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Alimentary Tract

Indicators of suboptimal tumor necrosis factor antagonist therapy in inflammatory bowel disease

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ABSTRACT

Background: Inflammatory bowel disease (IBD) is refractory to treatment in one-half of patients.
Aims: To evaluate the occurrence of suboptimal therapy among patients with IBD treated with tumor necrosis factor antagonists (anti-TNFs).
Methods: A multinational chart review in Europe and Canada was conducted among IBD patients diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) who initiated anti-TNF therapy between 2009 and 2013. The primary endpoint was the cumulative incidence of suboptimal therapy during a two-year follow-up period, defined by the presence of the following indicators: dose escalation, discontinuation, switching, non-biologic therapy escalation, or surgery.
Results: The study included 1195 anti-TNF initiators (538 UC and 657 CD). The majority of patients (64% of UC and 58% of CD) had at least one indicator of suboptimal therapy. The median time to suboptimal therapy indicator was 12.5 and 17.5 months for UC and CD patients, respectively. Among the 111 UC and 174 CD anti-TNF switchers, 51% and 56% had an indicator of suboptimal therapy, respectively. The median time to suboptimal therapy indicator with the second anti-TNF was 14.3 and 13.0 months for UC and CD patients, respectively.
Conclusion: The majority of IBD patients showed suboptimal therapy with current anti-TNFs.

1. Introduction

Both ulcerative colitis (UC) and Crohn's disease (CD) are most prevalent in Europe and North America and are increasing in incidence worldwide [1–3]. The prevalence of inflammatory bowel disease (IBD) in Europe is approximately 3 million, costing €5 billion annually in direct medical costs [3]. The US average annual cost per patient to insurers is $15,000–19,000, with most of the direct costs attributable to diagnostic testing and pharmacy costs [4,5]. Given the chronic, relapsing, recurring nature of IBD, diagnosis at a younger age expands the social and medical burden of disease at both the individual and population levels [6].

The 10-year colectomy rates for UC patients in Europe are approximately 3–10%; among those with CD, the proportions who require surgery within 10 years are much higher (37–61%) [3]. In the US, one-in-ten UC and one-in-three CD patients require surgical intervention within 5–10 years, with rates varying by treatment, extent of disease, and geographic location [7].

Tumor necrosis factor antagonists (anti-TNFs) were introduced into the treatment regimen in 1998 for CD and 2005 for UC, and are effective at inducing symptom relief, disease remission, and mucosal healing among patients with moderate to severe IBD [8,9]. Current treatment guidelines recommend anti-TNFs for patients who are refractory to other treatments [8,9]. While anti-TNFs have long been a mainstay in UC and CD management, a considerable

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proportion of patients do not respond to induction therapy (primary non-response) or will lose response to such therapies over time (secondary non-response or loss of response) [10–13]. Among patients initiating their first anti-TNF, nearly 60% of patients experienced a secondary loss of response despite initially experiencing therapeutic success [14]. Changes in anti-TNF therapy may serve as sentinel indicators of suboptimal anti-TNF therapy, such as dose escalation, switching to another anti-TNF, augmentation with other medications, discontinuation, or surgery [11].

The aim of this study was to estimate the incidence of suboptimal anti-TNF therapy among IBD patients in real-world clinical practices. The primary endpoints were the cumulative incidence within the first two years and time to the first indicator of suboptimal therapy among anti-TNF initiators. The secondary endpoint was the cumulative incidence of at least one indicator of suboptimal therapy among those who switched to a second anti-TNF. Given that a substantial proportion of patients experience suboptimal anti-TNF therapy, it is important to profile the course of treatment to inform clinical management and drug development.

2. Methods

2.1. Design and data collection

This retrospective medical chart review study was conducted among IBD patients initiating an anti-TNF therapy for the first time. The multinational cohort was selected from six countries (Canada, France, Germany, Italy, Spain, and the United Kingdom). The study period commenced with the index date, defined as the first dose of anti-TNF therapy. This period was between June 1, 2009 and June 1, 2013 for UC patients and June 1, 2009 through June 1, 2011 for CD patients. The eligibility period for UC was longer to include patients treated with newly approved second-line biologics. Data were extracted between August and December 2014 for all patients, with a minimum follow-up period of two years. The study sites were selected and managed by a contract research organization (CRO) to include approximately equal numbers of UC and CD patients seen at gastroenterology clinics treating patients with anti-TNFs.

