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Alimentary Tract

Incidence of suboptimal response to tumor necrosis factor antagonist therapy in inflammatory bowel disease in newly industrialised countries: The EXPLORE study ☆,☆☆

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ABSTRACT

Background: Incidence of inflammatory bowel disease (IBD) is increasing in newly industrialised countries (NICs); however, data on suboptimal response to anti-tumor necrosis factor (anti-TNF) agents are limited.
Objectives: To assess incidence and indicators of suboptimal response to first anti-TNF therapy in IBD patients in NICs.
Methods: A chart review was conducted in ten countries from Asia-Pacific (APAC), Latin America (LatAm), and Russia and the Middle East (RME) regions among patients diagnosed with ulcerative colitis (UC) or Crohn's disease (CD), initiating anti-TNF therapy in 2010–2015. The cumulative incidence of suboptimal response to anti-TNF therapy was assessed using the following indicators: dose escalation or discontinuation, augmentation with non-biologic therapy, IBD-related hospitalization, or surgery.
Results: The study included 1,674 patients (570 UC; 1,104 CD). At 24 months, 32.9% of UC (APAC: 45.1%; LatAm: 38.2%; RME: 23.8%) and 41.2% of CD patients (APAC: 54.1%; LatAm: 42.5%; RME: 29.5%) had experienced suboptimal response. The most frequent first indicator was non-biologic therapy augmentation in LatAm (41.7%), IBD-related hospitalization in RME (UC: 50.7%; CD:37.3%) and in APAC for CD (39.1%), and anti-TNF discontinuation in APAC for UC (38.3%).
Conclusion: Suboptimal response to anti-TNF agents is common in IBD patients in NICs. Observed regional differences in the incidence and indicators may reflect local practice and anti-TNF restrictions in IBD management.
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1. Introduction

Inflammatory bowel disease (IBD) is known to be prevalent in Western countries. However, recent studies show a pattern of rising incidence and prevalence across the newly industrialised countries (NICs) – Asia-Pacific (APAC), Latin American (LatAm) and Russia and the Middle East (RME) regions – most likely related to environmental changes, urbanization and lifestyle alteration, as well as increased disease awareness and diagnosis.[1-6]

Anti-tumor necrosis factor (anti-TNF) agents were introduced over the past two decades and have proved to be effective in inducing and maintaining remission in moderate-to-severe UC and CD patients. However, 12–22% of ulcerative colitis (UC) and 21–31% of Crohn's disease (CD) patients do not respond to anti-TNF induction therapy (primary non-response [PNR]). Furthermore, 49–59% of UC and 23–64% of CD patients lose response over time (secondary loss of response [SLOR]).[7-9] Consequently, patients treated with anti-TNF agents may require anti-TNF dose optimization (including escalation of dose and/or frequency), discontinuation and/or initiation of another biologic agent (switch/swap out of class), non-biologic therapy augmentation, or surgery, all of which may be considered as indicators of suboptimal response to the therapy.[9,10]

Data on anti-TNF treatment patterns and suboptimal response among IBD patients outside of Europe and North America are scarce. Although there seems to be a consensus across the NICs on the optimal therapeutic pathway for IBD patients (aligned with international guidelines), recent publications have highlighted the complexity of accurately applying these guidelines in clinical practice due to limitations in treatment availability, access and reimbursement.[3-6,11,12] The EXPLORE study aimed to describe the incidence and indicators of suboptimal response to anti-TNF therapy in UC and CD patients in real-world clinical practice in NICs within APAC, LatAm, and RME regions.

2. Methods

2.1. Design and data collection

This study was designed as a multinational, multicentre, retrospective medical chart review of adult (≥18 years) patients diagnosed with UC or CD, treated (or previously treated) in IBD-specialised centres, and who initiated anti-TNF therapy (index date) between 01 March 2010 and 01 March 2015 (eligibility period). The observational period ranged from two years (for patients who discontinued index therapy within two years of the index date) to up to five years (for those who continued therapy beyond two years) post-index, unless the patient died. IBD-specialised centres from ten NICs were included: Argentina, Colombia, Mexico (LatAm); Russia, Saudi Arabia, Turkey (RME); China, Singapore, South Korea, and Taiwan (APAC). Patients diagnosed with intermediate/unspecified type of IBD; were part of an IBD-related clinical trial during the observational period; received an anti-TNF agent for any non-UC or non-CD condition or outside of the labelled dosing regimen; had undergone a total colectomy pre-index (UC patients only); or whose medical records were unavailable, were excluded. All potentially eligible patients at each site were screened and randomly selected for enrolment.

Data were abstracted from either paper or electronic medical records (dependent on country) by site personnel and entered into a secure electronic data capture form. Patient characteristics assessed at index included demographics, IBD history, comorbidities (including, but not restricted to, extra-intestinal manifestations [EIMs], direct consequences of IBD, chronic conditions caused by IBD treatments and infections), history of any type of non-biologic therapy and concomitant use of aminosalicylates, corticosteroids and immunosuppressants, corticosteroid-dependence/intolerance status (based on clinician opinion), disease location, disease behavior (CD), and documented presence of complications (CD). Disease activity at index was based on the closest assessment, within six months pre-index, of any endoscopic measurement (Mayo endoscopic subscore and Simple Endoscopic Score for CD) if available, or of full or partial Mayo assessment (UC), CD Activity Index (CDAI), Harvey Bradshaw Index (HBI; for CD) or Physician Global Assessment. Biochemical activity was based on the closest assessment within six months pre-index for C-reactive protein (CRP) (active if ≥5 mg/l), albumin (active if <3.5 g/dl) or fecal calprotectin (active if ≥250 mg/kg).

The study was conducted in accordance with local regulatory and ethical committee approval of each country (including patient written informed consent, where required). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Study outcomes and statistical considerations

Suboptimal response was defined as experiencing at least one of the following indicators at any time during the observational period:

- **Anti-TNF dose escalation:** any increase in dose and/or frequency of anti-TNF therapy occurring more than four months after initiation (to allow for induction period adjustments) for reasons related to non-response.
- **Augmentation with non-biologic therapy:** initiating or increasing the dose and/or frequency of a concomitant non-biologic therapy (aminosalicylates, immunosuppressants, corticosteroids) for reasons related to non-response.
- **Discontinuation of anti-TNF therapy:** for reasons related to non-response (e.g. discontinuation due to reimbursement issues or adverse events were not considered), including switching to another anti-TNF agent (within two months of discontinuation).
- **IBD-related surgery:** colectomy, ileocolectomy, ostomy (colostomy or ileostomy), fistula repair (CD only), abscess repair (CD only), or strictureplasty (CD only).
- **IBD-related hospitalization:** for admission reasons related to non-response/disease worsening and with stay ≥3 days (except for diagnostic procedure or gastrointestinal [GI] test in Russia: ≥8 days).

