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Gastrointestinal Adverse Drug Reaction Profile of Etanercept: Real-world Data From Patients and Healthcare Professionals

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ABSTRACT. ***Objective.*** We aimed to describe the nature and frequency of gastrointestinal adverse drug reactions (GI-ADRs) of etanercept (ETN) using patient-reported and healthcare professional (HCP)-registered data and compared this frequency with the GI-ADR frequency of the widely used tumor necrosis factor-α inhibitor adalimumab (ADA).

Methods. Reported GI-ADRs of ETN for rheumatic diseases were collected from the Dutch Biologic Monitor and DREAM registries. We described the clinical course of GI-ADRs and compared the frequency with ADA in both data sources using Fisher exact test.

Results. Out of 416 patients using ETN for inflammatory rheumatic diseases in the Dutch Biologic Monitor, 25 (6%) patients reported 36 GI-ADRs. In the DREAM registries 11 GI-ADRs were registered for 9 patients (2.3%), out of 399 patients using ETN, with an incidence of 7.1 per 1000 patient-years. Most GI-ADRs consisted of diarrhea, nausea, and abdominal pain. GI-ADRs led to ETN discontinuation in 1 patient (4%) and dose adjustment in 4 (16%) in the Dutch Biologic Monitor. Eight GI-ADRs (73%) led to ETN discontinuation in the DREAM registries. The frequency of GI-ADRs of ETN did not significantly differ from GI-ADRs of ADA in both data sources (Dutch Biologic Monitor: ETN 8.7% vs ADA 5.3%, $P = 0.07$; DREAM: ETN 2.8% vs ADA 4.7%, $P = 0.16$).

Conclusion. Most GI-ADRs associated with ETN concerned gastrointestinal symptoms. These ADRs may lead to dose adjustment or ETN discontinuation. The frequency of ETN-associated GI-ADRs was comparable to the frequency of ADA-associated GI-ADRs. Knowledge about these previously unknown ADRs can facilitate early recognition and improve patient communication.

Key Indexing Terms: adverse drug reactions, biological therapy, drug monitoring, drug safety, registries

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Etanercept (ETN) is a widely used biologic disease-modifying antirheumatic drug (bDMARD) for the treatment of various inflammatory rheumatic diseases such as rheumatoid arthritis (RA) and spondyloarthritis (SpA). The most common adverse drug reactions (ADRs) associated with ETN use are infections and injection site reactions.[1,2] While various gastrointestinal (GI) ADRs such as nausea and abdominal pain are described in the European product labels of other tumor necrosis factor-α inhibitors (TNFi), such as adalimumab (ADA) and infliximab (IFX),[3,4] these ADRs have seldom been described for ETN. Abdominal pain and nausea have been described as reasons for ETN discontinuation in 2 children with juvenile idiopathic arthritis (JIA).[5] Additionally, inflammatory bowel disease (IBD) has been demonstrated in patients with GI complaints, such as diarrhea or abdominal pain, while using ETN for an inflammatory rheumatic disease, mostly JIA.[6–12]

Real-world data provide a useful source of information for drug safety studies in postmarketing surveillance. The perspectives of both healthcare professionals (HCPs) and patients should be taken into account when assessing ADR reports because they may approach and experience the effects of ADRs differently.[13,14] In the Netherlands, patient-reported ADRs experienced with biologics are systematically collected in the Dutch Biologic Monitor, a multicenter Web-based cohort event monitoring system. The Dutch Biologic Monitor was introduced by the Netherlands Pharmacovigilance Centre Lareb for collecting patient-reported information about ADRs that patients experience with biologics used for an immune-mediated inflammatory disease.[13,15] HCP-registered ADRs of biologics are also captured in the Dutch Rheumatoid Arthritis Monitoring (DREAM-RA) registry and the Dutch Registry for Spondyloarthritis (SpA-Net). The DREAM-RA and SpA-Net registries collect real-world data in participating hospitals on quality of care, including both clinical aspects and patient-reported outcomes, with the aim to monitor and evaluate safety and effectiveness of rheumatic treatment in daily clinical practice.[16,17,18] All clinically verified ADRs that are captured in these registries are forwarded directly to Lareb.[19]

Because little is known about the frequency and characteristics of GI-ADRs with ETN treatment, we aimed to describe the profile of GI-ADRs associated with ETN using the systematically collected patient-reported data from the Dutch Biologic Monitor and the HCP-registered and clinically verified data from the DREAM-RA and SpA-Net registries. Since ADA is the other most frequently used TNFi in the Netherlands, we also aimed to get an impression of the extent to which GI-ADRs occur with the use of ETN compared to those occurring with ADA in inflammatory rheumatic diseases.