Adult patients (aged ≥18 years at the index date) were included if they were naïve to anti-TNF therapy and initiated infliximab or adalimumab during the eligibility period. Patients were excluded if they: were diagnosed with an indeterminate/unspecified type of IBD; participated in an interventional clinical trial; had a total colectomy prior to their first anti-TNF therapy; received anti-TNF therapy for rheumatoid arthritis, ankylosing spondylitis, or psoriasis; initiated anti-TNF therapy for an episodic use rather than to follow an induction and maintenance plan of therapy; had a diagnosis of cancer; were lost to site follow-up for reasons other than death; or had not consented to participate in the study.

Baseline patient demographics were described, including age, sex, country, and smoking status. Baseline clinical characteristics included: diagnosis date of IBD; comorbid conditions; frequency of stools per day; rectal bleeding; endoscopic findings (if completed); physician global assessment of disease severity; Harvey–Bradshaw Index; abnormal C-reactive protein (CRP) levels within 4 weeks prior to the index date; and Mayo or Charlson Comorbidity Index score (if documented in the chart), a measure of a patient's overall illness profile. Baseline use of concomitant non-biological therapies was also collected, including the dose, route of administration, prescribed frequency, and start/stop dates of administration at each dose.

The CRO conducted a pre-collection and close-out visit with each study site to ensure a uniform approach to data abstraction. A web-based data entry form with integrated logical checks was used to capture data and identify data entry errors in real time. Data entry discrepancies were followed up until resolution either via direct inquiry with the site or a site visit. The data management plan included a process for data quality monitoring by automatic and human checks, including random sampling of a small number of records and identifying triggers for source data verification. Routine contact with study sites was maintained throughout the data collection process, and site visits were conducted when appropriate to resolve data discrepancies. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008), as reflected in a priori approval by the institution's human research committee.

2.2. Study endpoints and statistical considerations

Patients were stratified by disease state (UC or CD) for all analyses. The primary analysis comprised anti-TNF naïve patients during the study period. A second subset analysis was conducted among anti-TNF naïve patients who progressed to a second anti-TNF during the follow-up period (i.e., anti-TNF switchers). The primary endpoints were cumulative incidence of ≥1 indicator of suboptimal therapy and time to the first such indicator during the two-year follow-up period, defined as the first of any of the following:

1. Anti-TNF dose escalation included any increase in either dose, frequency, or both of the index anti-TNF therapy occurring >4 months post-index date to allow for initial dose adjustments.
2. Augmentation with non-biologic therapy was defined as starting a new non-biologic drug or increase in dose/frequency of the concurrent non-biological drugs with anti-TNF therapy. Non-biologic therapies included aminosalicylates, immunomodulators, and corticosteroids.
3. Discontinuation of initial anti-TNF therapy was based on documentation in patients' charts and excluded patients who discontinued anti-TNF treatment because it was ineffective during the follow-up period.
4. Switching was defined as initiating another anti-TNF therapy within the follow-up period.
5. UC-related surgery included colectomy and ostomy (colostomy or ileostomy) and CD-related surgery included colectomy, ostomy (colostomy or ileostomy), abscess drainage, and strictureplasty.

Primary reasons for dose escalations and alterations were also collected. The time-to-dose-escalation was analyzed using the Kaplan–Meier method to account for different follow-up periods and censoring at the end of the observation period. The entire study period was used for these analyses, whereas follow-up was restricted to two years for the indicators of suboptimal therapy.

For descriptive statistics, proportions were calculated for categorical variables and the mean ± SD for continuous variables. This study was conducted in accordance with local ethical committee approval in each country, including securing patient informed consent, according to local laws.

3. Results

3.1. Baseline characteristics

The study included 1195 IBD patients initiating anti-TNF therapy (45% with UC [n = 538] and 55% with CD [n = 657]). Mean age (SD) of patients with UC and CD was 41.6 (14.3) years and 39.2 (13.2) years, respectively; nearly half of UC and CD patients were male (Table 1). There were proportionately more smokers in the CD population than UC population (23% vs 6.5%). The anti-TNF switch-

Table 1
Baseline demographics and clinical characteristics of patients with inflammatory bowel disease at index date.

