Is there a beneficial effect of adding azathioprine to adalimumab in Crohn's disease patients?

Mark Löwenberg

Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

Correspondence to: Mark Löwenberg, MD, PhD. Department of Gastroenterology and Hepatology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Email: m.lowenberg@amc.uva.nl.

Comment on: Nakase H, Motoya S, Matsumoto T, *et al.* Significance of measurement of serum trough level and anti-drug antibody of adalimumab as personalised pharmacokinetics in patients with Crohn's disease: a subanalysis of the DIAMOND trial. Aliment Pharmacol Ther 2017;46:873-82.

Submitted Jun 04, 2018. Accepted for publication Jun 15, 2018.
doi: 10.21037/atm.2018.06.36
View this article at: http://dx.doi.org/10.21037/atm.2018.06.36

Crohn's disease (CD) is a debilitating chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract. The disease is characterized by transmural inflammation and typically has a relapsing course over time. Up to now, there is no curative treatment. Among the most powerful agents to treat patients with CD are therapeutic antibodies that bind to the pro-inflammatory cytokine tumor necrosis factor (TNF). Infliximab, a chimeric antibody that is administered by intravenous infusion, and adalimumab, a subcutaneously administered, recombinant, human, monoclonal antibody, are the most frequently prescribed TNF blockers to treat CD patients. Both agents can induce and maintain remission in CD (1-5). Although, anti-TNF agents have revolutionized the treatment of CD, primary non-response and secondary loss of response significantly complicates the clinical management and is observed in up to 50% of patients (6-8). It has been reported that the annual risk for loss of response to infliximab and adalimumab in CD patients is 13% and 25%, respectively (9,10). Loss of response to anti-TNF agents is often caused by the formation of neutralizing anti-drug antibodies (so called immunogenicity), which in turn can result in increased clearance of the drug and low or even undetectable serum drug concentrations (11-13). Addition of an immunomodulator to infliximab therapy is an effective approach to reduce immunogenicity of infliximab (14). The SONIC trial was the first prospective randomized controlled study in CD patients that compared therapeutic efficacy between anti-TNF monotherapy (infliximab) versus combination treatment consisting of infliximab plus azathioprine (15). Patients with active CD, who had not received prior treatment with immunomodulators and biologicals, were randomized into three groups. They either received infliximab, azathioprine, or the two drugs combined. This landmark study showed superior steroid free clinical remission rates (primary outcome parameter) in patients receiving combination therapy compared to patients who received infliximab monotherapy. Of note, median serum infliximab trough concentrations at week 30 and 46 (i.e., serum samples were collected prior to infliximab infusions at week 30 and 46) were significantly higher in patients receiving infliximab and azathioprine combination treatment as compared to patients receiving infliximab monotherapy. The authors concluded that there was a clear clinical benefit from adding azathioprine to infliximab therapy in CD patients and that infliximab serum levels were higher in patients receiving combination treatment versus patients who received infliximab monotherapy.

However, whether addition of an immunomodulator in CD patients receiving adalimumab will be of any benefit is still a matter of debate. Associations have been reported between loss of response to adalimumab (including lack of endoscopic remission) in CD patients who have low adalimumab trough levels and detectable anti-drug antibodies (16-18). Reenaers *et al.* performed a retrospective study in 181 CD patients and concluded that there is a beneficial effect from combining adalimumab with an immunomodulator during the first semester after starting adalimumab (19). A lower need for adalimumab dose intensification and a reduction in the number of flares was observed in the combination group versus patients receiving adalimumab monotherapy. In contrast, a systematic

review and meta-analysis concluded that combination therapy, consisting of adalimumab plus azathioprine, was not superior to adalimumab monotherapy in terms of maintenance of remission up to one year in patients with CD (20). More recently, Colombel and colleagues analyzed several post-hoc analysis of prospective clinical trials with adalimumab (21). In these randomized controlled trials, therapeutic efficacy was studied as well as adalimumab serum concentrations and anti-drug antibody levels in CD patients who failed on prior conventional therapy receiving adalimumab monotherapy or adalimumab plus an immunomodulator. The conclusions were that no benefit was found from adding an immunomodulator to adalimumab therapy compared to patients receiving adalimumab monotherapy. Another study, performed by Ungar *et al.*, also failed to show a beneficial effect of adding an immunomodulator to adalimumab (22). Twenty-two out of 67 adalimumab treated patients received co-treatment with an immunomodulator, but this did not have a significant effect on adalimumab serum levels. Hence, several studies point into the direction that no beneficial effects can be found by combining adalimumab with an immunomodulator compared to adalimumab monotherapy in CD. However, prospective trial data are needed in order to definitively answer the question if combination treatment with adalimumab and an immunomodulator is more efficacious compared to adalimumab monotherapy in patients suffering from CD. Another question that needs to be addressed in a prospective study, is whether combination treatment will result in high(er) adalimumab serum concentrations and reduced anti-drug antibody formation compared to adalimumab monotherapy.

