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Clinical Implications of the Recent Dose-Ranging Studies of Adalimumab

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G&H How was adalimumab dosing determined for the treatment of Crohn's disease and ulcerative colitis?

BF Currently, standard induction dosing is 160 mg initially, followed by 80 mg in 2 weeks. Thereafter, dosing is 40 mg every other week. The pivotal study on adalimumab dosing in Crohn's disease was the CLASSIC study, which was conducted over 10 years ago. In this study, the doses of 160 mg and then 80 mg were identified to be more effective than lower doses. However, it was notable that a dose-response relationship was not shouldered in the study; in other words, more intensive dosing regimens were not studied. In fact, it could have been argued at the time that the study did not actually identify the optimal dose because the higher end of the dose-response curve was not explored. Adalimumab was approved at an induction dosing regimen of 160 mg and then 80 mg, with a maintenance regimen of 40 mg every other week as a result of the CHARM study. This study had compared every-other-week dosing with weekly dosing, but there did not appear to be a clinically important difference between the regimens. Thus, every-other-week dosing was adapted into clinical practice for Crohn's disease and approved by the US Food and Drug Administration.

For ulcerative colitis, the Crohn's disease dosing regimens evaluated in the CLASSIC and CHARM studies were adapted in the ULTRA studies and found to be effective. In other situations with monoclonal antibodies, ulcerative colitis patients have higher drug clearances, so it could have been argued that a Crohn's disease dose that might not necessarily be the optimal dose, as previously discussed, might need to be higher in ulcerative colitis. However, more intensive dosing regimens were not explored.

G&H Why were dose-ranging studies recently conducted for adalimumab?

BF There were a number of reasons. One was the incomplete examination of adalimumab doses, as discussed previously. Another reason was the evolving recognition that the pharmacokinetics of monoclonal antibodies is more complicated than that of small molecules. Initially, dosing was approached with the belief that one size fits all and that there was no reason to worry about dose adjustment. In fact, a number of studies found that trough drug concentrations, which are determined by drug clearance, are highly variable in patients with inflammatory bowel disease. Several factors were identified, including the patient's body mass index or weight and the amount of disease activity. Serum albumin was also identified as a dominant marker for drug clearance; patients with low serum albumin clear drug faster. It was subsequently recognized that patients with ulcerative colitis cleared monoclonal antibodies, those being globulins, through an atypical mechanism of drug loss into the gut, where drug would be trapped and degraded by microbes. This led to the concept that monoclonal antibody therapy may have to be individualized. It was also recognized that because

monoclonal antibodies are foreign proteins, some patients become sensitized and lose response. Therefore, when a patient who had initially responded to treatment subsequently lost response, it became popular to measure drug concentrations to determine whether the patient should be given more drug. This led to the field of therapeutic drug monitoring and the recognition that perhaps monoclonal antibodies could be optimized by measuring drug concentrations and antidrug antibodies.

The final reason that dose-ranging studies were performed was the notion that there was a linear response relationship between exposure to drug (ie, the measurement of drug in the patient's serum at steady state) and clinical efficacy. Subgroup analyses of clinical trials and investigator-initiated observational studies suggested that there was a linear association in that the more drug that was given, the higher the efficacy, whether it was measured by clinical symptoms or endoscopy. However, these data were observational and do not necessarily imply causation. Nevertheless, many clinicians leapt to the conclusion that the relationship was causal and that some patients needed a lot more drug to achieve optimal efficacy. Therefore, it became common practice to treat patients with low exposures with more intensive dosing regimens. With the background that the CLASSIC study did not shoulder the dose-response curve and that observations suggested that greater drug exposure might improve efficacy, researchers conducted the SERENE-UC and -CD studies to compare high-dose induction therapy with conventional dosing.

G&H How were the SERENE studies designed?

BF The protocols were very similar for Crohn's disease and ulcerative colitis. Patients were randomized to either standard induction dosing (160 mg and then 80 mg) or a regimen that consisted of 4 times the first standard induction dose (160 mg administered at weeks 0, 1, 2, and 3). Patients were assessed for induction, and a separate component of the trials contained a maintenance phase. To date, only the 4-week induction data have been reported. Outcome measures differed in ulcerative colitis and Crohn's disease. Both studies measured drug exposure. Because of the known linear relationship between drug concentrations and adalimumab dosing, it could be expected that patients who were given 4 times the drug dose would have 4 times the exposure as measured by drug levels and, potentially, greater efficacy.

G&H What were the main findings of these studies?

BF Both studies showed similar results. In the Crohn's disease study, patients were randomized 3:2 to either the high dose or the standard dose. SERENE-CD was a large study, with 308 patients in the high-dose arm and 206 in the standard-dose arm. At 4 weeks, the rates of clinical remission (defined by a Crohn's Disease Activity Index score of less than 150) were highly similar, with 42.2% in the high-dose arm vs 43.7% in the standard-dose arm, which was not a statistically significant difference. At week 12, the rates of endoscopic remission were 28.6% in the high-dose arm vs 26.2% in the standard-dose arm. Thus, there appeared to be no benefit to the high-dose arm, despite the observational data that had suggested otherwise. When the investigators looked at the pharmacokinetic data, the high-dose arm had approximately 4 times the exposure, as had been predicted.

