05	9 (25.0)	12 (33.3)	0.55	18
Methotrexate use, n (%)	42 (71.2)	33 (91.7)	0.02	31 (86.1)	33 (91.7)	0.68	–
Steroid use, n (%)	18 (30.5)	17 (47.2)	0.13	12 (33.3)	17 (47.2)	0.38	–
Salazosulfapyridine use,* n (%)	9 (15.3)	3 (8.3)	0.53	4 (11.1)	3 (8.3)	1.00	9
Bisphosphonate use,* n (%)	13 (22.0)	4 (11.1)	0.27	6 (16.7)	4 (11.1)	0.68	16
Acid suppressants use,* n (%)	30 (50.8)	19 (52.8)	1.00	18 (50.0)	19 (52.8)	1.00	6
DAS28*	3.3±1.1	3.1±0.9	0.48	3.2±1.0	3.1±0.9	0.71	11

*Variable used to compute propensity scores.
ASD, absolute standardised difference; COX, cyclooxygenase; DAS28, disease activity score in 28 joints; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor.

Table 2 The relationship between the use of anti-TNF therapy and the risk of NSAID-induced severe damage or most severe damage

	Severe damage		Most severe damage	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Before propensity score matching				
Crude	0.23 (0.09 to 0.65)	<0.01	0.37 (0.16 to 0.86)	0.02
Adjusted for age	0.26 (0.09 to 0.74)	0.01	0.41 (0.17 to 0.97)	0.04
Adjusted for alcohol intake and smoking	0.23 (0.08 to 0.66)	<0.01	0.07 (0.01 to 0.52)	0.01
Adjusted for salazosulfapyridine use	0.23 (0.08 to 0.65)	<0.01	0.06 (0.01 to 0.47)	<0.01
Adjusted for bisphosphonate use	0.25 (0.09 to 0.71)	<0.01	0.07 (0.01 to 0.55)	0.01
Adjusted for acid suppressant use	0.23 (0.08 to 0.64)	<0.01	0.06 (0.01 to 0.50)	<0.01
Adjusted for DAS28	0.24 (0.09 to 0.65)	<0.01	0.37 (0.16 to 0.88)	0.02
Adjusted for age, alcohol intake, smoking and use of salazosulfapyridine and acid suppressants	0.23 (0.08 to 0.67)	<0.01	0.06 (0.01 to 0.47)	<0.01
After propensity score matching				
Crude	0.29 (0.09 to 0.87)	0.03	0.09 (0.01 to 0.70)	0.02
Adjusted for age	0.26 (0.08 to 0.86)	0.03	0.07 (0.01 to 0.86)	0.04
Adjusted for alcohol intake and smoking	0.26 (0.07 to 0.87)	0.03	0.11 (0.01 to 0.88)	0.04
Adjusted for salazosulfapyridine use	0.31 (0.10 to 0.94)	0.04	0.10 (0.01 to 0.78)	0.03
Adjusted for bisphosphonate use	0.30 (0.10 to 0.93)	0.04	0.11 (0.01 to 0.88)	0.04
Adjusted for acid suppressant use	0.27 (0.08 to 0.86)	0.03	0.09 (0.01 to 0.72)	0.02
Adjusted for DAS28	0.33 (0.10 to 1.04)	0.06	0.11 (0.01 to 1.18)	0.07
Adjusted for age, alcohol intake, smoking and use of salazosulfapyridine and acid suppressants	0.23 (0.05 to 1.01)	0.05	0.09 (0.01 to 1.32)	0.08

Capsule endoscopic findings of NSAID-induced enteropathy were scored from 0 to 4: 0, normal; 1, red spots; 2, one to four small erosions; 3, more than four small erosions; 4, large erosions/ulcers. The relationship between the use of anti-TNF therapy and the risk of severe damage (scores 3 or 4) or severest damage (score 4) was evaluated by logistic regression analysis.
DAS28, disease activity score in 28 joints; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor.

may have a protective effect against NSAID-induced enteropathy. As our study was a cross-sectional study, the possibility that the anti-TNF therapy accelerated the healing of such enteropathy should be considered. However, further studies are required to determine whether the anti-TNF biological agents exert these two effects (a protective effect and a wound-healing effect) in NSAID-induced enteropathy.

Recently, anti-TNF biological agents have been reported to be effective in the treatment of gastrointestinal lesions caused by several inflammatory disorders in which TNFα plays an important pathogenetic role. For example, a meta-analysis by Peyrin-Biroulet *et al*[17] demonstrated that anti-TNF biological agents such as infliximab and adalimumab were effective in inducing clinical remission and fistula closure in patients with Crohn's disease. Another meta-analysis demonstrated that infliximab was superior to placebo in inducing the remission of moderate to severely active ulcerative colitis.[18] Furthermore, Melikoglu *et al*[19] reported a significant improvement in the oral lesions associated with Behçet's syndrome with etanercept therapy. Multiple lines of evidence from experimental studies suggest that the overexpression of TNFα occurs in the early phase of NSAID-induced small intestine damage and that TNFα may play a crucial role in the subsequent induction of inflammatory responses, such as neutrophil infiltration, resulting in intestinal injuries.[12 13 20 21] These animal data have led to the hypothesis that anti-TNF therapy could also prevent NSAID-induced damage to the small intestine. As expected, we found that anti-TNF therapy had a protective effect against the damage. Moreover, we demonstrated for the first time a pathogenic role of TNFα in NSAID-induced enteropathy in humans.