Additional outcomes included PNR (defined as suboptimal response occurring within four months of index), SLOR (defined as suboptimal response occurring more than four months after index, among patients who did not experience PNR), anti-TNF therapy discontinuation (in general, regardless of the reason for discontinuation), and predictors of suboptimal response.

Patients were stratified by IBD condition (UC/CD) and by geographical region. The descriptive statistics included proportions for categorical variables, mean ± standard deviation (SD), median and interquartile range (IQR) for continuous variables. The Kaplan-Meier method was used to assess the cumulative incidence (CI) of suboptimal response and of anti-TNF discontinuation; patients were censored at the end of the observation period or, for suboptimal response analysis only, at treatment discontinuation (due to reasons unrelated to response such as adverse event or reimbursement), and a log-rank test was used for group comparison. A proportional hazards Cox model was used to describe the relationship between potential predictors and suboptimal response occurrence over time. Potential predictors included patient demographics, medical/treatment history, disease severity and activity characteristics at index. All covariates associated with suboptimal response with a level of significance of 20% (p-value<0.20) in univariate models were retained for the multivariable model.

3. Results

3.1. Demographic and clinical characteristics at index

The study included 1674 first-line anti-TNF patients, consisting of 570 UC (APAC: 30.4%; LatAm: 17.4%; RME: 52.3%) and 1104 CD patients (APAC: 45.0%; LatAm: 7.8%; RME: 47.2%) (Table 1). Patients from South Korea and Russia represented 23.0% ($n=131$) and 35.3% ($n=201$), of the UC population, respectively, and patients from China and Russia represented 22.8% ($n=252$) and 24.0% ($n=265$) of the CD population, respectively (Suppl Table 1). The median (IQR) observational period was 45.9 months (33.9–60.1) in the UC and 46.5 months (34.5–60.1) in the CD population.

Most patients were male (UC: 56.1%; CD: 61.2%) and the mean (SD) age was 40.9 years (14.1) for UC and 34.3 years (12.4) for CD patients. Median (IQR) duration of IBD disease was 3.0 years [1.0–6.0] for UC and 1.0 years [0.0–4.0] for CD. A history of EIMs was documented in 39 (6.8%) UC and 61 (5.5%) CD patients (Suppl Table 2). Most UC patients presented with extensive disease ($n=314$, 60.2%). The majority of CD patients presented with ileocolonic disease ($n=573$, 57.9%), and one in five with upper GI disease ($n=189$, 19.1%). CD disease behavior was mostly non-stricturing and non-penetrating ($n=404$, 41.9%), and two in five patients presented with perianal disease ($n=381$, 39.5%). Active fistulae were present in 171 (19.5%) CD patients.

Among patients with documented disease activity (UC: $n=355$; CD: $n=509$), most presented with moderate (UC: 37.5%; CD: 56.4%) or severe (UC: 55.5%; CD: 26.7%) disease activity. Most UC and CD patients with documented biochemical markers (UC: $n=427$; CD: $n=821$) presented with active disease (UC: 59.7%; CD: 65.9%).

3.2. Anti-TNF and non-biologic treatment history at index

Among patients initiating anti-TNF therapy, most UC patients received infliximab (including biosimilar, 83.6%), followed by adalimumab (14.6%) and golimumab (1.9%) (Table 2). Infliximab was prescribed to 60.3% of CD patients, followed by adalimumab (38.0%) and certolizumab pegol (1.6%). Half of UC (54.6%) and CD (52.2%) patients had a documented history of non-biologic therapy (of any type) within two years pre-index; this proportion was lower in UC patients in LatAm (42.4%) and RME (48.0%) than in APAC (72.8%). Most patients were receiving concomitant non-biologic therapy (aminosalicylates, corticosteroids and immunosuppressants) at index (UC: 70.5%; CD: 61.2%), the most frequent concomitant therapy was aminosalicylates for UC and immunosuppressants for CD regardless of the anti-TNF agent received. Among patients with known status (UC: $n=455$; CD: $n=718$), corticosteroid-dependence was observed for 59.3% of UC and 36.2% of CD patients, whereas 13.4% and 8.4%, respectively, were corticosteroid-intolerant.

3.3. Incidence of suboptimal response to anti-TNF therapy

One-third of UC patients (33.0%, $n=188$) and 41.1% ($n=454$) of CD patients experienced suboptimal response to anti-TNF therapy during the observational period, with the highest suboptimal response observed in APAC (UC: 46.8%; CD: 50.9%) (Table 3).

The CI of suboptimal response at 12 and 24 months was 24.4% and 32.9%, respectively, in UC patients and 30.0% and 41.2%, respectively, in CD patients. Overall, the CI of suboptimal response was higher in CD versus UC patients (log-rank p-value<0.004) (Fig. 1); and in APAC versus LatAm and RME (log-rank p-value<0.001 for both UC and CD) (Fig. 2).

The CI of PNR was 13.6% in UC and 16.9% in CD patients and was notably higher in APAC (UC: 20.2%, log-rank p-value=0.012; CD: 26.5%, $p<0.001$) compared to other regions. Among patients without PNR, the CI of SLOR at 12 and 24 months was 12.6% and 22.3% in UC patients, respectively, and 15.8% and 29.2% in CD patients, respectively. SLOR CI was notably lower in RME (UC: 8.5%;14.8%, log-rank p-value<0.001; CD: 12.4%; 22.9%, $p<0.001$).

Among patients experiencing suboptimal response, the most common first indicator was IBD-related hospitalization for both UC and CD patients (UC: $n=62$; 33.0%; CD: $n=164$; 36.1%), but regional disparities were observed (Table 3). The most frequent first indicator was augmentation with non-biologic therapy in LatAm (UC: $n=15$; 41.7%; CD: $n=14$; 35.0%), IBD-related hospitalization in RME (UC: $n=36$; 50.7%; CD: $n=60$; 37.3%) and in APAC for CD ($n=99$, 39.1%), and discontinuation in APAC for UC ($n=31$, 38.3%).

