Dig Dis Sci (2015) 60:2571–2573
DOI 10.1007/s10620-015-3673-1

EDITORIAL

Preemptive Dose Optimization Using Therapeutic Drug Monitoring for Biologic Therapy of Crohn's Disease: Avoiding Failure While Lowering Costs?

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Received: 13 April 2015 / Accepted: 16 April 2015 / Published online: 28 April 2015

Crohn's disease is associated with a high economic burden to society due to healthcare costs and productivity losses, of which, before the introduction of antitumor necrosis factor (TNF) therapy, half were driven by surgical and medical hospitalization, with decreased work productivity accounting for almost 50 % of total costs in Europe [1]. Since the introduction of biologicals, the traditional cost profile has changed: A recent cost-of-illness study analyzing healthcare costs and productivity losses in the Netherlands concluded that although total healthcare costs in Crohn's disease patients were stable, medication costs increased to 71 % of total healthcare costs, whereas hospitalization decreased to 19 % and surgery to <1 % [1]. Productivity losses due to sick leave decreased to 16 % of total costs in Crohn's disease. Even though healthcare costs between Europe and the USA differ to a large extent, comparable trends have been reported [2, 3]. Biologic therapy should be optimized early in the course of Crohn's disease due to the need for long-term treatment with few available alternatives.

Therapeutic drug monitoring (TDM) is an established strategy in medicine, whereby on the basis of a concentration of a specific drug in a body fluid, the dose is adjusted in order to diagnose or avoid toxicity, undertreatment, or failed therapy. In this issue of *Digestive Diseases and Sciences*, Steenholdt and colleagues reported on the long-term follow-up of their pioneering randomized controlled trial testing the implementation of a TDM algorithm, incorporating serum drug concentrations and antibodies to infliximab (ATI), in Crohn's disease patients with secondary loss-of-response to infliximab [4] with the purpose of diagnosing and correcting the cause for loss-of-response, in comparison with conventional dose escalation. Secondary loss-of-response to infliximab was defined as recurrence of active disease with a Crohn's disease activity index (CDAI) ≥220 and/or a minimum of one draining perianal fistula. In a prior publication, the authors reported superior economic outcomes and similar clinical outcomes for the TDM-based intervention arm versus the dose-escalation arm at week 12 [5]. Here, the authors provide longer follow-up and report that cost savings are maintained throughout week 20 and the first year of follow-up, with similar clinical outcomes observed in both groups.

Interestingly, the majority of patients included in the TDM-based intervention arm had therapeutic infliximab trough concentrations (here defined as >0.5 μg/ml) despite an elevated CDAI score, possibly reflecting the clinical basis of the CDAI, which only moderately correlates with disease activity [6]. Although the threshold drug concentration of 0.5 μg/ml is generally considered to be low, using higher thresholds made no difference according to a sensitivity analysis included in their original publication [5]. Nonetheless, an objective measure could have been used to confirm disease activity in the subpopulation of patients with "adequate" drug exposure, since the recommended TDM-based intervention for overcoming loss-of-response in this subgroup was to change to a different class of therapy, a consequential decision due to the limited salvage options available. A key study conclusion is that "similar clinical outcomes" were achieved at week 20 in

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Table 1 Implementation of therapeutic drug monitoring of anti-TNF biologicals in the treatment of inflammatory bowel disease patients

	Drug serum concentration			
	Supra-optimal	Optimal range	Suboptimal	
			Action	Re-evaluation[a]
Response to treatment				
Sustained response	Dose reduction	Dosage unchanged	Measure ADA	ADA↑: stop and switch *out-of-class*
				ADA↓: determine cause of accelerated drug clearance
Partial or secondary loss-of-response	Switch out-of-class[b]	Switch out-of-class[b]	Measure ADA	ADA↑: stop and switch *in-class*
			Dose optimize	ADA↓: continue and dose optimize

ADA: antidrug antibody; ↑ represents concentration increase; ↓ represents concentration decrease

[a] At the next administration of drug

[b] First confirm active inflammation, e.g., by endoscopy

all study subpopulations, which remains to be confirmed in an adequately powered non-inferiority trial.

Although optimizing management of secondary loss-of-response is highly relevant, the true value of TDM may lie in preemptive dose optimization as a proactive strategy (before loss-of-response) rather than a reactive approach (after loss-of-response). Given the annual risk of secondary loss-of-response to maintenance infliximab is 13 % [7], a recent randomized controlled trial reported that preemptive dose optimization based on TDM decreases risk of secondary loss-of-response compared to dosing of infliximab based on symptoms and inflammatory biomarkers [8]. With increasing knowledge of the anti-TNF pharmacokinetics–pharmacodynamics relationship, the transient nature of some antidrug antibodies [9], and improvements in inflammatory biomarkers, algorithms can be further refined (Table 1). Since thresholds may vary according to desired outcome measure (biochemical, fecal, clinical, or endoscopic), disease state (active vs. remission), time course (induction vs. maintenance), and use of concomitant medication, and may also differ among patient populations or vary in individual patients, a TDM-based dosing approach should be seen as a dynamic tool [10].

Since biologicals are now the main cost driver in the treatment of Crohn's disease, TDM could be used to reduce costs. In the paper of Steenholdt et al., costs were consistently reduced in patients randomized to the TDM arm in the intention-to-treat population (31 %), per-protocol population (49 %), and per-protocol completion end of trial week 12 population (50 %) [4]. They also reported that the economic superiority of the algorithm was maintained throughout 1 year, with stable cost reduction percentages. Importantly, reduction in costs was not attained at the expense of increases of other types of healthcare costs. A recent prospective study showed that additional cost savings can be achieved by dose reduction in patients with a stable clinical response to maintenance infliximab therapy who have supra-optimal drug trough concentrations [8].

In September 2013, the European Medicines Agency approved a biosimilar of infliximab, CT-P13, under trade names Remsima® and Inflectra®, which will be used in an effort to reduce costs to patients and to healthcare systems [11, 12]. The application of TDM to their use is undiminished given TDM's primary goal of treatment optimization. It is, however, important to confirm or reassess known efficacy thresholds by using validated techniques [13]. As such, combining the use of biosimilar and TDM may further increase savings.

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