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METHODS

Study design. This observational study describes GI-ADRs from 2 data sources: GI-ADRs experienced with ETN by patients in the Dutch Biologic Monitor, and HCP-registered and clinically verified GI-ADRs registered for ETN in the DREAM-RA and SpA-Net registries.

Dutch Biologic Monitor. The Dutch Biologic Monitor is a prospective cohort event monitoring system for patient-reported ADRs that were experienced with the use of biologics.[13,15] Nine Dutch hospitals participated in the Dutch Biologic Monitor between January 1, 2017, and March 1, 2020. Patients using one of the monitored biologics were consecutively invited to participate by HCPs of the respective hospitals. Patients were eligible for participation from age ≥ 18 years. Patients who had started using the biologic before they started participating in the Dutch Biologic Monitor were also eligible for participation.

Participating patients were asked to complete comprehensive Web-based baseline questionnaires (www.mijnbiologischmedicijn.nl). The questionnaires included demographic information (sex, date of birth, weight, height, smoking), biologic used, starting date, indication(s) for biologic therapy, combination therapy, comorbidities, and ADRs experienced with biologics. Information on ADRs that patients experienced with the used biologic included the type of ADR, start and stop date, course, burden using a 5-point Likert-type scale ranging from 1 (no burden) to 5 (very high burden), contact about ADR with an HCP, type of HCP, treatment or other actions taken by the HCP, and own action taken by the patient following the ADR. Subsequent questionnaires after baseline focused exclusively on drug use (biologic and combination therapy) and follow-up of ADRs or new ADRs, and included identical questions on these topics. Questionnaires were sent out bimonthly and patients received a reminder by email if they had not completed the questionnaire within 7–14 days. Questionnaires expired after 21 days and no more questionnaires were sent after expiration. Questionnaires were sent out until patients stopped participating. Patients could withdraw from participation at any time. All participants received information about the study prior to participation and signed a digital informed consent form. The Dutch Biologic Monitor received a waiver for the Dutch Medical Research Involving Human Subjects Act (WMO) by the Medical Research Ethical Committee of Brabant (file number: NW2016-66). The Dutch Biologic Monitor was approved by the medical ethics committees of the participating hospitals.

DREAM registries. DREAM is a network of Dutch hospitals aiming to stimulate quality of care, efficient use of means, and clinical research.[19] The initiative started in 2003 with the DREAM-RA registry, a registry for monitoring all patients with RA who started treatment with bDMARDs. The registry expanded from 2006 onwards with cohorts of early RA patients treated according to treat-to-target strategies.[20,21,22] The SpA-Net registry started in 2016 with the systematic monitoring of patients with axial and/or peripheral SpA.[17] SpA-Net is incorporated within the DREAM collaboration and both DREAM-RA and SpA-Net use a shared Web-based data acquisition system (www.mijnreumacentrum.nl) to collect, store, and use both HCP-reported clinical data and patient-reported outcomes. Upon patient inclusion in the registries, ADR history is registered retrospectively by the HCPs and new ADRs can be reported continuously by both HCPs and patients themselves. All patient-reported ADRs are systematically verified and scored by the respective HCP. All verified ADR reports in the DREAM-RA registry and all ADR reports leading to drug discontinuation in the SpA-Net registry are automatically forwarded to the Netherlands Pharmacovigilance Centre Lareb, beginning in December 2015. In addition, all ADRs that had been registered between 2003 and 2015 were retrospectively forwarded to Lareb.[18] All patients had given written consent before inclusion in the registries, including data assessments by Lareb. In the DREAM registries, no additional data, other than data collection in routine

clinical practice, are collected. Therefore, ethical approval was not required according to Dutch regulations.

