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Alimentary Tract

Addressing current treatment challenges in Crohn's disease in real life: A physician's survey

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ABSTRACT

Background: In recent years several trials have addressed treatment challenges in Crohn's disease. Clinical trials however, represent a very special situation.
Aims: To perform a cross-sectional survey among gastroenterologists on the current clinical real life therapeutic approach focussing on the use of biologics.
Methods: A survey including six main questions on clinical management of loss of response, diagnostic evaluation prior to major treatment changes, preference for anti-tumour necrosis factor (TNF) agent, (de-)escalation strategies as well as a basic section regarding personal information was sent by mail to all gastroenterologists in Switzerland ($n = 318$).
Results: In total, 120 questionnaires were analysed (response rate 37.7%). 90% of gastroenterologists in Switzerland use a thiopurine as the first step-up strategy (anti-TNF alone 7.5%, combination 2.5%). To address loss of response, most physicians prefer shortening the interval of anti-TNF administration followed by dose increase, switching the biologic and adding a thiopurine. In case of prolonged remission on combination therapy, the thiopurine is stopped first (52.6%) after a mean treatment duration of 15.7 months (biologic first in 41.4%).
Conclusions: Everyday clinical practice in Crohn's disease patients appears to be incongruent with clinical data derived from major trials. Studies investigating reasons underlying these discrepancies are of need to optimize and harmonize treatment.

1. Introduction

The introduction of tumour necrosis factor (TNF) inhibitors more than 10 years ago in the treatment of Crohn's disease (CD) represented a major therapeutic breakthrough [1]. Since the first double-blind, placebo-controlled trial with infliximab (IFX) [2] numerous pivotal trials on the efficacy of infliximab, adalimumab (ADA) and certolizumab pegol (CTZ) in inducing and maintaining clinical response and remission and achieving mucosal healing have been published [2–7].

Since the early days, concerns regarding safety, above all opportunistic and severe infections and also neoplastic diseases have been raised [2,8]. Even after extensive worldwide experience with anti-TNF therapy in IBD and other indications, such as rheumatological or dermatological diseases, there still is some uncertainty about potential risks [9–13]. In the last years, there is an increasing trend towards an earlier introduction of Anti-TNF agents (which is associated with a better efficacy [14]) either via a rapid step-up [15,16] or top down [17] approach, to avoid prolonged steroid exposure and minimizing CD-associated morbidity and the need for surgery. Since the SONIC-trial [18] the initial use of anti-TNF in

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combination with a thiopurine has been advocated at least in patients with high-risk characteristics for a disabling disease course. This approach has consecutively also been included in treatment guidelines [19]. Aside from treatment optimization de-escalation of therapy after variable duration of clinical remission and associated factors predicting success have been studied [20–22].

In parallel, the question of applying the best clinical strategy when confronted with loss of response (LOR) in patients receiving maintenance anti-TNF therapy has emerged. LOR occurs in a significant fraction of patients and has been reported to occur in about 20–50% of patients within the first year of therapy [5,23]. Switching anti-TNF has been shown to be an effective strategy in case of LOR and drug intolerance [24–27] but should be omitted simply for the reason of a more convenient route of drug administration [28]. However, prior to switching, dose intensification ideally guided by anti-TNF trough levels and anti-drug antibodies measurement should always be considered, due to both, the still limited number of biologic agents available and the high success rates (about 50–70%) of dose intensification in regaining response [23,29,30]. Even after failure of two anti-TNF agents, there may be considerable rates of response and remission using a third one [31]. Nonetheless, at this point in time only in the US and Switzerland such a third agent is available without a specific reimbursement application.

Even with similar treatment guidelines in the US (ACG) and Europe (ECCO) attitude towards anti-TNF treatment and immunosuppression in CD patients may differ between physicians (depending on their experience), treatment facilities (specialized centre, hospital and private practice) and countries. The few studies having looked at adherence to guidelines among gastroenterologists have revealed equivocal results [32,33]. However, the treatment of CD appeared to be appropriate in most patients according to cohort studies from Switzerland and Europe [34,35].

Despite a multitude of randomized trials, clinical real life differs: looking at a selection of pivotal IBD trials, less than a third of unselected real life IBD patients would have been actually suited for inclusion [36]. We thus aimed to obtain a comprehensive overview on the clinical practice of GI specialists in Switzerland involved in the care of CD patients in the biologics era with a special focus on the current use of anti-TNF agents, including their position in the therapeutic armamentarium and to gain insights on how the published treatment paradigms are currently addressed in a real-life setting.

