Drug Level–based Anti-Tumor Necrosis Factor Therapy: Ready for Prime Time?

See "Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease," by Vande Casteele N, Ferrante M, Van Assche G, et al, on page 1320.

The therapeutic goal in the care of inflammatory bowel disease (IBD) patients has evolved in recent years, moving away from mere symptom control to a more ambitious aim of prevention of functional intestinal damage and future disease complications.[1,2] To achieve this end, optimization of therapy is critical, taking into account pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drug). In the absence of a single definitive measurable biologic function affected by anti-tumor necrosis factor (TNF) agents, control of inflammation has become an accepted pharmacodynamic measure, and has been reproducibly associated with better long-term clinical outcomes and fewer disease complications.[3,4] How to better harness pharmacokinetics to improve disease control is the other side of the equation and is the focus of the Trough level Adapted infliXImab Treatment (TAXIT) trial reported in this issue of *Gastroenterology* by Vande Casteele et al.[5] This groundbreaking trial investigated whether a proactive strategy of adjusting infliximab dosing based on drug-level measurements is superior to the conventional act-upon-symptoms approach in IBD patients receiving and responding to maintenance infliximab therapy.

The importance of individualized pharmacokinetics was established by previous studies showing that low anti-TNF drug levels during maintenance treatment are associated with concurrent reduced clinical efficacy and suboptimal control of inflammation and can even predict ensuing disease flares later in the course of the disease.[6–8] Emerging evidence suggests that suboptimal drug levels may also play a role in the induction phase, in particular for patients with high inflammatory burden, such as is the case in acute severe colitis, or in those with individual characteristics increasing drug clearance. These findings have been observed with infliximab as well as adalimumab in patients with ulcerative colitis.[9,10] However, by and large, pharmacokinetic measures have been hitherto put into practice mostly in patients losing response to maintenance therapy. Observational studies showed that measuring drug and antidrug antibodies (ADA) levels can guide the appropriate intervention in such patients losing response to anti-TNF drugs.[11–13] A drug/ADA-level–based intervention strategy was also shown to provide significant cost savings compared with conventional infliximab dose intensification in a randomized, controlled, clinical trial of Crohn's disease patients with loss of response,[14] although clinical superiority was not demonstrated in that particular trial, likely owing to the small size.

The TAXIT trial has taken a more proactive approach, whereby instead of awaiting for and acting upon clinical loss of response, therapeutic drug monitoring (TDM) was implemented electively in patients still responding to maintenance therapy. The design employed a lead-in optimization phase in which patients' infliximab dose was titrated down if their drug levels were found to be above the predefined therapeutic range of 3-7 μg/mL, or was titrated up (by interval shortening mostly) if levels were found to be below this desirable range. After this leveling up of infliximab pharmacokinetics across all subjects, patients were then randomized to either a TDM arm whereby infliximab dosing was continuously adjusted as needed to keep drug levels within the 3-7 μg/mL range, or to a conventional therapy arm with continued unaltered infliximab dosing unless a clinical flare has occurred. The primary outcome of the study was not met because similar rates of patients in the 2 arms were in clinical and biochemical remission at the end of this 54-week trial.

Why was the primary outcome not met? One explanation is the initial optimization phase that, surpassing current practice standards, actively measured and acted on drug levels in patients responding to maintenance therapy. Notably, for patients with low drug levels, this was not a single-time dose increase, because the adjusted dose that brought a patient into the therapeutic range continued to be administered throughout the main study phase. This likely diminished interindividual differences in infliximab pharmacokinetics between the 2 arms at trial onset, making it harder to demonstrate additional benefit upon subsequent drug level measurements. One cannot help to wonder if the primary outcome would have been met had a less ambitious design was in place, that is, randomizing all patients from day 0 to either a standard care follow-up arm reacting only upon clinical inflammatory flares or to a TDM arm proactively dose adjusting per drug levels from trial outset. An additional cause for the unmet primary outcome is possibly related to the primary outcome being defined as a single time-point determination of remission at week 54, contrasting with the intervention-tolerant design, which allowed flaring patients in the conventional arm to be dose optimized throughout the study duration without this being considered a trial termination event. This probably further reduced the differences between the 2 strategies when gauged at a single eventual timepoint. It also explains why there were significantly greater rate of relapses in the conventional arm compared with the TDM arm, although the final remission rate was not different. Finally, TAXIT was launched in 2011, antedating several seminal works that advanced our understanding of TDM. For instance, patients with drug levels of <3 μg/mL were uniformly regarded as subtherapeutic levels and dose

escalated if they were in the TDM arm. However, it is possible that a subdivision exists within this range, because infliximab drug levels of <2 μg/mL identified patients with higher chance of remaining in remission after discontinuation of infliximab in the STORI trial.[15] Such patients' outcomes would be likely unchanged whether they underwent dose intensification or not, in the TDM or the conventional arms, respectively, further diminishing the ability to detect differences between the 2 strategies. Similarly, recent data using drug-tolerant assays show that drug+/ADA+ patients have unfavorable outcomes similar to patients with absent drug and positive ADA,[16,17] implying that these patients may benefit from some intervention to reduce immunogenicity and improve the pharmacokinetic profile. However, the assay employed in TAXIT was unable to distinguish between drug+/ADA+ and drug+/ADA- patients, and both would receive unaltered therapy. Moreover, it was recently shown that immunogenic-driven pharmacokinetics problems rarely evolve beyond the first year of therapy.[18] This implies that the patients enrolled in TAXIT, who have been receiving maintenance infliximab for a longer time (median, 4.6 years), might have been a selected group with a lower risk of immunogenic/pharmacokinetic problems, making it more difficult to demonstrate the efficacy of TDM. Finally, our knowledge about the drug concentrations that constitute a 'therapeutic window' is still evolving, with recent data suggesting that the optimal therapeutic range may depend on the outcome being sought, and may be different for clinical remission, C-reactive protein normalization, or mucosal healing.[19] Arguably, using a 3-7 μg/mL range in the TAXIT trial could therefore further diminish the difference between the 2 arms by setting too low a threshold for infliximab target concentrations, at least for some patients.