The reports Lareb received from the registries included action taken with the drug following the ADR (dose adjustment, dose not changed, or discontinuation) and the outcome of the ADR (recovered, recovered with sequel, recovering, or not recovered). Seriousness of GI-ADRs in the registry reports was determined according to the Council for International Organizations of Medical Sciences (CIOMS) criteria.[23] The criteria for serious reports are ADRs resulting in death, life-threatening situations, (prolonged) hospitalization, persistent or significant disability, or a congenital anomaly.

Data selection. All ADRs from both data sources were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology by trained pharmacovigilance assessors.[24] GI-ADRs were defined by MedDRA System Organ Class "gastrointestinal disorders," excluding MedDRA High Level Group Term, "dental and gingival disorders." All reported ADRs were explicitly attributed to the biologic by patients in the Dutch Biologic Monitor and by HCPs in the DREAM registries. Therefore, all reported GI-ADRs that were attributed to ETN used for inflammatory rheumatic diseases were selected. ADRs were selected at the MedDRA Preferred Term (PT) level, which is the most distinctive descriptor within each System Organ Class. Patient-reported data were collected from the Dutch Biologic Monitor from January 1, 2017, until March 1, 2020. All DREAM-RA data forwarded to Lareb from patients from the rheumatology department of Medisch Spectrum Twente (Enschede, the Netherlands) who participated from the onset in the DREAM-RA registry was used for analysis in the current study. For SpA-Net, all data from the rheumatology departments of both Medisch Spectrum Twente and Maastricht University Medical Center were used. The first registered GI-ADR with ETN in the DREAM registries occurred on June 22, 2004, and therefore, data from the DREAM-RA and SpA-Net registry collected from June 22, 2004, until January 1, 2020, were used.

Data analysis. Data from the Dutch Biologic Monitor (patient-reported) and DREAM registries (HCP-registered) were analyzed separately and could not be compared due to differences in method, frequency of ADR assessment, and registration of ADR details such as actions following the ADR. We calculated the incidence of GI-ADRs associated with ETN use in the registries as the number of reported GI-ADRs per total number of patient-years (PY) of ETN use in patients for whom start and stop dates of ETN were available. PY were calculated from the start date of ETN use until the start date of the GI-ADR or until January 1, 2020, in case no GI-ADR was reported. The incidence could not be calculated with Dutch Biologic Monitor data since we did not monitor all patients from start of ETN use.

Patient-reported GI-ADRs in the Dutch Biologic Monitor. We investigated the following GI-ADR characteristics using descriptive statistics for data from the Dutch Biologic Monitor: outcome of the ADR, action following the ADR, hospitalization following the ADR, the reported ADR burden, and Naranjo Probability Scale.[25] The Naranjo Probability Scale is a quantitative tool for estimating the probability of an ADR and the likelihood that it is caused by the drug. The scale ranges from 0 (doubtful) to 10 (definite). We included the outcome of the ADR in the last completed questionnaire in the Dutch Biologic Monitor.

HCP-registered GI-ADRs in the DREAM registries. We investigated the following characteristics using descriptive statistics for GI-ADRs in the DREAM registries: outcome of the ADR, action with ETN following the ADR, seriousness according to CIOMS criteria, and Naranjo Probability Scale.

Frequency of GI-ADRs associated with ETN and ADA. The frequency of GI-ADRs associated with ETN was defined as the total number of unique GI-ADRs per total number of patients using ETN for inflammatory rheumatic diseases. Long-term or recurring ADRs with the same MedDRA PT reported for the same patient were counted once. The frequency of GI-ADRs reported for ETN was compared with that of GI-ADRs reported for ADA used for inflammatory rheumatic diseases using Fisher exact test. We did not adjust for potential confounders since ADRs were explicitly attributed to the biologic by the patients. We compared GI-ADR frequency between ETN and ADA in patient reports from the Dutch Biologic Monitor, as well as between ETN and ADA in HCP reports from the DREAM registries. Additionally, for the DREAM registries, we compared the incidence of GI-ADRs per total number of PY between ETN and ADA using chi-square test. Statistical analysis was performed in IBM SPSS Statistics 22 (IBM Corp.).

RESULTS

The Dutch Biologic Monitor included 416 patients using ETN for inflammatory rheumatic diseases and a total of 25 patients (6%) reported 36 GI-ADRs (Table 1). The DREAM registries included 399 patients using ETN for inflammatory rheumatic diseases, with 11 HCP-registered GI-ADRs in 9 patients (2.3%), with an incidence of 7.1 per 1000 PY. No GI-ADRs of ETN concerning the same patient were reported in both the DREAM registries and the Dutch Biologic Monitor.