Recently, a multicenter, randomized, prospective, open-label clinical study (DIAMOND trial) investigated the impact of adding azathioprine to adalimumab in CD patients (23). The authors evaluated whether the combination of adalimumab and azathioprine may be more effective than adalimumab monotherapy in inducing and maintaining clinical remission, and endoscopic responses at week 26 and 52 were also evaluated. The authors undertook an ambitious task and enrolled in total 176 patients with active CD, who were naïve to biologics and thiopurines. Patients were randomized in a 1 to 1 fashion into two groups to receive either adalimumab monotherapy (n=85) or combination treatment with adalimumab and azathioprine (n=91). No significant differences were seen in clinical remission rates (primary endpoint) at week 26 [defined by a Crohn's Disease Activity Index (CDAI) score below 150 points] between the adalimumab monotherapy and adalimumab—azathioprine combination therapy group (71.8% *vs.* 68.1%, P=0.63, respectively). In addition, adverse events were similar in the two groups. Thus, no beneficial effect could be observed by adding azathioprine to adalimumab therapy with regard to clinical remission in these patients. The authors also evaluated endoscopic outcomes at baseline and at week 26 and 52, that represents a more objective measure of efficacy compared to clinical remission. Combination therapy was significantly more effective versus adalimumab monotherapy in achieving endoscopic response at week 26 (84.2% *vs.* 63.8%, P=0.019, respectively), but no significant differences were observed at week 52 (79.6% *vs.* 69.8%, P=0.36). Yet, a major limitation of this trial was the fact that no blinding was performed. In line with that notion, no central reading of endoscopy was done. However, I have to congratulate the authors for conducting the first randomized trial that prospectively compared adalimumab monotherapy to combination treatment with adalimumab and azathioprine in CD patients.

A recent sub-analysis of the Japanese DIAMOND trial was performed by Nakase *et al.* (24). Possible correlations were studied between clinical remission at week 26 and 52 and adalimumab trough levels and the occurrence of anti-drug antibodies (both measured at week 26) in patients who participated in the DIAMOND trial. Adalimumab trough levels and the presence of anti-drug antibodies were analyzed in 75 patients in the adalimumab—azathioprine combination group and in 76 patients who were enrolled in the adalimumab monotherapy arm. Moreover, the effect of co-treatment with azathioprine on adalimumab trough concentrations and anti-drug antibody levels were analyzed. The authors also examined associations between 6-thioguanine-nucleotide (6-TGN) levels (i.e., the active metabolite of azathioprine) and anti-drug antibodies. Lastly, factors were studied that could affect adalimumab trough levels and anti-drug antibody development. In short, significant higher adalimumab trough levels at week 26 were observed in patients who were in clinical remission compared to patients who were not in clinical remission at week 52 (7.7±3.3 *vs.* 5.4±4.3 μg/mL, P<0.001, respectively). An adalimumab trough cut-off level at week 26 of 5.0 μg/mL yielded optimal sensitivity (80%) and specificity (56%) for predicting clinical remission at week 52. The presence of anti-drug antibodies at week 26 was associated with clinical disease activity at week 52, and patients with elevated anti-drug antibodies had low(er) adalimumab

trough levels. Female gender and an increased body weight were independently associated with low adalimumab trough levels. However, no significant associations were found in trough levels between patients receiving combination treatment versus adalimumab monotherapy. Multivariate logistic regression analysis found a significant association between female sex and the occurrence of anti-drug antibodies, but no significant association was found with azathioprine co-administration (combination therapy group). 6-TGN levels in red blood cells at week 12 were measured in 71 patients who were randomized to the combination therapy arm and outcomes were correlated with anti-drug antibody outcomes. A 6-TGN cut-off level higher than 223 pmol/8×10^8 yielded optimal sensitivity (100%) and specificity (60.6%) outcomes for predicting anti-drug antibody negativity. These are interesting observations. Nevertheless, there are several limitations to this study. An important shortcoming is the fact that adalimumab serum levels and anti-drug antibody formation were not related to endoscopic outcomes and biochemical markers of disease activity, such as C-reactive protein or fecal calprotectin. Moreover, the sample size might be too small and, last but not least, adalimumab serum levels and anti-drug antibodies were measured at only one time point (i.e., at week 26), hence, no serial time points were analyzed.