	Crohn's disease (N = 657)	Ulcerative colitis (N = 538)
Gender: female (n, %)	333 (50.7)	252 (46.8)
Age (years) (mean, SD)	39.2 (13.2)	41.6 (14.3)
Charlson score (mean, SD)	0.2 (0.5)	0.2 (0.6)
Country (n, %)		
Italy	144 (21.9)	132 (24.5)
Germany	109 (16.6)	149 (27.8)
Spain	144 (21.9)	80 (14.9)
United Kingdom	120 (18.3)	45 (8.4)
France	76 (11.6)	81 (15.1)
Canada	64 (9.7)	51 (9.5)
Smoking status (n, %)		
Never smoked	252 (38.4)	280 (52.0)
Ex-smoker	104 (15.8)	109 (20.3)
Current smoker	152 (23.1)	35 (6.5)
Unknown/missing	149 (22.7)	114 (21.2)
Duration of IBD disease (years)		
Mean (SD)	8.8 (8.6)	7.1 (7.2)
Median	6.3	4.5
Physician global assessment (n, %)		
Normal	29 (4.4)	7 (1.3)
Mild	102 (15.5)	43 (8.0)
Moderate	262 (39.9)	276 (51.3)
Severe	75 (11.4)	116 (21.6)
Unknown/missing	189 (28.8)	96 (17.9)
Most abnormal CRP value within prior 4 weeks (mg/L)		
Mean (SD)	25.0 (39.18)	24.4 (40.09)
Median	9.9	8.0
Frequency of stools (per day)		
Mean (SD)	4.7 (3.84)	7.1 (4.57)
Median	4	6

CRP: C-reactive protein; IBD: inflammatory bowel disease; SD: standard deviation.

ers comprised 111 UC and 174 CD patients (see Supplementary Tables S1 and S2 in the online version at DOI:10.1016/j.dld.2017.07.010 for disease-specific clinical characteristics).

Among the patients initiating anti-TNF therapy, the majority of UC patients were treated with infliximab (92.2%) while 7.8% were treated with adalimumab. The first-line anti-TNF distribution was more even among CD patients: 55.6% with infliximab and 44.4% with adalimumab. The Mayo scores and Harvey–Bradshaw scores were not well documented among UC patients. CRP values were documented in 70% of UC patients and 69% of CD patients within 4 weeks prior to the start of anti-TNF therapy.

Approximately one-in-five UC patients (20.6%) and one-in-four CD patients (26.5%) were treated with a second anti-TNF (anti-TNF switchers), primarily adalimumab (90% in UC, 63% in CD). Prior surgery was uncommon among UC patients (2.8%), while approximately one-half of CD patients had undergone CD-related surgery (46.3%). When starting anti-TNF therapy, 83.6% of UC and 70.6% of CD patients received at least one concomitant non-biologic therapy (Table 2).

3.2. Time to event analyses

Overall, within two years, 64.1% of UC and 58.1% of CD patients initiating anti-TNF therapy had at least one indicator of suboptimal therapy (Table 3). Median time to at least one of the indicators of suboptimal therapy was 12.5 and 17.5 months for UC and CD patients, respectively, for anti-TNF initiators (Fig. 1). While for UC patients, the median time to any indicator of suboptimal therapy was similar for both anti-TNF initiators and switchers (12.5 vs 14.3 months), for CD patients the median time to the first indicator was lower in the anti-TNF switchers than the anti-TNF initiators (13.0 vs 17.5 months). Among UC patients on their second anti-TNF, 49% had experienced at least one indicator of suboptimal therapy by 12 months compared with 44% of CD patients over the same interval.

3.3. Indicators of suboptimal therapy

The most frequently reported indicators were anti-TNF dose escalation and discontinuation. Among the anti-TNF initiators, dose-escalation was needed in 25.8% of UC patients and 19.2% of CD patients. Among patients who received an escalated anti-TNF dose, the primary reason for therapy alteration was worsening of signs and symptoms (94.2% UC and 94.5% CD) (data not shown).

Table 2
Use of non-biologic therapies among inflammatory bowel disease patients at index date.