Patient-reported GI-ADRs in the Dutch Biologic Monitor. Most patient-reported GI-ADRs in the Dutch Biologic Monitor were GI symptoms (Table 2). Diarrhea, nausea, and gastrointestinal or abdominal pain and discomfort were the most frequently reported GI-ADRs. One patient reported Crohn disease (CD) as ADR. In total, 10 reported GI-ADRs (28%) developed within 1 month after start with ETN. A pattern of recurring GI-ADRs after every ETN administration was described by 9 patients (36%) for 11 ADRs (31%), including 3 reports of nausea, 3 reports of diarrhea, and 5 reports of abdominal pain or discomfort. These ADRs developed within 1–3 days after each administration and patients recovered within several days. The Naranjo Probability Scale was probable in 2 GI-ADRs and possible in 34 GI-ADRs (Table 3). The probable ADRs were stomatitis and GI pain.

Table 1. Demographics and clinical characteristics of patients with GI-ADRs associated with etanercept for inflammatory rheumatic diseases in the Dutch Biologic Monitor and DREAM registries.

	Patients With GI-ADRs in Dutch Biologic Monitor	Patients With GI-ADRs in DREAM Registries
Patients, n	25	9
Age, yrs, mean ± SD	57 ± 13	59 ± 8
Female sex	22 (88)	7 (78)
Indication		
Rheumatoid arthritis	19 (76)	9 (100)
Axial spondyloarthritis	3 (12)	0
Psoriatic arthritis	6 (24)	0
Combination therapy	18 (72)	5 (56)
Methotrexate	12 (48)	2 (22)
Corticosteroids[a]	1 (4)	2 (22)
Sulfasalazine	2 (8)	2 (22)
Hydroxychloroquine	3 (12)	0
Leflunomide	1 (4)	0

Values are expressed as n (%) unless otherwise indicated. [a] Dutch Biologic Monitor: prednisolone (1); DREAM registries: prednisolone (1), triamcinolonacetonide used once (1). GI-ADR: gastrointestinal adverse drug reaction; DREAM: Dutch Rheumatoid Arthritis Monitoring.

Table 2. The Medical Dictionary for Regulatory Activities (MedDRA) terminology Preferred Term (PT) of GI-ADRs associated with etanercept by patients (Dutch Biologic Monitor) and registered by healthcare professionals (DREAM registries).

MedDRA PTs in Dutch Biologic Monitor (36 GI-ADRs)	MedDRA PTs in DREAM registries (11 GI-ADRs)
Nausea: 6	Diarrhea: 5
Diarrhea: 5	Nausea: 2
Gastrointestinal pain: 3	Abdominal pain: 1
Abdominal discomfort: 2	Abdominal discomfort: 1
Abdominal distension: 2	Constipation: 1
Abdominal pain upper: 2	Rectal spasm: 1
Aphthous ulcer: 2	
Dry mouth: 2	
Abdominal pain: 1	
Constipation: 1	
Anal pruritus: 1	
Flatulence: 1	
Crohn disease: 1	
Enteritis: 1	
Angina bullosa hemorrhagica: 1	
Anal hemorrhage: 1	
Stomatitis: 1	
Glossodynia: 1	
Breath odor: 1	
Oral pain: 1	

GI-ADR: gastrointestinal adverse drug reaction; DREAM: Dutch Rheumatoid Arthritis Monitoring.

Table 3. Profile of patient-reported GI-ADRs associated with etanercept in the Dutch Biologic Monitor.