3.4. Cumulative incidence of suboptimal response by documented history of non-biologic therapy within two years pre-index

The observed proportion of patients with documented non-biologic therapy history prior to anti-TNF initiation was lower than expected. To assess the impact of this potential gap of documentation on the observed incidence of suboptimal response (augmentation with non-biologic therapy being amongst the indicators), a sensitivity analysis described the CI of suboptimal response according to patients' documented history of non-biologic therapy (any type including immunosuppressants, corticosteroids, aminosalicylates, antibiotics and nutritional therapies) within two years prior to index.

The CI at 24 months post-index was higher in patients with a documented history of non-biologic therapy (UC: 42.0%; CD: 43.0%) than in patients with no documented history (UC: 22.3%; CD: 39.0%) (Suppl Figure 1); this difference was significant for UC but not CD (log-rank p-value at 60 months: UC, $p<0.001$; CD, $p=0.128$). The difference was particularly marked in RME (UC: $p<0.001$; CD: $p=0.004$) and in LatAm for UC patients (UC: $p=0.002$).

3.5. Cumulative incidence of anti-TNF treatment discontinuation by suboptimal response status and first indicator

To assess the impact of suboptimal response on anti-TNF treatment persistence, the CI of anti-TNF therapy discontinuation (due to any reason) was described by suboptimal response status (i.e. presence or absence of suboptimal response) and by first suboptimal response indicator. At 24 months after index, the CI of anti-TNF discontinuation in the absence versus the presence of suboptimal response was 11.7% vs. 38.4% in UC, respectively, and 18.7% vs. 26.6% in CD patients, respectively (log-rank p-value

Table 1
Demographics and clinical characteristics of UC and CD patients at index date.

	Ulcerative Colitis				Crohn's Disease			
	Overall (*N* = 570)	APAC (*N* = 173)	LatAm (*N* = 99)	RME (*N* = 298)	Overall (*N* = 1104)	APAC (*N* = 497)	LatAm (*N* = 86)	RME (*N* = 521)
Gender: Male (n,%)	320 (56.1)	106 (61.3)	48 (48.5)	166 (55.7)	676 (61.2)	350 (70.4)	48 (55.8)	278 (53.4)
Age, n								
Mean (SD)	40.9 (14.10)	46.8 (14.67)	41.1 (13.84)	37.5 (12.68)	34.3 (12.40)	33.5 (11.98)	40.1 (16.72)	34.1 (11.71)
Median (IQR)	39.0 (29.0–52.0)	47.0 (34.0–58.0)	40.0 (29.0–50.0)	35.0 (28.0–48.0)	31.0 (25.0–41.0)	30.0 (24.0–39.0)	33.0 (26.0–54.0)	31.0 (25.0–42.0)
Duration of IBD (years)								
Mean (SD)	4.3 (4.76)	4.2 (4.69)	5.7 (6.24)	3.9 (4.13)	3.1 (4.49)	2.8 (4.30)	3.6 (5.57)	3.2 (4.46)
Median (IQR)	3.0 (1.0–6.0)	3.0 (1.0–6.0)	4.0 (1.0–8.0)	3.0 (1.0–6.0)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	2.0 (0.0–4.0)
Missing	10	2	1	7	21	5	2	14
Any IBD-related hospitalization within 2 years pre-index (n,%)								
Yes	296 (56.3)	80 (47.6)	47 (51.1)	169 (63.5)	663 (65.8)	299 (63.3)	36 (44.4)	328 (72.1)
No	230 (43.7)	88 (52.4)	45 (48.9)	97 (36.5)	345 (34.2)	173 (36.7)	45 (55.6)	127 (27.9)
Unknown	44	5	7	32	96	25	5	66
Any IBD-related surgery since diagnosis (n,%)[a]								
Yes	2 (0.4)	1 (0.6)	1 (1.1)	0 (0.0)	242 (23.6)	105 (21.8)	21 (24.7)	116 (25.2)
No	528 (99.6)	161 (99.4)	94 (98.9)	273 (100.0)	785 (76.4)	376 (78.2)	64 (75.3)	345 (74.8)
Unknown	40	11	4	25	77	16	1	60
Disease location UC (n,%)								
Proctitis involvement	44 (8.4)	19 (11.8)	14 (14.7)	11 (4.1)	–	–	–	–
Left-sided involvement	164 (31.4)	57 (35.4)	29 (30.5)	78 (29.3)	–	–	–	–
Extensive involvement	314 (60.2)	85 (52.8)	52 (54.7)	177 (66.5)	–	–	–	–
Unknown	48	12	4	32	–	–	–	–
Disease location CD (n,%)								
Ileal with upper GI disease (L1)					55 (5.6)	26 (5.6)	2 (2.4)	27 (6.1)
Ileal without upper GI disease (L1)	–	–	–	–	173 (17.5)	77 (16.6)	17 (20.2)	79 (18.0)
Colonic with upper GI disease (L2)	–	–	–	–	32 (3.2)	19 (4.1)	1 (1.2)	12 (2.7)
Colonic without upper GI disease (L2)	–	–	–	–	156 (15.8)	71 (15.3)	19 (22.6)	66 (15.0)
Ileocolonic with upper GI disease (L3)	–	–	–	–	102 (10.3)	65 (14.0)	4 (4.8)	33 (7.5)
Ileocolonic without upper GI disease (L3)	–	–	–	–	471 (47.6)	207 (44.5)	41 (48.8)	223 (50.7)
Unknown	–	–	–	–	115	32	2	81
Disease behavior CD (n,%)								
Non-stricturing, non-penetrating with perianal disease (B1)	–	–	–	–	139 (14.4)	84 (18.5)	6 (7.1)	49 (11.5)
Non-stricturing, non-penetrating without perianal disease (B1)	–	–	–	–	265 (27.5)	117 (25.8)	29 (34.5)	119 (27.9)
Stricturing with perianal disease (B2)	–	–	–	–	138 (14.3)	73 (16.1)	7 (8.3)	58 (13.6)
Stricturing without perianal disease (B2)	–	–	–	–	222 (23.0)	87 (19.2)	21 (25.0)	114 (26.7)
Penetrating with perianal disease (B3)	–	–	–	–	104 (10.8)	40 (8.8)	10 (11.9)	54 (12.6)
Penetrating without perianal disease (B3)	–	–	–	–	97 (10.1)	53 (11.7)	11 (13.1)	33 (7.7)
Unknown	–	–	–	–	139	43	2	94
Disease activity (n,%)[b]								
Normal	2 (0.6)	2 (1.4)	0 (0.0)	0 (0.0)	34 (6.7)	24 (9.6)	4 (10.0)	6 (2.7)
Mild	23 (6.5)	11 (7.7)	7 (11.7)	5 (3.3)	52 (10.2)	36 (14.5)	6 (15.0)	10 (4.5)
Moderate	133 (37.5)	54 (37.8)	22 (36.7)	57 (37.5)	287 (56.4)	151 (60.6)	18 (45.0)	118 (53.6)
Severe	197 (55.5)	76 (53.1)	31 (51.7)	90 (59.2)	136 (26.7)	38 (15.3)	12 (30.0)	86 (39.1)
Unknown	215	30	39	146	595	248	46	301
Biochemical activity (n,%)[c]								
Normal	172 (40.3)	84 (51.9)	28 (38.4)	60 (31.3)	280 (34.1)	157 (37.1)	16 (27.1)	107 (31.6)
Active disease	255 (59.7)	78 (48.1)	45 (61.6)	132 (68.8)	541 (65.9)	266 (62.9)	43 (72.9)	232 (68.4)
Unknown	143	11	26	106	283	74	27	182