In conclusion, there is conflicting data as to which addition of azathioprine to adalimumab will increase adalimumab serum levels and reduce anti-drug antibody formation resulting in improved clinical outcomes in CD patients. The DIAMOND trial was the first randomized controlled trial that compared adalimumab monotherapy to simultaneous treatment with adalimumab and azathioprine in CD. Although no differences could be observed with regard to clinical remission at week 26, improved endoscopic outcomes at week 26 were seen in patients receiving combination treatment, suggesting that combining adalimumab with azathioprine induces mucosal improvement more rapidly compared to adalimumab monotherapy. The recently reported sub-analysis of the DIAMOND trial provides us with important information. Significantly higher adalimumab trough levels at week 26 were found in patients who were in clinical remission at one year compared to patients who were not in clinical remission. Adalimumab trough cut-off levels at week 26 ≥5.0 µg/mL yielded optimal sensitivity and specificity for predicting clinical remission at one year. Moreover, detectable anti-drug antibodies at week 26 were associated with lower adalimumab trough levels and with clinical disease activity at week 52. Due to several limitations of the DIAMOND trial and the sub-analysis of this clinical study, prospective double blind studies are needed with sufficient patient numbers using objective (endoscopic) endpoints and serial time points for measuring adalimumab serum concentrations and anti-drug antibody levels. Only then we can draw firm conclusions as to which combined treatment with adalimumab and azathioprine should be advised for all CD patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: M Löwenberg has served as speaker and/or principal investigator for: Abbvie, Celgene, Covidien, Dr. Falk, Ferring Pharmaceuticals, Gilead, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, Protagonist therapeutics, Receptos, Takeda, Tillotts, Tramedico.

References

1. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541-9.
2. Watanabe M, Hibi T, Lomax KG, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. J Crohns Colitis 2012;6:160-73.
3. Peyrin-Biroulet L, Deltenre P, de Suray N, et al. Efficacy and safety of anti-tumor necrosis factor agents in Crohn's disease: a meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol 2008;6:644-53.
4. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323-33.
5. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52-65.
6. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther 2011;33:987-95.
7. Roda G, Jharap B, Neeraj N, et al. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management.

Clin Transl Gastroenterol 2016;7:e135.
8. Khan KJ, Dubinsky MC, Ford AC, et al. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2011;106:630-42.
9. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol 2009;104:760-7.
10. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. Am J Gastroenterol 2011;106:674-84.
11. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology 2009;137:1628-40.
12. West RL, Zelinkova Z, Wolbink GJ, et al. Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease. Aliment Pharmacol Ther 2008;28:1122-6.
13. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348:601-8.
14. Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72:1947-55.
15. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383-95.
16. Yanai H, Lichtenstein L, Assa A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. Clin Gastroenterol Hepatol 2015;13:522-30.e2.
17. Mazor Y, Almog R, Kopylov U, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther 2014;40:620-8.
18. Ungar B, Chowers Y, Yavzori M, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut 2014;63:1258-64.
19. Reenaers C, Louis E, Belaiche J, et al. Does co-treatment with immunosuppressors improve outcome in patients with Crohn's disease treated with adalimumab? Aliment Pharmacol Ther 2012;36:1040-8.
20. Kopylov U, Al-Taweel T, Yaghoobi M, et al. Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: a systematic review and meta-analysis. J Crohns Colitis 2014;8:1632-41.
21. Colombel JF, Jharap B, Sandborn WJ, et al. Effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in patients with Crohn's disease or ulcerative colitis who had failed conventional therapy. Aliment Pharmacol Ther 2017;45:50-62.
22. Ungar B, Levy I, Yavne Y, et al. Optimizing Anti-TNF-α Therapy: Serum Levels of Infliximab and Adalimumab Are Associated With Mucosal Healing in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol 2016;14:550-7.e2.
23. Matsumoto T, Motoya S, Watanabe K, et al. Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: A Prospective, Randomized Trial. J Crohns Colitis 2016;10:1259-66.
24. Nakase H, Motoya S, Matsumoto T, et al. Significance of measurement of serum trough level and anti-drug antibody of adalimumab as personalised pharmacokinetics in patients with Crohn's disease: a subanalysis of the DIAMOND trial. Aliment Pharmacol Ther 2017;46:873-82.

Cite this article as: Löwenberg M. Is there a beneficial effect of adding azathioprine to adalimumab in Crohn's disease patients? Ann Transl Med 2018;6(13):278. doi: 10.21037/atm.2018.06.36