	GI-ADRs in the Dutch Biologic Monitor (36 ADRs)
Burden score[a], mean ± SD	2.6 ± 0.8
No. of ADRs with contact HCP[b]	24 (67)
Medical specialist	15 (63)
General practitioner	14 (58)
Nurse	7 (29)
Pharmacist	2 (8)
Other HCP[c]	6 (25)
No. of ADRs with action by HCP	
Discontinuation	1 (4)
Dose adjustment	4 (17)
Treatment	8 (33)
Referral to other HCP	7 (30)
Mentioned, no action	11 (46)
Other action[d]	3 (13)
No. of ADRs with own action	23 (64)
No. of ADRs with outcome	
Recovered	12 (33)
Improving	8 (22)
Not recovered	15 (42)
Aggravating	1 (3)
No. of ADRs leading to hospitalization[e]	2 (6)
Naranjo Probability Scale	
Definite	0
Probable	2 (6)
Possible	34 (94)
Doubtful	0

Values are expressed as n (%) unless otherwise indicated. [a] 5-point Likert-type scale. [b] Patients could report > 1 HCP. [c] Contact with other HCPs include dental HCPs (dental hygienist or dentist): 5; nutritionist: 1. [d] Other actions include examination: 2; adjusted moment of administration to the evening: 1. [e] The 2 ADRs leading to hospitalization were described by 1 patient. ADR: adverse drug reaction; GI-ADR: gastrointestinal ADR; HCP: healthcare professional.

Actions following GI-ADRs. Hospitalization was described by 1 patient following a combination of 2 included GI-ADRs: oral pain and breath odor. This patient also reported tooth disorder. No further information about hospitalization was described and the exact cause of hospitalization remains unclear. Patients in the Dutch Biologic Monitor contacted an HCP for 24 ADRs (67%), which was a medical specialist for 15 of these ADRs (63%; Table 3). HCP contact for ADRs included abdominal pain (n = 5), diarrhea (n = 4), nausea (n = 3), and oral issues (n = 3).

Drug discontinuation. ETN discontinuation was reported by 1 patient who switched to ADA due to upper abdominal pain. The symptoms disappeared after switching. Prior to using ETN, this patient had used certolizumab pegol without experiencing GI-ADRs. Another patient with upper abdominal pain mentioned that ETN will be withdrawn in the future because of a combination of aggravating abdominal pain (a reported ADR) and aggravating rheumatic complaints (no ADR).

Dose adjustment. ETN dose adjustment was reported for 4 GI-ADRs by 4 patients: 2 reports of GI pain, 1 stomatitis, and 1 nausea. The ETN administration frequency was adjusted in 2 patients reporting GI pain, which was effective for 1 patient. The patient for whom the adjusted frequency was not effective was eventually referred to a gastroenterologist. The patient reporting stomatitis recovered after temporary withdrawal and treatment with unknown antibiotics. Stomatitis recurred after 2 years, and the patient recovered after 3 weeks following diet adjustments and improved oral hygiene. The patient with nausea recovered after adjusting the time of administration to the evening.

Treatment of GI-ADRs. Treatment of the ADR was reported for 8 GI-ADRs by 5 patients. A patient with GI pain resulting in vomiting described effective treatment with metoclopramide and dose reduction of concomitant sulfasalazine (SSZ). A patient with diarrhea described effective treatment with psyllium fibers. A patient with constipation and abdominal pain described effective treatment with laxatives and diet adjustments. A patient with rectal bleeding described improvement after using hemorrhoid ointment. A patient with breath odor, oral pain, and chest pain received dental treatment and was also effectively treated with pantoprazole since the general practitioner of this patient suspected an esophageal issue for the symptom of breath odor combined with chest pain.

Other information in patient reports. A total of 15 (60%) patients described that they acted on their own initiative following 23 GI-ADRs (64%). These actions varied from adjusting diet or

improving dental care to altering injection time, changing injection site, and trying different over-the-counter drugs.

A patient reporting nausea after every ETN and methotrexate (MTX) administration described improvement after MTX dose reduction, adjusting the order of administration and food intake in between administering both drugs. Three patients described that they switched to another biologic during participation for reasons other than a GI-ADR. One of these patients recovered from nausea after switching to unknown therapy and a patient with oral blood blisters improved from this ADR after switching to rituximab. Another patient described improvement in diarrhea after skipping an ETN dose for other reasons.

The patient reporting CD also reported oral aphthous ulcers as an ADR and mentioned this was probably related to CD, which was was diagnosed 3 years after ETN start. The patient switched to IFX and recovered from oral aphthous ulcers. CD improved after switch, but the patient was not in full remission 1 year after the switch.

Burden of GI-ADRs. The mean burden score of all 36 GI-ADRs was 2.6 (SD 0.8) on a scale from 1 (no burden) to 5 (very high burden). Patients elucidated this GI-ADR burden score with various explanations, including affecting the mood and leading to insecurity, anxiety, or a feeling of loss of control. Patients also described that GI-ADRs resulted in sleep disturbance or influenced daily life and led to avoiding leaving the house.