APAC: Asia-Pacific; CD: Crohn's Disease; IBD: Inflammatory Bowel Disease; GI: gastrointestinal; IQR: Interquartile Range; LatAm: Latin America; RME: Russia-Middle East; SD: Standard Deviation; UC: Ulcerative Colitis.

[a] IBD-related surgeries including total proctocolectomy, total and partial colectomy, ileocolonic bowel resection, small bowel resection, strictureplasty, perianal surgery, ileostomy reversal.

[b] Disease activity primarily based on the closest assessment within 6 months prior to the index date of any endoscopic measurement if available, or of any documented measurement of full Mayo (UC; 0–2 Normal, 3–5 Mild, 6–10 Moderate, 11–12 Severe), partial Mayo (UC; 0–1 Normal, 2–4 Mild, 5–7 Moderate, >7 Severe), CDAI (CD; <150 Normal, 150–219 Mild, 220–450 Moderate, >450 Severe), HBI (CD; 0–4 Normal, 5–7 Mild, 8–16 Moderate, = >16 Severe) or PGA (0 Normal, 1 Mild, 2 Moderate, 3 Severe).

[c] Biochemical activity based on the closest assessment within 6 months prior to the index date of C-reactive protein (active if ≥5 mg/l), albumin (active if <3.5 g/dl) or fecal calprotectin (active if ≥250 mg/kg).

at 60 months: <0.001 for UC and CD, Suppl Figure 2). At 12 months post the first indicator of suboptimal response, the CI of anti-TNF discontinuation was 14.4% in CD patients experiencing an IBD-related surgery as a first indicator, and 24.6% in UC and 16.8% in CD patients experiencing an IBD-related hospitalization as a first indicator (Suppl Table 3).

Table 2
Anti-TNF and non-biologic treatment history at index date.

	Ulcerative Colitis				Crohn's Disease			
	Overall (*N* = 570)	APAC (*N* = 173)	LatAm (*N* = 99)	RME (*N* = 298)	Overall (*N* = 1104)	APAC (*N* = 497)	LatAm (*N* = 86)	RME (*N* = 521)
First line of anti-TNF therapy (n,%)								
Infliximab	466 (81.8)	153 (88.4)	63 (63.6)	250 (83.9)	660 (59.8)	377 (75.9)	26 (30.2)	257 (49.3)
Adalimumab	83 (14.6)	10 (5.8)	35 (35.4)	38 (12.8)	420 (38.0)	114 (22.9)	58 (67.4)	248 (47.6)
Golimumab	11 (1.9)	0 (0.0)	1 (1.0)	10 (3.4)	–	–	–	–
Certolizumab pegol	–	–	–	–	18 (1.6)	0 (0.0)	2 (2.3)	16 (3.1)
Infliximab biosimilar	10 (1.8)	10 (5.8)	0 (0.0)	0 (0.0)	6 (0.5)	6 (1.2)	0 (0.0)	0 (0.0)
Documented history of non-biologic therapy within 2 years pre-index date[a]	311 (54.6)	126 (72.8)	42 (42.4)	143 (48.0)	576 (52.2)	276 (55.5)	45 (52.3)	255 (48.9)
Aminosalicylates	211 (37.2)	82 (47.4)	34 (34.3)	95 (31.9)	302 (27.4)	177 (35.6)	23 (26.7)	102 (19.6)
Corticosteroids	192 (33.7)	66 (38.2)	21 (21.2)	105 (35.2)	272 (24.6)	130 (26.2)	15 (17.4)	127 (24.4)
Immunosuppressants	158 (27.7)	63 (36.4)	28 (28.3)	67 (22.5)	387 (35.1)	159 (32.0)	28 (32.6)	200 (38.4)
Concomitant non-biologic therapy[b]	402 (70.5)	116 (67.1)	76 (76.8)	210 (70.5)	676 (61.2)	279 (56.1)	54 (62.8)	343 (65.8)
Aminosalicylates	272 (47.7)	77 (44.5)	70 (70.7)	125 (41.9)	367 (33.2)	191 (38.4)	33 (38.4)	143 (27.4)
Corticosteroids	187 (32.8)	52 (30.1)	21 (21.2)	114 (38.3)	264 (23.9)	97 (19.5)	17 (19.8)	150 (28.8)
Immunosuppressants	213 (37.4)	56 (32.4)	44 (44.4)	113 (37.9)	418 (37.9)	139 (28.0)	30 (34.9)	249 (47.8)
Corticosteroid dependence status								
Intolerant	61 (13.4)	21 (14.5)	4 (4.5)	36 (16.3)	60 (8.4)	24 (9.3)	0 (0.0)	36 (9.4)
Dependent	270 (59.3)	64 (44.1)	61 (68.5)	145 (65.6)	260 (36.2)	80 (31.1)	23 (28.8)	157 (41.2)
Not dependent or intolerant	124 (27.3)	60 (41.4)	24 (27.0)	40 (18.1)	398 (55.4)	153 (59.5)	57 (71.3)	188 (49.3)
Unknown	115	28	10	77	386	240	6	140

APAC: Asia-Pacific; LatAm: Latin America; RME: Russia-Middle East; TNF: tumor necrosis factor.
[a] Any non-biologic therapy including immunosuppressants, corticosteroids, aminosalicylates, antibiotics and nutritional therapies.
[b] Non-biologic therapy including immunosuppressants, corticosteroids, aminosalicylates only.