	Crohn's disease (N = 657)	Ulcerative colitis (N = 538)
Non-biological treatments (n, %)		
At least one unique type of medication	464 (70.6)	450 (83.6)
With 1 unique type of medication	273 (41.6)	174 (32.3)
With 2 unique types of medication	151 (23.0)	198 (36.8)
With 3 unique types of medication	37 (5.6)	74 (13.8)
With at least 4 unique types of medication	3 (0.5)	4 (0.7)
Type of non-biological treatment (n, %)		
Aminosalicylate	159 (24.2)	290 (53.9)
Antibiotic	44 (6.7)	19 (3.5)
Corticosteroid	203 (30.9)	274 (50.9)
Azathioprine	221 (33.6)	182 (33.8)
Mercaptopurine	18 (2.7)	16 (3.0)
Methotrexate	35 (5.3)	13 (2.4)
Other[a]	19 (2.9)	14 (2.6)
Non-biological treatment combinations (n, %)		
Aminosalicylate only	63 (9.6)	70 (13.0)
Corticosteroids only	64 (9.7)	54 (10.0)
Immunomodulator only	135 (20.5)	48 (8.9)
Aminosalicylate and corticosteroids only	35 (5.3)	95 (17.7)
Immunomodulator and aminosalicylates only	19 (2.9)	48 (8.9)
Immunomodulator and corticosteroids only	62 (9.4)	50 (9.3)
Aminosalicylates, corticosteroids and immunomodulator only	25 (3.8)	57 (10.6)

[a] Other therapies comprised cyclosporine A, mycophenolate mofetil, tacrolimus, and nutritional therapies.

Table 3
Proportion of inflammatory bowel disease patients with indicator of suboptimal therapy among anti-tumor necrosis factor initiators and switchers.

	Crohn's disease		Ulcerative colitis	
	Anti-TNF initiators (N = 657)	Anti-TNF switchers (N = 174)	Anti-TNF initiators (N = 538)	Anti-TNF switchers (N = 111)
≥1 of following indicators	58.1%	56.3%	64.1%	51.4%
Anti-TNF dose escalation	21.3%	16.7%	29.7%	17.1%
Augmentation with non-biologic drug	17.8%	14.9%	21.0%	16.2%
Surgery	16.9%	16.7%	8.9%	3.6%
Discontinuation	31.1%	29.9%	34.2%	27.9%
Of those who discontinued: switch to another anti-TNF	62.7%	25.0%	49.5%	38.7%

TNF: tumor necrosis factor.

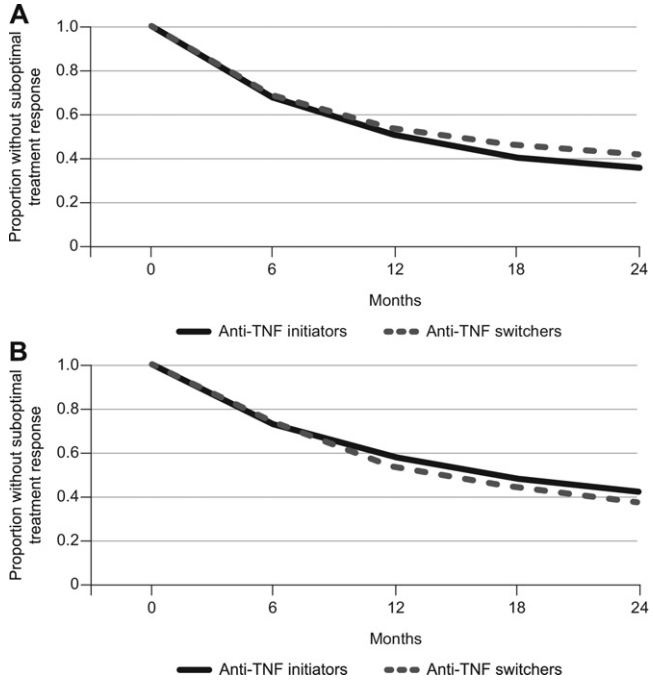

Fig. 1. Time to any of the indicators of suboptimal therapy among ulcerative colitis anti-tumor necrosis factor initiators and switchers (A) and Crohn's disease anti-tumor necrosis factor initiators and switchers (B).
TNF: tumor necrosis factor.

