Journal of Crohn's and Colitis, 2016, 1257–1258
doi:10.1093/ecco-jcc/jjw119
Advance Access publication July 7, 2016
Editorial

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Adalimumab and Azathioprine Combination Therapy for Crohn's Disease: A Shining Diamond?

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The management of Crohn's disease [CD] patients has been rapidly evolving in recent years. Besides the development of new drugs with new mechanisms of action for patients who do not respond to conventional therapies, several studies have been conducted to evaluate the best strategies to optimise response and remission.[1,2] It is currently clear that the combination of infliximab and azathioprine is significantly more effective in inducing and maintaining clinical response and remission in naïve CD patients compared with infliximab and azathioprine monotherapies.[1] This combination is also effective in reducing the immunogenicity of infliximab,[3] thus reducing the risk of loss of response over time.

Matsumoto *et al.*[4] reported the results of a randomised open-label trial [DIAMOND] to evaluate whether the combination of adalimumab and azathioprine may be more effective than adalimumab monotherapy in inducing and maintaining clinical remission, and endoscopic response, at Weeks 26 and 52; 167 CD patients were randomised to receive a combination of adalimumab and azathioprine [n = 85] or adalimumab monotherapy [n = 92]. At Week 26 and Week 52, no differences in terms of clinical remission, defined as a Crohn's Disease Activity Index [CDAI] < 150, were found among the two groups [p = 0.63 at Week 26]. Also, adverse events related to study drugs were similar in both groups, and trough levels of adalimumab and anti-drug antibodies were similar in the two groups. However, combination therapy was significantly more effective than adalimumab monotherapy in achieving endoscopic response at Week 26 [84.2% vs 63.8%, p = 0.019], whereas no differences were found at Week 52 [79.6% vs 69.8%, p = 0.36], suggesting that combination is able to induce mucosal improvement more rapidly than monotherapy.

The study results suggest that therapeutic strategies could have different results, even within the same drug class. Although they share the same mechanism of action, every single anti-tumour necrosis factor [TNF] has got a particular molecular structure and pharmacokinetic and pharmacodynamic features.[5] This may affect significantly the interaction with other molecules and the consequent clinical efficacy. The different data on the combination of azathioprine with infliximab and adalimumab, even considering that the study population in the SONIC[1] and the DIAMOND[4] trials were quite similar in terms of inclusion and exclusion criteria, suggest that any clinical aspect regarding anti-TNF therapy should be investigated on each molecule, rather than extrapolating data across anti-TNF agents.

The effectiveness of combination therapy on endoscopic improvement, but not on clinical symptoms, confirms that the assessment of efficacy should go beyond the clinical symptoms based on the CDAI. The disconnection between symptoms and endoscopic findings in CD is well established[6] and a symptom-based therapeutic strategy may be less effective in achieving mucosal healing and preventing CD progression.[7,8]

Looking at the results of this study, combination appears to be unnecessary if only clinical remission is the goal, but may be recommended at least for the first 6 months if endoscopic response is considered as a primary target. Such difference confirms the need for objective measures of efficacy, such as endoscopic or cross-sectional imaging parameters and biomarkers, as recently proposed by the STRIDE consensus.[9]

The study by Matsumoto *et al.* confirms that combination of adalimumab and azathioprine may be considered useful to achieve rapid mucosal healing, at least in the first 6 months of treatment. Mucosal healing is established to be the main goal in CD patients together with clinical remission and restoration of quality of life, since it is associated with lower risk of abdominal surgery and complications.[10] Data from the SONIC[11] and the EXTEND trials[12] clearly show that the achievement of clinical remission and mucosal healing [deep remission] is associated with higher quality of life and less risk of hospitalisation and surgery, compared with those who achieve only remission of symptoms. Moreover, the combination of anti-TNF and thiopurines may significantly reduce the risk to develop structural bowel and consequent disease progression to complications, compared with conventional therapy [steroids + thiopurines], as recently shown by the REACT trial.[8] Further clinical trials on therapeutic strategies based on a treat-to-target approach are very much needed to understand whether mucosal healing can block bowel damage progression and dramatically change the natural course of the disease.

Funding

No funding received for this editorial.

Conflict of Interest

GF served as a consultant and advisory board member for MSD, AbbVie, Takeda, Janssen, Mundipharma, Sandoz, Pfizer; SD has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck, UCB-pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Danone, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, Johnson & Johnson.

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