Table 3
Overall frequency and cumulative incidence of suboptimal response to anti-TNF therapy in UC and CD patients.

	Ulcerative Colitis				Crohn's Disease			
	Overall (*N* = 570)	APAC (*N* = 173)	LatAm (*N* = 99)	RME (*N* = 298)	Overall (*N* = 1104)	APAC (*N* = 497)	LatAm (*N* = 86)	RME (*N* = 521)
Overall frequency of suboptimal response to anti-TNF therapy (n,%)	188 (33.0)	81 (46.8)	36 (36.4)	71 (23.8)	454 (41.1)	253 (50.9)	40 (46.5)	161 (30.9)
Cumulative incidence of suboptimal response (%)								
At 12 months	24.4	34.4	25.9	18.2	30.0	40.4	30.7	19.9
At 24 months	32.9	45.1	38.2	23.8	41.2	54.1	42.5	29.5
Cumulative incidence of PNR (%)[a]	13.6	20.2	11.4	10.5	16.9	26.5	10.8	8.6
Cumulative incidence of SLOR,n[b]	440	121	83	236	847	340	72	435
At 12 months (%)	12.6	17.8	16.4	8.5	15.8	18.9	22.4	12.4
At 24 months (%)	22.3	31.2	30.2	14.8	29.2	37.5	35.5	22.9
First indicator of suboptimal response (n,%)	188	81	36	71	454	253	40	161
Anti-TNF dose escalation	23 (12.2)	3 (3.7)	12 (33.3)	8 (11.3)	65 (14.3)	34 (13.4)	9 (22.5)	22 (13.7)
Augmentation with non-biologic therapy	57 (30.3)	25 (30.9)	15 (41.7)	17 (23.9)	108 (23.8)	68 (26.9)	14 (35.0)	26 (16.1)
Anti-TNF discontinuation including switch	45 (23.9)	31 (38.3)	5 (13.9)	9 (12.7)	42 (9.3)	18 (7.1)	4 (10.0)	20 (12.4)
IBD-related surgery	7 (3.7)	2 (2.5)	2 (5.6)	3 (4.2)	79 (17.4)	35 (13.8)	8 (20.0)	36 (22.4)
IBD-related hospitalization	62 (33.0)	20 (24.7)	6 (16.7)	36 (50.7)	164 (36.1)	99 (39.1)	5 (14.6)	60 (37.3)

APAC: Asia-Pacific; IBD: Inflammatory Bowel Disease; LatAm: Latin America; PNR: Primary non-response; RME: Russia-Middle East; SLOR: Secondary loss of response; TNF: tumor necrosis factor.
[a] Cumulative incidence at 4 months.
[b] Among patients who did not experience PNR and who are still on anti-TNF at 4 months.

3.6. Predictors of suboptimal response to therapy

In the Cox model for UC, documented hospitalization pre-index was significantly associated with a greater risk of suboptimal response (hazard ratio [HR] [95% CI]: 2.1 [1.4, 3.3], p-value<0.001) (Suppl Table 4). A similar result was observed for CD (HR [95% CI]: 1.4 [1.1, 1.9], p-value=0.008). In addition, UC corticosteroid-dependent patients had a greater risk of suboptimal response than patients who were not dependent nor intolerant (HR [95% CI]: 1.8 [1.1, 2.8]; p-value=0.016). CD patients with active disease at index, defined by biochemical markers, had a greater risk of suboptimal response than patients with normal markers (HR [95% CI]: 1.6 [1.2, 2.1]; p-value<0.001), and CD patients with stricturing disease had a greater risk of suboptimal response than patients with non-stricturing disease (HR [95% CI]: 1.5 [1.1, 2.1]; p-value=0.011). Among the other factors explored, it was noted that concomitant

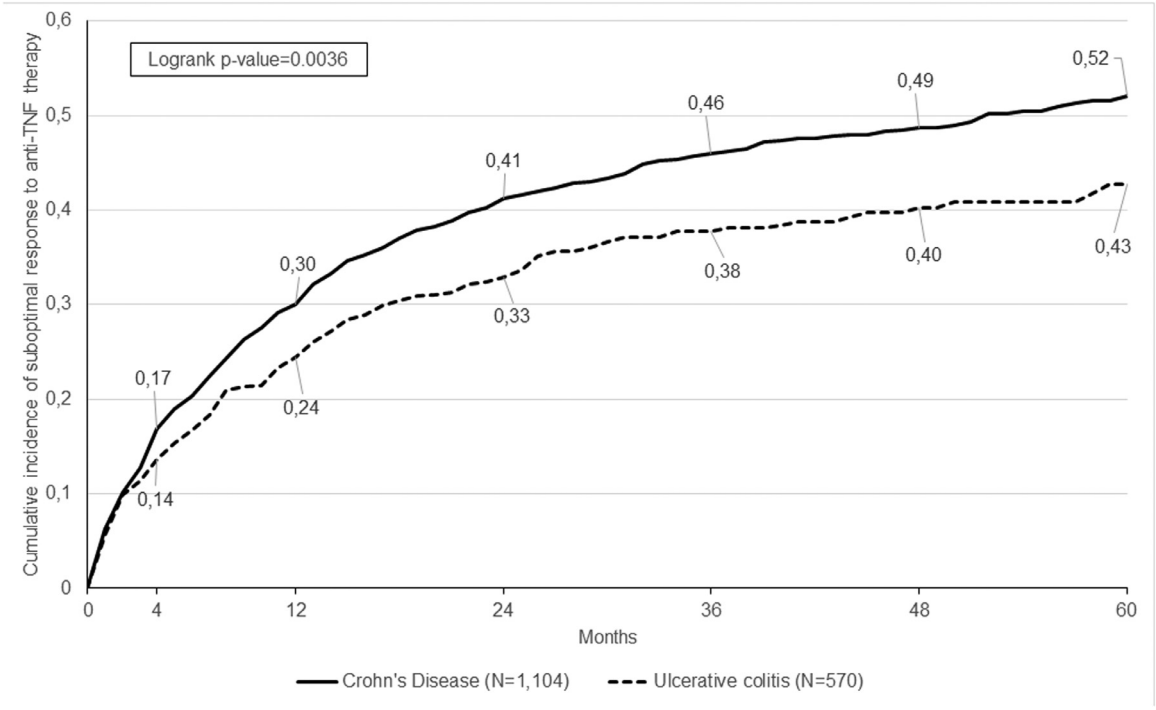


Fig. 1. Cumulative incidence of suboptimal response to first anti-TNF therapy in UC and CD patients.

non-biological therapy at anti-TNF therapy initiation was not significantly associated with the risk of suboptimal response.

