

DIAMOND study: an additional evidence of the interest of being proactive in IBD

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The DIAMOND study is a multicenter, randomized, open-label study comparing adalimumab (ADA) with ADA plus azathioprine (AZA) in immunosuppressant-naïve CD patients (1). The primary endpoint of the study, clinical remission at week 26, did not differ between the monotherapy group and the combination group (71.8% *vs.* 68.1%; OR 0.84, *P*=0.63). Two post-hoc analyses of the DIAMOND study have recently been published. In the first analysis, published in this journal, the authors evaluated ADA trough levels (TLs) and anti-ADA antibodies (AAA) at week 26 and their significance for predicting clinical remission at week 52 (2). The ADA TLs at week 26 were not significant predictors of remission at week 52 in either the combination group or the monotherapy group (7.6±3.6 and 6.5±3.9 µg/mL respectively; *P*=0.084). However, there was a significant difference in adalimumab TLs at week 26 between patients with or without clinical remission at week 52 (7.7±3.3 *vs.* 5.4±4.3 µg/mL; *P*<0.001). A minimal cut-off drug level of 5.0 µg/mL at week 26 was determined to predict clinical remission at week 52. The development of AAA (in 13 patients) at week 26 was significantly associated with low ADA TLs and disease activity at week 52 (*P*=0.021). The authors also revealed a cut-off for 6-thioguanine (TGN) level of >222.5 pmol/8×10⁸ RBCs to suppress development of AAA, with a good sensitivity and specificity (100% and 62.5%, respectively).

In contrast to the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease study (SONIC), which demonstrated the superiority of a combination

therapy versus a monotherapy (infliximab + azathioprine *vs.* infliximab alone) on clinical, endoscopic and pharmacological evaluations (3), the DIAMOND study did not show any difference between the two strategies (ADA + azathioprine *vs.* ADA alone). However, the two studies differ in their methodologies: double blind *vs.* open label, lower dose of azathioprine in the DIAMOND study (maximal dose of 100 mg/day *vs.* 2.5 mg/kg/day). Nevertheless, in two post-hoc analyses of SONIC and DIAMOND, the authors demonstrated that the rate of clinical remission was dependent on the TLs of TNF alpha antagonist evaluated a few weeks previously (2,4). Thus, as for infliximab, obtaining adequate ADA TLs could be an important point to obtain a clinical remission. For this, many studies have indicated the need for ADA TLs around 5 µg/mL (5,6). Other studies have evaluated whether ADA TLs could predict endoscopic remission. In a large retrospective and observational study, Ungar *et al.* showed that levels of infliximab (IFX) above 5 µg/mL [area under the curve (AUC) =0.75; *P*<0.0001] and adalimumab above 7.1 µg/mL (AUC =0.7; *P*=0.004) identified patients with mucosal healing with 85% specificity (7). Vande Castele *et al.* reported for different thresholds that the proportion of patients not in remission progressively decreased from 17% when using an ADA threshold ≥5.0±1 µg/mL, to 10% with an ADA TC of ≥7.5±1 µg/mL (8). With these different considerations, what would be the targeted threshold to achieve clinical remission? This will need to be better evaluated, but a minimal level of 5 mg/mL must be considered and it may be that a level of >7.5 mg/mL would

be more favorable.

Moreover, it has been demonstrated that adding an immunosuppressor decreases the risk of immunogenicity and improves the pharmacokinetic profile of patients treated with a monotherapy of TNF alpha antagonists. Some studies have analyzed the best cut-off value of 6-TGN associated with clinical remission in patients under IFX-azathioprine (AZA). Yarur *et al.* recommended 6-TGN >125 pmoles as an optimal cut-off level to suppress antibodies to IFX (9). Similarly, in a prospective study analyzing the interest of decreasing the dose of AZA in patients with clinical remission under IFX-AZA, Roblin *et al.* demonstrated that a threshold of 6-TGN <105 pmoles/8×10⁸RBC was associated with an unfavorable evolution of IFX pharmacokinetics (10). Regarding the 6-TGN cut-off from DIAMOND, the results should be used with caution because of the limited numbers of CD patients positive for AAA in this study (13 patients) (2).

Proactive therapeutic drug monitoring (TDM) could be interesting for IBD patients with clinical remission and unfavorable PK; in this case, with drug optimization and improvement of PK, the risk of primary nonresponse or secondary loss of response to the drug should be decreased. This DIAMOND sub-study is heading in this direction. The higher the TL at week 26, the higher the rate of clinical remission at week 52.

In another recent sub-analysis of the DIAMOND trial, the authors found that higher ADA TL at week 26 was associated with mucosal healing at week 52 (OR, 1.34; 95% CI, 1.14–1.58; P for trend =0.001) and TL was significantly higher in patients with endoscopic response than in patients without endoscopic response at weeks 26 and 52 (P<0.001) (11).

Similarly, other studies have analyzed the impact of ADA TLs on the clinical or endoscopic outcome, but measured at the induction phase. Baert *et al.* observed in a cohort of 536 patients that a drug concentration below 5 µg/mL at week 4 was significantly associated with a risk of anti-adalimumab antibody formation (P=0.0002), a forthcoming elevated CRP, and adalimumab discontinuation related to loss of response (P=0.034) (12). In ulcerative colitis, a retrospective single-center study identified ADA concentration ≥7.5 µg/mL at week 4 (odds ratio 15.7; P=0.029) and baseline endoscopic Mayo score of 3 (odds ratio 0.13; P=0.047) as factors independently associated with short-term mucosal healing (13).

Conclusions

It is clearly established that both clinical and endoscopic remission (mucosal healing) are agreed targets in CD and UC (14). In a recent analysis, Colombel *et al.* demonstrated that timely escalation with an anti-tumor necrosis factor antibody could improve these targets, especially with the help of biomarkers. Indeed, in patients with early Crohn's disease, timely escalation of drug therapy on the basis of clinical symptoms combined with biomarkers (tight control group) results in better clinical and endoscopic outcomes than symptom-driven decisions alone. A significantly higher proportion of patients in the tight control group achieved the primary endpoint at week 48 than in the clinical management group (46% vs. 30%, P=0.010). Unfortunately, the authors did not report TDM for adalimumab (15).

Although clinical remission was not superior with a combination therapy as compared with monotherapy in the DIAMOND sub-study, the ADA TLs were able to predict the clinical and endoscopic outcome. Thus, whatever the modality of treatment used (mono- or combotherapy), the main goal is to obtain adequate TLs for the patients. Being proactive improves the management of IBD patients. The future will require a better identification of the pharmacokinetic target to be achieved.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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