HCP-registered GI-ADRs in the DREAM registries. Most GI-ADRs in the registries were general GI symptoms, similar to the patient-reported GI-ADRs (Table 2). Out of 11 GI-ADRs, 5 GI-ADRs (45%) developed within 5 months after start. ETN was discontinued for 8 GI-ADRs in 6 patients (Table 4): diarrhea (5 ADRs), nausea, constipation, and abdominal pain. Patients recovered from the GI-ADR in 10 cases, including the GI-ADRs leading to ETN discontinuation. Three of these patients did not use combination therapy. The outcome of 1 ADR concerning rectal cramps is unknown. Recurrence of nausea and diarrhea was reported for 1 patient when ETN was later restarted. This patient used MTX concomitantly. In addition to ETN, MTX was also suspected to cause nausea in 1 patient. In 3 cases of diarrhea, the patient had experienced diarrhea prior to ETN use with SSZ or leflunomide (LEF). A patient with abdominal pain had collagenous colitis with variable activity, which had been diagnosed before ETN was started. This patient later also experienced abdominal pain during use of LEF. It is unknown if the abdominal pain during ETN use was related to collagenous colitis.

The Naranjo Probability Scale was probable in 2 GI-ADRs and possible in 9 GI-ADRs. The probable ADRs were nausea and diarrhea which recurred after rechallenge with ETN.

Frequency of reported GI-ADRs associated with ETN and ADA. Patients reported GI-ADRs of ETN in the Dutch Biologic Monitor with a frequency of 8.7%, and GI-ADRs of ADA with a frequency of 5.3% (Table 5). The frequency of GI-ADRs associated with ETN in the DREAM registries was 2.8% and the frequency of GI-ADRs associated with ADA was 4.7%. The difference in frequency of GI-ADRs between ETN and ADA was not statistically significant in the Dutch Biologic Monitor ($P = 0.07$) nor in the DREAM registries ($P = 0.16$). The incidence of GI-ADRs attributed to ADA in the DREAM registries was 14.0 ADRs per 1000 PY. This was not statistically significantly different from 7.1 GI-ADRs per 1000 PY attributed to ETN ($P = 0.09$). One GI-ADR of ADA concerning the same patient was reported in both the DREAM registries and the Dutch Biologic Monitor.

Table 4. Profile of HCP-reported GI-ADRs associated with etanercept.

	GI-ADRs in DREAM Registries (11 ADRs)
No. of ADRs with action taken	
Discontinuation	8 (73)
Dose reduced	0
Dose not changed	3 (27)
No. of ADRs with outcome	
Recovered	10 (91)
Recovered with sequel	0
Recovering	0
Not recovered	0
Unknown	1 (9)
No. of serious ADRs	0
Naranjo Probability Scale	
Definite	0
Probable	2 (18)
Possible	9 (82)
Doubtful	0

Values are expressed as n (%). ADR: adverse drug reaction; GI-ADR: gastrointestinal ADR; DREAM: Dutch Rheumatoid Arthritis Monitoring; HCP: healthcare professional.

DISCUSSION

In this study, we describe previously unknown GI-ADRs of ETN treatment for inflammatory rheumatic diseases. Both patient and HCP reports mostly concerned GI symptoms such as diarrhea, nausea, and abdominal pain. Many reported GI-ADRs leading to ETN dose adjustment or discontinuation, HCP contact, and treatment of the ADR.

Table 5. Frequency of patient-reported (Dutch Biologic Monitor) and HCP-reported (DREAM registries) GI-ADRs associated with ETN and ADA for inflammatory rheumatic diseases.

Patients	ETN	ADA	*P*
Dutch Biologic Monitor, n = 757			
unique patients	n = 416	n = 360	
	8.7%	5.3%	
	(36/416)	(19/360)	0.07
DREAM Registries, n = 724			
unique patients	n = 399	n = 486	
	2.8%	4.7%	
	(11/399)	(23/486)	0.16

ADA: adalimumab; DREAM: Dutch Rheumatoid Arthritis Monitoring; ETN: etanercept; GI-ADR: gastrointestinal adverse drug reactions; HCP: healthcare professional.