4. Discussion

The EXPLORE study is, to the authors' knowledge, the first to comprehensively report on IBD patients initiating anti-TNF therapy in NICs and to describe treatment patterns and suboptimal response to first anti-TNF therapy in real-world clinical practice. Suboptimal response was common in this heterogenous IBD patient cohort, experienced by over one-third of patients within 24 months of anti-TNF initiation (increasing to 38% and 46% in UC and CD, respectively, after 36 months). Disparities were observed across countries and indications in the incidence of suboptimal response, and in the most frequent first suboptimal indicator, likely reflecting different IBD management practices across the countries.

The number of real-world studies in IBD patients initiating anti-TNF therapies (with larger cohort sizes) is limited, although two recent studies were conducted in this disease population in Western countries using similar indicators of suboptimal response.[13,14] The overall CI of suboptimal response in the EXPLORE study was lower than that observed in a US claims analysis (90% within 36 months of anti-TNF initiation for both UC and CD). However, several of the NICs (China, Taiwan, Singapore and Colombia) had a comparable CI of suboptimal response to that observed in a chart review study conducted in Canada and Europe (58% for UC and 64% for CD, within 24 months of anti-TNF initiation). Surprisingly, we identified a lower than expected frequency of non-biologic therapy prescriptions prior to anti-TNF therapy initiation, especially in LatAm and RME (where the incidence of suboptimal response to anti-TNF was lower), inconsistent with most clinical guidelines.[15-19] The assumption that this gap in documentation might have led to an underestimation of the incidence of suboptimal response in our study was supported by the higher CI of suboptimal response observed in patients with a documented history of non-biological therapy within two years prior to anti-TNF initiation versus those with no history on non-biologic use.

Some specificities of the IBD anti-TNF initiators population in NICs may also partly explain the lower incidence of suboptimal response as compared to Western countries. A recent survey conducted among IBD specialists in NICs highlighted that a large proportion of IBD patients eligible for biologics in IBD-specialised centres in APAC (median across physicians 20% of UC and 40% of CD) and in RME (median 20% of UC and 20% of CD) do not receive it.[20] This low coverage of anti-TNF therapies could be explained in countries such as Taiwan, Mexico and Russia, by the favouring of surgery as the first-line intervention for more severe IBD cases.[3-5] This risk-based approach may have led patients with a presumed higher risk of suboptimal response not to initiate anti-TNF therapy. Another possible factor could be the more benign course of the disease (caused by multiple genetic factors) in some patients from the NICs.[5] Furthermore, the observed disease duration was also markedly shorter than in Western cohorts, especially for CD, which may suggest less progressed disease at anti-TNF initiation.[14]

The observed regional differences in the rate of suboptimal response likely reflect local variations and restrictions in the utilization of anti-TNF therapies during the EXPLORE study observational period (2010–2015). In Taiwan, anti-TNF agents were not indicated for UC patients, and in CD, reimbursement restrictions were in place for biologic therapies, with treatment limited to a one-year cycle.[4] In South Korea, similar restrictions were in place for infliximab (in UC until October 2010,) and for adalimumab (in CD until May 2011 and UC until July 2013).[1,12] In Russia, the incidence of suboptimal response was low and mainly triggered by IBD-related hospitalisations, which could reflect the lack of insurance coverage for outpatient care.[6]

The overall CI of anti-TNF dose escalation and discontinuation of anti-TNF therapy indicators of suboptimal response, which were the two most frequent indicators in the aforementioned European and Canadian chart review study, was low in the current study.[14] The lower rate of anti-TNF dose escalation in APAC and RME could be explained by reimbursement restrictions, in South Korea; for example, dose escalation of infliximab (above 5 mg/kg)