2. Materials and methods

A questionnaire was sent to all Swiss gastroenterologists by conventional mail. There is no approved and regularly updated list of all actively practising gastroenterologists maintained by an official institution, such as the Swiss Society of Gastroenterology (SGG). However, facilitated by the relatively small size of the country, there is a comprehensive list of all Swiss gastroenterologists available, used for various purposes, such as invitation to educational events in and outside of Switzerland or information on announcements for research grants or prices. In total, after discarding those gastroenterologists on the list without valid mail address (either directly available on the list or after a search in an online phone book, harbouring the complete official and up-to-date Swiss telephone registry), the questionnaire was sent to 318 gastroenterologists in April 2012. Physicians were asked to return the questionnaire either by conventional mail, fax or email (after scanning) until the end of 2012. This questionnaire included six questions addressing the following parameters: step-up strategy (question V), preference for any specific TNF antagonist (question IV), diagnostic evaluation antecedent to any major treatment change (question III), addressing loss of response (questions I, II) as well as de-escalation strategy in the event of prolonged remission on combination therapy (question VI). It also included a basic section about practice characteristics of the respondent, such as age, gender, years in gastroenterology (GI) practise, practise setting, numbers of IBD patients seen/followed and treated with anti-TNF per year (Supplementary Table S1).

The main outcome – the percentage of Swiss gastroenterologists voting for a given option (questions IV–VI), voted sequence of given options (question I), mean rating (question II and three III) or mean interval (question VI, 2nd part), respectively – was analysed both globally as well as stratified according to the number of IBD patients seen and treated with anti-TNF agents per year, years in clinical practice and practice setting. Statistical analyses were performed with SPSS (Version 21; IBM, Armonk, NY, USA) and Prism (Version 6, GraphPad Software, La Jolla, CA, USA). To investigate potential differences between the pre-specified subgroups Chi-Square testing was used. Regarding the interval on prolonged remission prior to stopping one or both medical treatments D'Agostino & Pearson omnibus normality test was used, revealing a non-normal distribution. Consecutively Kruskal–Wallis test was used to evaluate whether there are any differences in mean values between the subgroups. Mann–Whitney test was then applied to directly compare between subgroups.

3. Results

3.1. Response rate and characteristics of responders

Out of 318 Swiss gastroenterologists invited to participate in the survey 120 (37.7%) responded and were analysed. The mean age of the responding GI specialists was 48.4 ± 9.8 years (89.1% male) with a mean professional experience as a gastroenterologist of 15.1 ± 9.3 years. About a third of gastroenterologists provide clinical care in each of the following sections: private practice (32.5%), smaller hospitals (district hospital 26.7% and private hospital 5.8%), as well as larger hospitals, such as university hospitals (20%) or large non-university hospitals (15%). Further information on baseline characteristics of gastroenterologists according to practise setting is given in Table 1.

3.2. Preferred step-up strategy

After lack of response to systemic steroids, budesonide, 5-aminosalicylates or an inability to taper these agents, the majority of Swiss gastroenterologists (90%) use a conventional step-up strategy with a thiopurine as a first-line therapy. Only 7.5% of responders use anti-TNF therapy alone, 2.5% use combination therapy (thiopurine combined with anti-TNF) as a first-line therapy. We did not observe any statistical differences in the strategy with regard to any of the pre-specified subgroups (number of IBD patients seen and treated with anti-TNF per year, years in clinical practice and practice setting). Notably, there is not an increased primary use of anti-TNF (either as mono-therapy or in combination with thiopurine) in referral centres versus smaller hospitals or private practice (Supplementary Figure S1). Based on the data from the SONIC trial we calculated the efficacy of the treatment strategies according to the practicing physicians from our survey as well as the efficacy gap, assuming that in the comparison group all 1000 imaginary patients would have received a combo-therapy (Supplementary Figure S2).

3.3. Preference for a specific anti-TNF agent

Almost half (41.2%) of Swiss gastroenterologists have no preference for a specific anti-TNF agent. Among responders having a preference for a given anti-TNF, IFX is by far the preferred anti-TNF