Most UC patients who discontinued their initial anti-TNF therapy did so due to poorly controlled symptoms (45.6%), although one-in-five experienced an adverse reaction (23.2%). Of those UC patients who discontinued the index anti-TNF, 49.5% switched to another anti-TNF therapy. Among CD patients who discontinued their initial anti-TNF therapy, a similar proportion discontinued treatment due to poorly controlled symptoms (36.3%) or an adverse reaction to treatment (27.4%); 62.7% of CD patients who discontinued anti-TNF therapy switched to another anti-TNF. One-fifth (21.0%) of UC and 17.8% of CD patients had non-biologic therapy augmentations, and 8.9% and 16.9%, respectively, underwent surgery.

3.4. Anti-TNF switchers

Among anti-TNF switchers, approximately half of both UC and CD patients had at least one indicator of suboptimal therapy (Table 3). For this nested cohort of patients, 27.9% of UC and 29.9% of CD patients discontinued their second anti-TNF therapy; 38.7% and 25.0%, respectively, switched to a third anti-TNF (infliximab and adalimumab). Among the UC patients, 17.1% had anti-TNF dose escalation, 16.2% had non-biologic therapy augmentation, and 3.6% underwent UC-related surgery during treatment with their second anti-TNF. Among CD patients who switched to a second anti-TNF, 16.7% had anti-TNF dose escalation, 14.9% had non-biologic therapy augmentation, and 16.7% underwent surgery during treatment with their second anti-TNF.

Almost two-thirds of UC anti-TNF switchers discontinued therapy because of worsening signs and symptoms (48.1%) or a drug-related acute reaction or adverse event related to the anti-TNF therapy (14.8%). Similarly, among CD anti-TNF switchers, the most common reasons for discontinuation of the second anti-TNF included worsening of signs and symptoms (28.3%) and a drug-related acute reaction or adverse event related to the anti-TNF therapy (20.0%).

4. Discussion

This retrospective, multicenter, multinational chart review gathered data on clinical response patterns among IBD patients treated with anti-TNFs. Consistent with the literature, the incidence of suboptimal therapy indicators in real-world clinic settings throughout Europe and Canada was substantial among anti-TNF therapy initiators and anti-TNF switchers. The most frequent suboptimal therapy indicators were anti-TNF dose escalation and discontinuation. These therapy changes were made primarily due to lack of clinical response, often manifesting in worsening symptoms. While anti-TNFs are a mainstay in IBD management, they are not without risk; one-in-five of the UC and CD patients in this multinational cohort experienced an adverse reaction to their anti-TNF therapy. Better identification of patients who are likely to succeed treatment, or at least quicker recognition of possible treatment failure, may reduce societal and medical costs incurred during courses of treatment ending with suboptimal response.

Previous analyses corroborate these study findings in that a substantial proportion of patients experience suboptimal treatment outcomes with anti-TNFs [10–13]. Due to the variability in definitions of loss of response to anti-TNFs, a wide range of results were reported for dose intensification (23–46%) or anti-TNF discontinuation (5–13%) within 12 months of anti-TNF initiation [11]. Allez et al. highlighted a series of studies reporting a wide range of loss of response rates among patients using anti-TNFs (11–71%) [10]. Gisbert and Panes analyzed 16 studies evaluating loss of response to infliximab and reported a 13% per patient-year risk of loss of response, which they defined by increased dose per administration or increased infusion frequency [13]. This current analysis used a more robust definition of suboptimal treatment, including treatment discontinuation due to failure, switching to another biologic, and surgery.

The outcomes reported here are similar to previous studies, including trends identifying factors indicating an unfavorable response to treatment among patients with IBD. The majority of studies suggest that severity of UC disease is correlated with likelihood of non-response [15–17]. A recent chart review study

reported similar clinical outcomes between UC patients treated with infliximab and adalimumab in the US, but also reported lower rates of anti-TNF discontinuation, switching, dose escalation, or treatment augmentation than this current analysis; it is unclear, however, if these differences are due to study location or analytic definitions [18]. Recently, attention has turned to immunological markers for a response. For example, the absence of perinuclear antineutrophil cytoplasmatic antibodies (p-ANCA) was strongly predictive of response to infliximab [19]. UC patients naïve to immunosuppressants seem to respond better to anti-TNF agents [20]. Prior research among CD patients has, likewise, identified risk factors for non-response, some of which include male gender, lack of concomitant immunosuppression, older age, longer duration of disease, smoking, and disease not limited to the colon [21]. Additionally, lower levels of anti-IFX antibodies have been associated with remission.