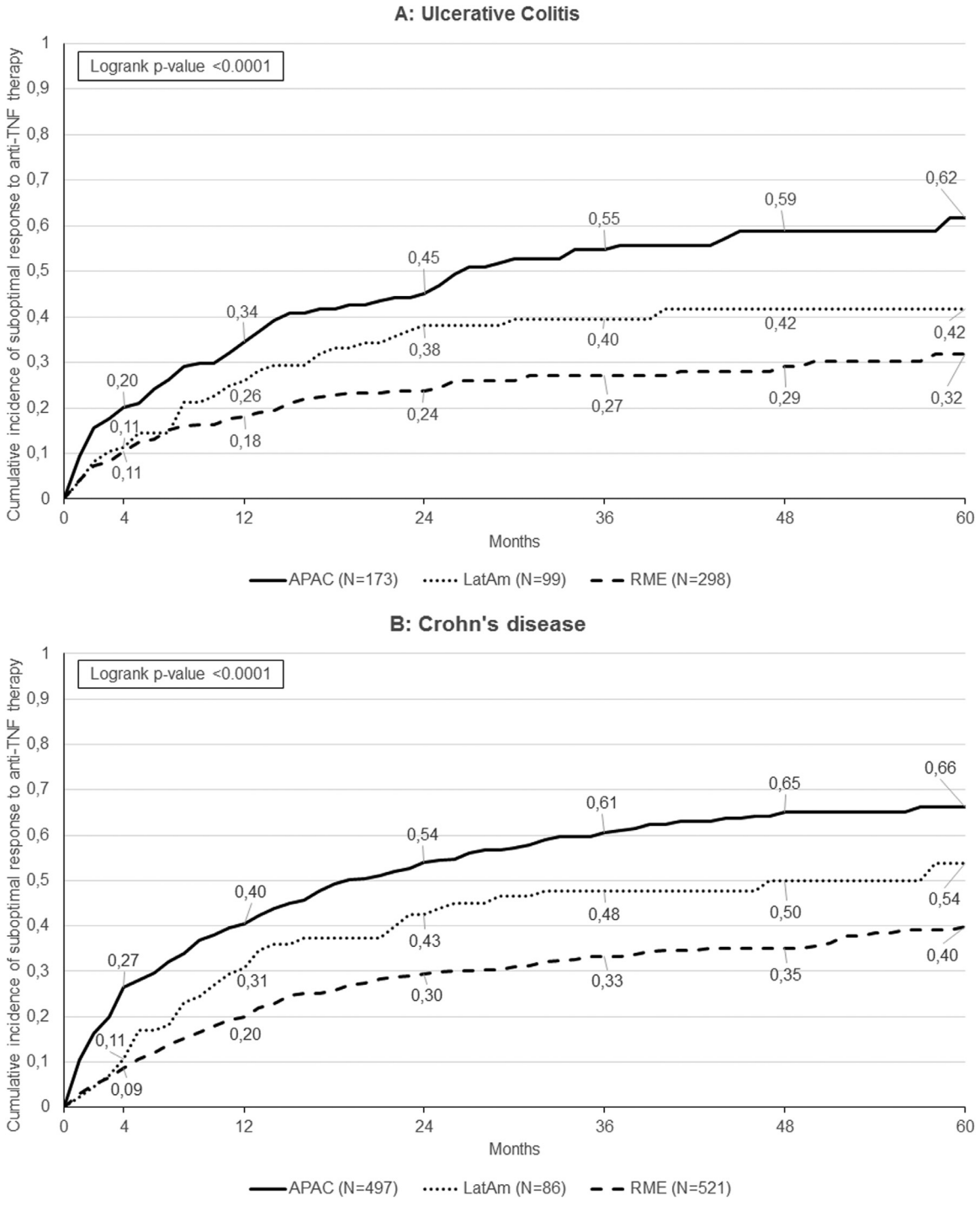


Fig. 2. Cumulative incidence of suboptimal response to first anti-TNF therapy by region in UC (Panel A) and CD patients (Panel B).

was not reimbursed in CD until April 2013.[21] Reimbursement challenges are unlikely to have been restricted to these two countries. In the aforementioned survey, patient affordability and complex reimbursement process were among the most commonly reported barriers to anti-TNF therapy prescription across all NICs surveyed.[20] Site infusion capacity challenges associated with the administration of anti-TNF's in some centres in NICs may also have delayed or prevented regimen intensification.[20]

The lower rate of anti-TNF therapy discontinuation could be due to the lack of biologic alternatives available during the study period. For example, only one anti-TNF agent was available for CD in China (infliximab) and Taiwan (adalimumab), and a second anti-TNF agent only became available for UC in 2013 in Russia and in 2012 in Saudi Arabia. The EXPLORE study demonstrated that a substantial proportion of patients continued to receive their initial anti-TNF therapy, despite the occurrence of serious events such as surgeries and hospitalisations. Determining whether switching to another anti-TNF therapy or out of class is the most appropriate therapeutic option in patients with PNR or SLOR, and thus avoid severe outcomes such as surgeries, should ideally be based on results of therapeutic drug monitoring, which was unavailable in the NICs at the time of the EXPLORE study.[16,18,22] Thus, if available,

patients may have benefited from receiving or switching to alternative biologic therapies earlier on.[15-19]

Through the analysis of potential predictors, the EXPLORE study also aimed to identify patient subgroups at higher risk of suboptimal response to first anti-TNF therapy, who could therefore benefit from alternative treatment options. The study highlighted that CD patients with active biochemical disease activity or stricturing disease, UC patients deemed corticosteroid-dependent, and UC and CD patients hospitalised for IBD-related complications in the two years prior to anti-TNF therapy initiation, would be more likely to experience suboptimal response. A similar retrospective study in Canada and Europe reported that the absence of rectal bleeding and moderate/severe endoscopic scores for UC, higher CRP and higher number of liquid or soft stools per day for CD at initiation were associated with a higher risk of suboptimal response.[23] Most studies assessing the predictors of suboptimal response identified factors of non-remission measured after the anti-TNF initiation (i.e. antibodies formation, anti-TNF treatment regimens, concomitant use of non-biologics).[15,16,18,24] It may be beneficial for physicians to identify early, the patients exhibiting these high-risk profiles for suboptimal response in order to explore alternative biologic therapies which may provide better treatment outcomes. Further research is warranted, through large prospective cohort studies, to identify patient profiles at high-risk of suboptimal response to anti-TNF therapy and better guide therapeutic decisions to a patient-tailored approach.

Inherent limitations of the retrospective design of the EXPLORE study could have impacted the observed incidence of suboptimal response. Information was collected from medical records from which data necessary to identify cases of suboptimal response may likely have been incomplete (e.g. reasons for discontinuation, dose escalation, hospitalization). In addition, in some countries such as Russia, patient medical history and data collected during visits to local practitioners, such as non-biological therapy prescriptions, might not have been transferred to IBD centres due to the lack of electronic data transmission.[6]

In conclusion, this study found that suboptimal response to first anti-TNF therapy in real-world clinical practice in IBD is common in NICs, and in some NICs may be as common as observed in Western countries. However, the true extent of suboptimal response may be greater than reported here due to documentation gaps on suboptimal response indicators, especially non-biologic therapies. The findings of this study add to the current evidence-base on the unmet need associated with anti-TNF therapies, where a risk-based approach to targeting potential responders (and non-responders), an earlier recognition of treatment failures to allow timely alternative treatment decisions, revised reimbursement policies and/or new therapeutic options may improve long-term patient outcomes in IBD in NICs.

