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Review

Optimizing anti-TNF treatments in inflammatory bowel disease ☆

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ABSTRACT

Background: Failure of anti-TNF treatment in inflammatory bowel disease (IBD) patients can take on several forms, each posing distinct etio-pathogenic considerations and management dilemmas.
Aim: The aim of this study is to review the mechanisms responsible for the various forms of anti-TNF failures in IBD and to elucidate strategies for optimizing clinical efficacy.
Results: Primary failures of anti-TNF induction therapy occur in up to 40% of patients in clinical trials and in 10–20% in clinical series. Longer disease duration, smoking and several genetic mutations are predisposing factors for primary failures. Curiously, primary non-response is probably not a class-effect phenomenon since switching to another anti-TNF is effective in over 50% of such patients. Secondary loss of response is also a common clinical problem with incidence ranging between 23 and 46% at 12 months after anti-TNF initiation. Underlying mechanisms are often related to increased anti-TNF clearance by anti-drug antibodies, but may also include other causes for recalcitrant IBD activity as well as disorders that are unrelated to IBD itself. Astute management begins with verifying the presence of uncontrolled inflammatory IBD activity as a cause for patient's symptoms. Next, it is prudent to consider a trial of wait-and-see approach, since in some patients with mild-moderate symptoms, loss of response may resolve without alteration of therapy. If it does not, measuring anti-TNF trough levels and anti-drug antibodies may clarify the underlying mechanism in individual patients although there are still limited and conflicting data regarding the role of these measurements in guiding the choice between dose-intensification, switch to another anti-TNF or to another immunomodulator, and the addition of an immuno-modulator as a combination therapy with the failing anti-TNF. Anti-TNF re-induction after prior drug-holiday is a distinct clinical scenario and scarce evidence suggests re-induction outcome to be dependent on the circumstances when drug-holiday was commenced. Finally, discontinuation of anti-TNF in patients with stable deep clinico-biologic and mucosal remission may be a viable option, as in these carefully selected patients the majority may enjoy long-term remission without the need for continued anti-TNF treatment.

Contents

Abbreviations: LOR, loss of response; CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; ATI, antibodies to infliximab; ATA, antibodies to adalimumab.

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1. Introduction

The anti-TNF monoclonal antibodies (infliximab, adalimumab and certolizumab) are efficacious agents for the treatment of inflammatory bowel disease (IBD) and several other immune-driven disorders [1,2]. However, treatment failures do occur in the form of primary non-response, secondary loss of response or secondary–primary non response (i.e. failure of re-induction in a patient previously exposed to the drug). In addition, although not strictly a failure of the drug, unnecessary continuation of anti-TNF may be considered a specific type of treatment shortcoming in the broad sense as it may severely impede patients' quality of life and impose adverse effects' risk without clinical justification. Diverse and probably distinct mechanisms underlie the different forms of anti-TNF treatment failures in both IBD and in other immune-driven disorders [3,4]. Although it probably has little role in mediating primary non-response, immunogenicity has emerged as an important mechanism driving secondary loss of response in a subset of patients. Nonetheless, other mechanisms also play a role in propagating uncontrolled IBD inflammation despite anti-TNF treatment, thereby dictating an individualized approach in diagnosing and identifying the pathogenesis of loss of response in individual patients.

The aim of this review is to provide an overview of the incidence, predisposing factors and causes of primary, secondary and secondary–primary non-response to anti-TNF treatments in IBD, with a specific focus on immunogenicity role in this respect. It also aims to elucidate management strategies to prevent and to treat the diverse forms of non-response to anti-TNFs.