Future research should continue to identify clinical markers for successful treatment, focusing on earlier indicators of suboptimal therapy. This current analysis found similar treatment patterns between anti-TNF initiators and anti-TNF switchers, suggesting that cycling between anti-TNF therapies did not improve patient odds for successful treatment. Prior research has found long-term use of both adalimumab and infliximab to be associated with the development of neutralizing antibodies, which may partially explain the necessity for dose escalation with these agents [22,23]. Further, development of neutralizing antibodies impacts response to all anti-TNFs, offering a possible explanation for why patients switching from one anti-TNF therapy to another did not experience improved outcomes [24,25].

The study design and data source have some inherent limitations. While this study was multinational, it only included patients treated at the participating clinics in each country, which may not represent broader treatment patterns and practices. Additionally, the extent of missing data and inherent biases can be difficult to assess in a chart review study; however these are mitigated by the fact that a large cohort of IBD patients were examined in the current study. Newer agents (both anti-TNF and other classes) were not included in this analysis due to insufficient sample sizes during the study period. We acknowledge that our findings may include patients without optimal dosing of anti-TNFs [26,27], which needs to be considered as previous literature has shown that attaining anti-TNF trough concentration of >3 ug/mL is associated with clinical response [28]. The pharmacokinetics of anti-TNF levels may be influenced by factors including albumin, weight, gender, inflammation, route of administration, and development of immunogenicity. The study period for this analysis is before the establishment of routine therapeutic drug monitoring; thus, we have relied on the recorded changes to interventions as proxies for understanding rates of loss of response.

In conclusion, this study found that suboptimal therapy with anti-TNFs was common among IBD patients initiating anti-TNF therapy or switching to a second anti-TNF. More than one-half of patients had an indicator of suboptimal therapy within two years and switching to a second anti-TNF yielded similar outcomes.

Conflicts of interest

Dr. Armuzzi reports personal fees from Takeda, during the conduct of the study; personal fees from AbbVie, personal fees from Astra-Zeneca, personal fees from Biogen, personal fees from Chiesi, personal fees from Ferring, personal fees from Hospira, personal fees from Janssen, grants and personal fees from MSD, personal fees from Mundipharma, personal fees from Pfizer, personal fees from Samsung, personal fees from Sofar, personal fees from Takeda, personal fees from Zambon, outside the submitted work.

Dr. Bokemeyer reports grants, personal fees and non-financial support from AbbVie, personal fees and non-financial support from MSD, personal fees and non-financial support from Takeda, grants, personal fees and non-financial support from Janssen, personal fees from Celltrion, personal fees from Mundipharma, personal fees from Pfizer, personal fees from Biogen, personal fees from Boehringer, during the conduct of the study; grants from Given Imaging, grants, personal fees and non-financial support from Ferring, personal fees from Shield, outside the submitted work.

Javier P. Gisbert has served as a speaker, a consultant and advisory member for or has received research funding from MSD, AbbVie, Hospira, Pfizer, Kern Pharma, Biogen, Takeda, Janssen, Roche, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical and Vifor Pharma.

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Dr. Nguyen has nothing to disclose.

Dr. Peyrin-Biroulet reports personal fees from AbbVie, personal fees from MSD, personal fees from Janssen, personal fees from Genentech, personal fees from Mitsubishi, personal fees from Ferring, personal fees from Norgine, personal fees from Tillots, personal fees from Vifor, personal fees from Shire, personal fees from Pharmacosmos, personal fees from BMS, personal fees from UCB-pharma, personal fees from Hospira, personal fees from Takeda, personal fees from Boehringer Ingelheim, personal fees from Pfizer, personal fees from Lilly, personal fees from Celltrion, outside the submitted work. Michael Smyth is a former employee of Takeda Pharmaceuticals International, Inc.

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