We compared GI-ADR occurrence of ETN with ADA since both TNFi are widely used in the Netherlands and GI-ADRs are included in the European product label of ADA but not in that of ETN.[2,4] This comparison provides an impression of the extent to which GI-ADRs were attributed to both TNFi and we found a similar frequency of GI-ADRs reported for ETN and ADA in both patient and HCP reports. This is remarkable since GI-ADRs had previously not been described in adults using ETN, except for several cases of IBD.[6,7,26,27] The high frequency of patient-reported GI-ADRs (8.7%) in relation to the frequency of HCP-reported GI-ADRs (2.8%) of ETN is also surprising because we did not observe a similar discordance with ADA. However, we could not directly compare data from the Dutch Biologic Monitor with data from the DREAM registries due to differences in design. Since GI-ADRs are included in the European product label of ADA and are not included in that of ETN, HCPs may recognize GI-ADRs more regularly with ADA treatment than with ETN treatment and therefore might not always attribute GI complaints to ETN.

The mechanism by which ETN may cause GI-ADRs remains unknown. ETN has been demonstrated to modify gut microbial communities, which could be involved in causing GI symptoms, even though these alterations in gut microbiota were beneficial for RA-associated gut dysbiosis.[28] Some GI complaints could also be symptoms of an infection. One patient reported CD that improved after a switch to IFX. Even though the exact mechanism is uncertain, ETN may unmask underlying IBD in predisposed patients or induce IBD by increased inflammatory cytokine production.[7,27,29] IBD as a possible ADR of ADA or IFX has also been suggested, but an increased risk has not been demonstrated in literature, whereas an increased risk of IBD has been described for ETN.[30,31]

Despite a causality assessment of all GI-ADR reports, a limitation of this study is that we cannot confirm a causal relationship between ETN and the reported GI-ADRs. Although the included GI-ADRs were actively registered and verified by HCPs or were explicitly attributed as an ADR of ETN by patients, concomitant medication, an underlying infection, or the underlying disease could have affected the reported complaints.[32,33] Twelve out of 26 patients (46%) in the Dutch Biologic Monitor and 2 out of 9 patients (22%) in the DREAM registries used MTX as combination therapy, for which GI-ADRs are common.[34] One patient described that the GI-ADR improved after dose reduction of MTX, suggesting a role of MTX in the occurrence of the GI-ADR in this specific case. In another reported GI-ADR, MTX was also suspected to cause the ADR in addition to ETN. However, 28% of the patients with GI-ADRs in the Dutch Biologic Monitor and 44% of the patients with GI-ADRs in the DREAM registries did not use combination therapy. Half of these patients in the DREAM registries and 14% of these patients in the Dutch Biologic Monitor recovered after ETN discontinuation, indicating a relationship between the use of ETN and the incurred GI complaints. Additionally, we found a probable or possible association for all GI-ADR reports of ETN using the Naranjo Probability Scale.

The results of this study contribute to unmasking the ADR profile of ETN by using real-world data, which included both patient-reported and clinically verified HCP-registered data. Including patient-reported data is a strength because the assessment of questionnaires with patient-reported data contributes to a better understanding of the patient's experience and the consequences of these GI-ADRs. These patient-reported outcomes also provide us with more knowledge about the course of GI-ADRs. Patients, for example, reported a pattern of recurring GI-ADRs after every ETN administration—information which we did not capture in HCP reports and which may be valuable information for other or future ETN users. Therefore, systematically questioned patient-reported ADR experiences should be included more often in assessing the ADR profile of treatment options in inflammatory rheumatic diseases. Unfortunately, we were not able to compare GI-ADR frequencies between HCP-reported and patient-reported data because of the differences in design between the 2 data sources. This would be a valuable comparison for future research. However, with our study we demonstrated that patient-reported data on ADRs can complement HCP-reported data.

We described the GI-ADR profile registered by both patients and HCPs. The described actions, course, and burden by patients are considerable, and clinicians should be alert toward GI-ADRs in patients using ETN. Knowledge about these previously unknown ADRs can facilitate early recognition and allow improved communication with patients. Not recognizing ETN-associated GI-ADRs may delay ETN discontinuation or may initiate unnecessary treatment of GI complaints before switching to other, better-tolerated treatment.

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