So what can be learned from a study that failed its primary outcome? There are many important lessons from this trial, as often is the case when one delves more deeply into studies with a missed primary outcome. First, the lead-in dose optimization phase is a landmark step forward in TDM-based patient care. It shows that a single time measurement of drug/ADA levels during seemingly successful

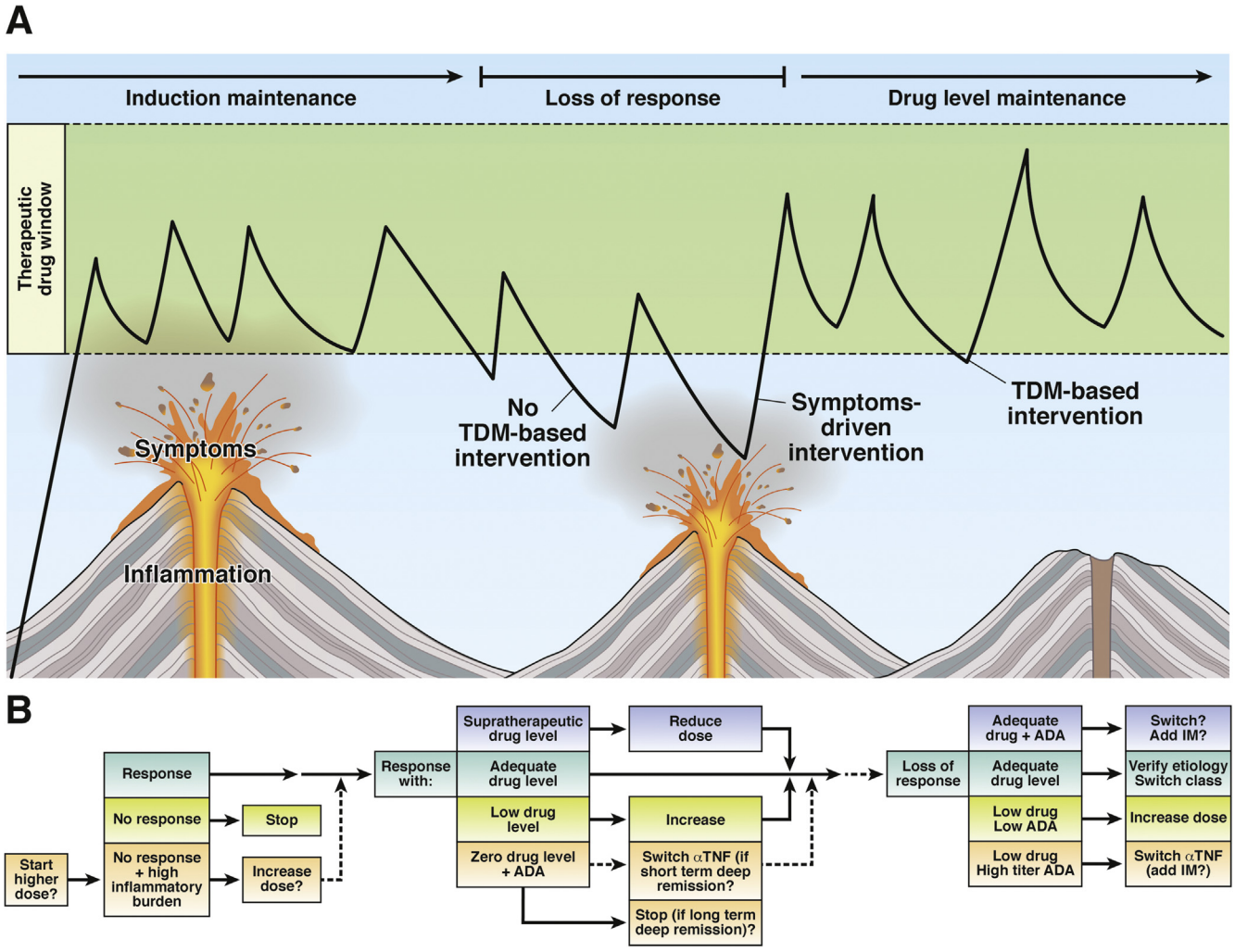

Figure 1. (*A*) Graphic illustration of how conventional infliximab therapy may lead to unsuspected drops of drug levels to subtherapeutic levels, instigating eruption of underlying gut inflammation and symptoms. An alternative strategy is also illustrated whereby pre-emptive dose-adjustments restore therapeutic drug-level before resurgence of inflammation and symptoms. (*B*) Proposed 3-tier algorithm for personalizing interventions based on therapeutic drug monitoring during anti-TNF induction, maintenance and loss of response.