Editorial Commentary

Adalimumab for Crohn disease: does more mean better?

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Adalimumab, a human monoclonal anti-tumor necrosis factor (TNF)-α antibody, is approved for moderate to severe Crohn disease in adult and pediatric patients and has been shown to be effective for induction and maintenance of clinical remission (1). However, clinical remission is not always sufficient for long-term outcomes, and multiple studies have supported endoscopic improvement or healing as more appropriate targets (2,3). Given that the majority of patients will experience either primary or secondary loss of response to anti-TNF-α biologic therapy (4), strategies to improve outcomes, such as using higher drug doses and adjusting drug dosing based on serum drug levels, are important areas of research. In fact, some studies suggest that higher drug levels are associated with better endoscopic and long-term outcomes (5).

Adalimumab induction dosing of 160 mg at week 0 and 80 mg at week 2 is the current standard induction dose for patients with Crohn disease, based on the CLASSIC trial, demonstrating a superior clinical remission rate compared to 80/40 or 40/20 mg induction doses (6). This would suggest that more drug would yield better outcomes, and indeed, higher adalimumab serum drug levels have been found to be associated with increased remission rates (5,7,8), however there have also been studies that have found no such association (9). Given this potential relationship between dosing, serum drug levels, and clinical outcomes, the question of whether higher adalimumab induction dosing could lead to increased clinical efficacy led to the development of the SERENE CD trial, and was the main focus of this study (10). Following serum drug levels and adjusting maintenance dosing frequency and dosing for low drug levels [referred to as therapeutic drug monitoring (TDM)], compared to escalating dosing based only on clinical data, was also of interest and explored in the maintenance phase of the SERENE CD trial.

The SERENE CD trial compared high (160 mg at 0, 1, 2, and 3 weeks) to standard dose (160 mg at 0 weeks and 80 mg at 2 weeks) adalimumab induction therapy in adults with moderate to severe Crohn disease, who had failed previous therapy (steroids, immunosuppressants, and/or infliximab). Both study groups then followed the same standard maintenance adalimumab dosing (40 mg every 2 weeks, starting at 4 weeks), and were then re-randomized at week 12 to be adjusted (escalation to 40 mg every week) based on clinical parameters [Crohn's Disease Activity Index (CDAI) ≥220 and C-reactive protein (CRP) ≥10 mg/L] or guided by TDM (adalimumab serum level <5 µg/mL or 5–10 µg/mL if CDAI ≥220 or CRP ≥10 mg/L).

For the induction phase, 308 patients were included in the high induction arm and 206 in the standard arm; 92 adults were randomized to each study group in the maintenance phase and followed for 56 weeks. Comparing high to standard dose induction, there were no significant differences in clinical remission (week 4; 44% in both groups), endoscopic response (week 12; 43% in high induction *vs.* 39% in standard induction, P=0.462), or safety. Both maintenance drug adjustment strategies had similar efficacy at week 56. Therefore, the primary outcomes of this study were not achieved, and quite conclusively, this study supported the continued use of standard adalimumab

dosing strategies for adults with Crohn disease.

Nevertheless, this study does raise some important issues to consider, and one needs to interpret the findings with caution. Regarding induction with higher doses, higher induction doses did lead to higher serum drug levels, but this did not translate into early clinical or endoscopic remission. Some studies have supported higher doses at induction of remission and dose intensification with both infliximab (another anti-TNF therapy) and adalimumab, but most were not randomized controlled studies like the current one (11,12).

It is thought that serum drug levels are an accurate measure of the amount of drug in one's system. However, the plasma drug concentration can be affected by a patient's inflammatory burden, gender, concurrent medications, albumin, and presence of anti-drug antibodies (13). Different assay techniques introduce additional variability, making it difficult to compare levels drawn at different sites and between studies. To date, there has been no reliable threshold serum adalimumab drug level cut-off that can be consistently associated with remission (7). Current available guidelines have variable recommendations. Proactive (pre-specified time points) versus reactive (at times of suspected loss of response) drug level monitoring has also been debated. Having at least one proactive adalimumab drug level over several years has been shown to be associated with a reduced risk of treatment failure in a retrospective cohort study (14). A study conducted in children with Crohn disease (called PAILOT), compared reactive and proactive (driven solely by drug levels) TDM approaches and did show a benefit to the proactive approach, with 82% reaching the primary end point of steroid-free clinical remission at 72 weeks, compared to 48% in the reactive arm (P=0.01) (15). Based on this and other studies, the European pediatric inflammatory bowel disease (IBD) guidelines do recommend proactive TDM for management of Crohn disease (16).

The same pediatric guidelines, as well as the American Gastroenterological Association (AGA) recently published suggested adalimumab maintenance therapy trough levels to be ≥7.5 µg/mL (16,17). Induction trough levels were not discussed. However, in contrast to the pediatric guidelines, the AGA and the European Crohn's and Colitis Organization (ECCO) determined that there is currently insufficient evidence to make recommendations on the proactive use of anti-TNF-α serum drug levels in patients with Crohn disease (12). Therapeutic serum drug monitoring is recommended in patients with secondary loss of response by the Australian and British societies (18).

In conclusion, the SERENE CD trial did not demonstrate a clinical, biochemical, or endoscopic benefit of a higher adalimumab induction dose or therapeutic drug monitoring, in adults with moderate to severe Crohn disease who had failed previous therapies. It is still unknown if there is more utility in using TDM in select patients (e.g., those with higher inflammatory markers or longer segments of inflamed bowel), rather than as a blanket approach to all patients. More specifically, there is good rationale for use of higher induction doses in young children for anti-TNF therapies (19), and biologic naïve patients might behave differently. It is also unknown if targeting a higher adalimumab drug level threshold (e.g., 7.5 µg/mL) in the SERENE CD trial would have led to different results. Further research is needed to analyze more homogenous study populations, since this study did have patients who were on steroids and/or immunomodulators (which can affect adalimumab drug levels), although this did not differ between the study groups.

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Footnote

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