The data from the ulcerative colitis study were similar. The study also used 3:2 randomization and was larger than the Crohn's disease study, with 512 patients in the high-dose arm and 340 in the standard-dose arm. The endpoint was clinical remission, which is a composite endpoint of cessation of bleeding, decreased stool frequency, and endoscopy. At the end of week 8, the rate of clinical remission was 13.3% for the high-dose arm vs 10.9% in the standard-dose arm, which meant that, again, there was no statistically or clinically meaningful difference between the 2 dosing strategies. The pharmacokinetic data were similar to those in the Crohn's disease study.

Patients who had high exposures continued to the maintenance phase. Maintenance results will likely be released within the next year.

In summary, these studies showed that there was no benefit to going beyond standard 160 mg/80 mg dosing in groups of patients with Crohn's disease or ulcerative colitis, that dose response had been shouldered by the CLASSIC study, and that for most patients the most appropriate dosing is the standard regimen. These studies put to rest the idea that there is a causal relationship between exposure and efficacy at the group level. These findings show the importance of not interpreting an association as being causal until an experiment is performed. What these findings likely mean is that patients who have high drug clearance also have poor prognosis for other reasons that do not involve drug exposure. This concept is very important and is true in both Crohn's disease and ulcerative colitis.

G&H Do these findings mean that dose intensification should not be used?

BF Many clinicians will say that these findings do not make sense, based on their experiences with patients who were underexposed and then responded to increasing the drug dose. Clinicians recognize when their patients are not doing well or have had a partial response.

If therapeutic drug monitoring is used to measure drug exposure in a trough sample and the patient has low exposure, sensible clinicians tend to treat such a patient with higher drug doses. I think this is a successful strategy in real-world practice and that these clinicians are not wrong; it is just that the SERENE studies did not evaluate this issue. What I mean is that the studies did not take patients who were at the lowest quartile of exposure and randomize them to high- or standard-dose adalimumab for induction; the studies randomized all patients, not just those with inadequate exposure. Thus, in my opinion, the SERENE findings do not preclude dose intensification in patients with inadequate exposure. Like many clinical trial results, the SERENE findings have not answered all of the questions that we have but raised another question—if the focus is only on patients who had high drug clearance and low exposure, would there, in fact, be a benefit to greater intensification of dosing? That question has not been answered.

G&H Could you place these findings in further context in the literature, and discuss more specifically the other studies that have been conducted on dose intensification?

BF Dose intensification, which is an off-label practice, has not been well studied scientifically. However, there have been several randomized, controlled trials performed in Crohn's disease patients taking adalimumab. The TAILORx study and other studies in the literature had inconclusive results. There was an Israeli study that did show benefit for dose intensification in children taking tumor necrosis factor (TNF) antagonists; however, there were several methodologic issues with the study that prevent us from concluding that there are definitive data supporting therapeutic drug monitoring–based treatment. Thus, dose intensification remains a controversial issue.

There have also been several open-label, observational, investigator-initiated studies on dose intensification with other inflammatory bowel disease drugs. However, none of these studies were done with the methodologic rigor of the SERENE trials, which were very high-quality, large-scale, randomized, controlled trials.

G&H Are there any other findings from the SERENE studies that should be pointed out?

BF The Crohn's disease study provided endoscopic data suggesting that it is possible to achieve endoscopic remission in approximately 20% of patients after 12 weeks of adalimumab therapy, which is similar to what was seen in the EXTEND study several years ago. Also important was the lack of evidence that greater drug exposure resulted in any safety or tolerability issues.

G&H What are the next steps in research in this area?

BF The most important next step is to conduct high-quality studies in patients with low drug exposure, or in patients in whom low drug exposure is predicted, rather than treating all patients with high drug doses at induction. That is the logical corollary of the results of the SERENE studies. The current findings clearly show that high-dose induction is not appropriate for all patients.

In addition, more research is needed on improving induction rates. A number of different inflammatory bowel disease drugs are currently available for induction (eg, TNF antagonists, the anti-integrin agent vedolizumab [Entyvio, Takeda], and the anti-interleukin agent ustekinumab [Stelara, Janssen]). However, we do not have high induction rates, especially in patients who have already failed a biologic drug. How can we achieve induction rates of 70% to 80%, when the current rates are much lower, as shown by the SERENE studies? In my opinion, the real question is whether higher rates can be achieved with single agents or whether combinations are needed.

Dr Feagan has been a consultant to AbbVie, Janssen, and Takeda Pharmaceuticals.

Suggested Reading

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