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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-

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