Declaration of Competing Interests

Qasim M Rana Khan, Olga Fadeeva and Dirk Demuth are employees of Takeda Pharmaceuticals Company Ltd. Morgane Guennec and Cecilia Sison are employees of IQVIA, which was funded by Takeda Pharmaceuticals Company Ltd to conduct this study. Jesús K. Yamamoto-Furusho is an advisory committee/board member for Takeda Pharmaceuticals Company Ltd; has received honoraria from AbbVie, Takeda, Janssen, Farmasa, Ferring, Alfasigma, Hospira, UCB, Danone, Almirall and Pfizer as a speaker, key opinion leader, and member of national and international advisory boards; has received research funds from Bristol, Shire, Pfizer and Takeda and former President of the Pan American Crohn's and Colitis organisation (PANCCO). Othman Al Harbi is a consultant or advisory committee/board member for AbbVie, Janssen, Pfizer and Takeda Pharmaceuticals Company Ltd. Alessandro Armuzzi is a consultant or advisory/board member for AbbVie, Allergan, Amgen, Biogen, Celgene, Celltrion, Ferring, Hospira, Janssen, Lilly, MSD, Mundipharma, Mylan, Pfizer, Roche, Samsung Bioepis, Sofar, and Takeda Pharmaceuticals Company Ltd; has received lecture fees from AbbVie, Amgen, AstraZeneca, Chiesi, Ferring, Hospira, Janssen, Medtronic, MSD, Mitsubishi Tanabe, Mundipharma, Nikkiso, Otsuka, Pfizer, Samsung Bioepis, Takeda, Tigenix, and Zambon; and research funding from MSD, Pfizer and Takeda. Webber Chan indicated no relevant financial relationships. Enrique Ponce de Leon is a consultant or advisory/board member for AbbVie, Janssen and Takeda Pharmaceuticals Company Ltd. Jiaming Qian is an advisory committee/board member for Takeda Pharmaceuticals Company Ltd. Marina Shapina is an advisory committee/board member for Takeda Pharmaceuticals Company Ltd. Murat Toruner is an advisory committee/board member for Takeda Pharmaceuticals Company Ltd; has received consulting fees from AbbVie Turkey, MSD Turkey, Janssen Turkey, Takeda Turkey and has received lecture fees from AbbVie Turkey, MSD Turkey, Janssen Turkey, Takeda Turkey, Ferring Turkey and UCB Turkey. Chia-Hung Tu is an advisory committee/board member for Takeda Pharmaceuticals Company Ltd. Byong Duk Ye has received a research grant from Celltrion and Pfizer Korea; is a consultant or advisory/board member for AbbVie Korea, Celltrion, Chong Kun Dang Pharm., Daewoong Pharma., Ferring Korea, Janssen Korea, Kangstem Biotech, Kuhnil Pharm., Medtronic Korea, Shire Korea, Takeda Korea, IQVIA, Cornerstones Health, Robarts Clinical Trials Inc. and Takeda; has received lecture fees from AbbVie Korea, Celltrion, Ferring Korea, Janssen Korea, Shire Korea, Takeda Korea, and IQVIA.

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Supplementary materials

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References

[1] Kim ES, Kim WH. Inflammatory bowel disease in Korea: epidemiological, genomic, clinical, and therapeutic characteristics. Gut Liver 2010;4:1.
[2] Hafiz TA. Inflammatory Bowel Disease in Saudi Arabia: challenges and Perspectives. EC Microbiol 2019;15:217–26.
[3] Wei S-C, Chang T-A, Chao T-H, et al. Management of ulcerative colitis in Taiwan: consensus guideline of the Taiwan Society of Inflammatory Bowel Disease. Intest Res 2017;15:266.
[4] Wei S-C, Chang T-A, Chao T-H, et al. Management of Crohn's disease in Taiwan: consensus guideline of the Taiwan Society of Inflammatory Bowel Disease. Intest Res 2017;15:285–310.
[5] Yamamoto-Furusho J, Gutiérrez-Grobe Y, López-Gómez J, et al. The Mexican consensus on the diagnosis and treatment of ulcerative colitis. Revista de Gastroenterología de México (English Edition) 2018;83:144–67.
[6] Khalif IL, Shapina MV. Inflammatory bowel disease treatment in Eastern Europe: current status, challenges and needs. Curr. Opin. Gastroenterol. 2017;33:230–3.
[7] Allez M, Karmiris K, Louis E, et al. Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. J Crohns Colitis 2010;4:355–66.

[8] Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther 2011;33:987–95.
[9] Ma C, Huang V, Fedorak DK, et al. Outpatient Ulcerative Colitis Primary Anti-TNF Responders Receiving Adalimumab or Infliximab Maintenance Therapy Have Similar Rates of Secondary Loss of Response. J Clin Gastroenterol 2015;49:675–82.
[10] Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007;146:829–38.
[11] Nakase H, Keum B, Ye BD, et al. Treatment of inflammatory bowel disease in Asia: the results of a multinational web-based survey in the 2(nd) Asian Organization of Crohn's and Colitis (AOCC) meeting in Seoul. Intest Res 2016;14:231–9.
[12] Jang EJ, Ha JE, Im SG, et al. A Real-World Analysis of Prescribing Patterns and Non-persistence of Anti-TNFα Therapy for Inflammatory Bowel Disease. Clin Drug Investig 2019;39:625–30.
[13] Patel H, Lissoos T, Rubin DT. Indicators of suboptimal biologic therapy over time in patients with ulcerative colitis and Crohn's disease in the United States. PLoS ONE 2017;12:e0175099.
[14] Lindsay JO, Armuzzi A, Gisbert JP, et al. Indicators of suboptimal tumor necrosis factor antagonist therapy in inflammatory bowel disease. Dig Liver Dis 2017;49:1086–91.
[15] Roda G, Jharap B, Neeraj N, et al. Loss of response to anti-TNFs: definition, epidemiology, and management. Clin Transl Gastroenterol 2016;7:e135.
[16] Papamichael K, Gils A, Rutgeerts P, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. Inflamm Bowel Dis 2015;21:182–97.
[17] Danese S, Fiorino G, Reinisch W. causative factors and the clinical management of patients with Crohn's disease who lose response to anti-TNF-α therapy. Aliment. Pharmacol. Ther. 2011;34:1–10.
[18] Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. The Lancet Gastroenterology & Hepatology 2019;4:341–53.
[19] Van Assche G, Vermeire S, Rutgeerts P. Management of loss of response to anti-TNF drugs: change the dose or change the drug? Journal of Crohn's and Colitis 2008;2:348–51.
[20] Ye BD, Yamamoto Furusho J, Rana Qasim Khan M, et al. P432 Barriers to prescribing anti-TNF therapy in inflammatory bowel disease (IBD) across newly industrialised emerging market countries: an analysis of the 'EXPLORE' study. Journal of Crohn's and Colitis 2019;13:S324–S3S5.
[21] Revised the details (pharmaceutical) notice regarding the standards and methods for applying for medical care. Notice No. 2013-54. 2013. (Accessed 28th April 2020, at http://www.mohw.go.kr/react/jb/sjb0406vw.jsp?PAR_MENU_ID=03&MENU_ID=030406&CONT_SEQ=321604.)
[22] Kamperidis N, Middleton P, Tyrrell T, et al. Impact of therapeutic drug level monitoring on outcomes of patients with Crohn's disease treated with Infliximab: real world data from a retrospective single centre cohort study. Frontline Gastroenterol 2019 flgastro-2018-101024.
[23] Khalid JM, Peyrin-Biroulet L, Armuzzi A, et al. Predictors of Non-response or Loss of Response to Tumour Necrosis Factor Antagonist Therapies in Inflammatory Bowel Disease: 699. American Journal of Gastroenterology 2016;111:S316.
[24] Naviglio S, Giuffrida P, Stocco G, et al. How to predict response to anti-tumour necrosis factor agents in inflammatory bowel disease. Expert Rev Gastroenterol Hepatol 2018;12:797–810.