In addition to TNFα, various factors such as enteric bacteria, deficiency of prostaglandins and bile have been shown to be involved in the pathogenesis of NSAID-induced small intestinal damage, and in experimental studies, many agents have shown the potential to prevent the damage.[3 12 20 21] However, only a small number of these agents have been demonstrated to be effective for NSAID-induced enteropathy in clinical studies. Misoprostol[22] and rebamipide[23] (a muco-protective drug) exerted protective effects against diclofenac-induced small-intestinal mucosal injuries in humans. Importantly, these studies were conducted in young, healthy volunteers with low risks, and the efficacy of these agents was assessed after the short-term administration of NSAID. Furthermore, no drugs have been proved to be effective in the treatment of NSAID-induced severe enteropathy, which is thought to be a clinically significant condition. Therefore, therapies targeting TNFα, and particularly anti-TNF biological therapy, should be considered as a novel treatment for NSAID-induced severe small intestinal pathologies such as bleeding ulcers and large ulcers. Considering that anti-TNF therapy is expensive and NSAID-induced damage in the small intestine, similar to that observed in the upper gastrointestinal tract, is believed to heal spontaneously after the cessation of NSAID administration, patients with severe enteropathy for whom NSAID administration cannot be discontinued (eg, low-dose aspirin) may be candidates for anti-TNF biological therapies.

In the present study, the patients receiving anti-TNF therapy had a tendency to use a selective COX-2 inhibitor, celecoxib, more frequently compared to those who did not receive such therapy, although the difference between these two groups did not reach statistical significance. Previous studies have demonstrated that the short-term administration of selective COX-2 inhibitors had less ulcerogenic effects on the small intestine than that observed by the administration of non-selective COX inhibitors.[4 24] No difference in the incidence of injury to the small intestine was observed between chronic users of the two types of NSAID.[25] Therefore, long-term use of selective COX-2 inhibitors may abolish their beneficial effect on the small intestine, and the chronic use of both types of NSAID may result in similar intestinal ulcerogenicity. Furthermore, propensity score matching resulted in a similar rate of celecoxib use between the

anti-TNF therapy and anti-TNF therapy-naive groups and yielded results similar to those obtained before propensity score matching in terms of the protective effects of anti-TNF therapy, suggesting that this prescription bias did not affect our main results.

In addition to NSAID, several anti-RA drugs such as steroids and methotrexate have been reported to induce upper gastrointestinal injuries.[26 27] Although the small intestinal toxicity of these drugs remains unclear, concomitant use of these drugs and NSAID might increase the severity of enteropathy. However, in the present study, compared to the anti-TNF therapy-naive group, the rates of the concomitant use of NSAID and steroids or methotrexate were higher in the anti-TNF therapy group, in which severe NSAID-induced small bowel damage was reduced. Therefore, the bias in the prescription of these anti-RA drugs would also not affect our main result that anti-TNF therapy reduced severe NSAID-induced enteropathy.

Recent animal studies indicated that both PPI and H_2RA exacerbated NSAID-induced small intestinal injury[28 29] and our clinical study demonstrated that the use of PPI and H_2RA was associated with an increased risk of severe NSAID-induced small intestinal damage with OR of 5.22 and 3.95, respectively.[30] Therefore, in the present study, we included the use of acid suppressants (PPI or H_2RA) in the confounding variables and found that the preventive effect of anti-TNF therapy on NSAID-induced severe small intestinal damage remained robust to adjustment for the use of acid suppressants, thus further confirming the reduction of the risk for NSAID-induced severe enteropathy through anti-TNF therapy.

This study had several limitations. First, as the number of patients was relatively small, the OR 95% CI of the relationship between the use of anti-TNF therapy and the development of severe damage or most severe damage was wide, allowing for the possibility that the protective effect of anti-TNF therapy on severe damage, although significant, may be of minor clinical importance. Second, in this study, some patients received non-selective COX inhibitors, whereas others were being treated with a selective COX-2 inhibitor, celecoxib. Although small intestinal ulcerogenicity seems to be similar between non-selective NSAID and selective COX-2 inhibitors in chronic users, data obtained from a study using a single non-selective NSAID would be more convincing. Third, in the propensity score matching analysis, we employed a 1:1 matching without replacement by using an optimal matching technique. Therefore, of the 59 patients in the anti-TNF therapy-naive group, 23 patients (39.9%) were unmatched and not accounted for in the conditional logistic regression analysis. A better matching technique could have improved the current propensity score matching. Fourth, in the present study, the ASD values ranged from 6% to 35%. In general, ASD values less than 10% indicate a balancing of baseline variables between treated and untreated cohorts;[31] therefore, the ASD values noted in this study indicate that our propensity score matching could not completely remove the imbalance of variables, possibly because of the relatively small number of patients in both groups. To resolve these limitations, prospective, randomised, large-scale studies using a single NSAID to evaluate the effect of anti-TNF therapy on NSAID-induced severe enteropathy are needed.

In conclusion, these results suggest that anti-TNF therapy may protect against NSAID-induced small intestinal damage in RA patients. Drugs targeting TNFα may be effective in the treatment of NSAID-induced enteropathy. Prospective studies with repeated VCE before and after anti-TNF therapy are needed to validate our findings.

Contributors Conception and design of the study: TW, TT, TK and TA; statistical analysis: MS; acquisition of the data: YN and SS; analysis and interpretation of the data: TW, YN, KT and YF; obtaining informed consent: TT, HY and KW; recruiting of patients: TK; drafting of the manuscript: TW and TT; critical revision of the manuscript for important intellectual content; TW and TA.

Competing interests None.

Ethics approval The protocol for the study was approved by the ethics committee of the Osaka City University Graduate School of Medicine.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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