2. Results and discussion

2.1. Primary non-response

2.1.1. Definition and incidence

There is no unanimous definition of primary non-response. Indeed, even the time-points at which to gage primary non-response are not consensual, being different between clinical trials evaluating the same drug. This, in turn, makes the discussion about the incidence and impact of this phenomenon to be fraught with inherent inconsistencies. For instance, primary non-response to infliximab in ACCENT I study of Crohn's disease (CD) was defined as lack of response at 2 weeks after a single first infusion, whereas in the ACCENT II infliximab trial in fistulizing CD and in ACT1 and ACT2 trials of infliximab in ulcerative colitis (UC), response to induction or conversely primary non-response, was determined at week 10/14 or week 8, respectively, and following 3 infusions at weeks 0–2–6 [1,5,6]. In clinical practice, however, primary non-response to anti-TNFs should not be assessed before weeks 8–12 as successful remission induction may still be accrued after 3 infliximab infusions at weeks 0, 2, and 6 or after 3–5 bi-weekly adalimumab injections [7]. The incidence of primary non-response is quite variable. It was reported to affect between 20 and 40% of IBD patients in clinical trials with both infliximab and adalimumab, whereas lower rates of 10–20% primary non-response are generally reported in clinical 'real life' series (Fig. 1). Intriguingly, this is somewhat opposite to the situation in rheumatoid arthritis where response rates in clinical trials are generally better than those observed in 'real life' case series [8], although the overall response rates in these two diseases is quite similar.

2.1.2. Predisposing factors for primary non-response

Several factors have been associated with increased risk for primary non-response by most, albeit not all, studies [7,9]. Interestingly, these factors seem to echo the interplay between genetic background, phenotypic attributes and exogenous insults that are also implicated in the mosaic etiogenesis of many auto-immune diseases [10]. In particular, longer (>2 years) disease duration, small bowel extent of disease, smoking and normal CRP were reported to confer increased risk for primary non-response [7,9]. Certain genetic mutations and/or polymorphism in the apoptosis-related genes of FAS-L and Caspase 9, as well as in the IBD5 locus were also associated with primary non-response, although alterations in TNFR genes were not [9]. It is certainly plausible that the interplay between these different factors may be such as to create a risk-scale for poor response to anti-TNFs in IBD and in other disorders [11]. However, incorporating these diverse factors into a unified model for a risk-scale predicting primary non-response has not been hitherto performed.

2.1.3. Management of primary non-response

As a golden rule of thumb, prevention is the best way to manage a clinical problem. Thus, although there is yet no direct evidence that smoking cessation will improve the response rate to anti-TNFs, we believe it is imperative to underscore to the patient the adverse impact of smoking on response to these drugs and strongly advocate cessation of smoking before anti-TNF initiation. Another point to consider when primary non-response occurs is whether there is indeed evidence for inflammatory activity, or do the patient's symptoms stem from non-inflammatory causes unlikely to respond to anti-TNFs. Finally, an important question arises when primary non-response to inflammatory IBD activity is faced by the clinician: Is this a class effect phenomenon mandating a switch to another immuno-modulator, or can another anti-TNF agent be still effective for induction of response in these patients? Somewhat unexpectedly, several small-scale reports indicate

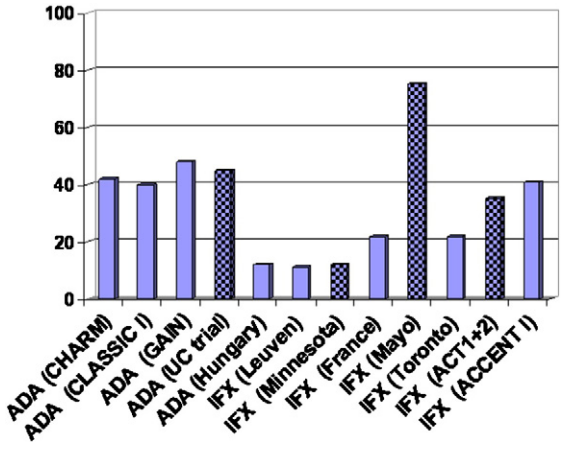

Fig. 1. The rate of primary non-response in selected published case-series and in clinical trials of CD (blank bars) and UC (chess-board bars) patients.