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Letter: immunogenicity of infliximab—ready for routine prediction? Authors' reply

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EDITORS,

We thank Professor Amiot for his interest in our study and his comments pertaining to the use of *HLA-DQA1*05* genotyping for assessing the need for co-immunosuppression.[1,2] We agree that immunogenicity is not the sole determinant of infliximab loss of response. Other causes include low drug concentrations and/or exposure due to non-immune pharmacokinetic mechanisms, activation of non-tumor necrosis factor-α pathways and the coexistence of other disease processes such as irritable bowel syndrome or infection.[3-6] In our study, factors affecting infliximab exposure such as dose, interval, weight and use of combination therapy were accounted for in the multivariable analysis and the *HLA-DQA1*05* genotype remained an independent predictor of loss of response. Indeed, treatment discontinuation is not synonymous with immunogenicity as a multitude of factors may contribute to discontinuation of infliximab over the course of a patient's care. Adverse drug events, patient preference, loss of response as previously described, in addition to immunogenicity, may all play a role.

In our data set, co-immunosuppression appeared to reduce the risk of infliximab anti-drug antibody formation in variant carriers, while having little impact on wild-type individuals. Similarly, co-immunosuppression was associated with a reduction in loss of response and treatment discontinuation in variant carriers, while no apparent difference was seen in these outcomes between wild type individuals with or without co-immunosuppression. The effect of co-immunosuppression was outlined in Tables S2 and S3 of the original manuscript.[2] Specifically, co-immunosuppression was estimated to reduce the risk of infliximab loss of response and infliximab treatment discontinuation in variant and nonvariant carriers by 28% (hazard ratio [HR] = 0.72, 95% confidence interval [CI] = 0.43-1.2, P = 0.2) and 27% (HR = 0.73, 95% CI = 0.47-1.13, P = 0.16). A figure that further demonstrates this finding, in terms of proportion of patients who remain (Figure 1A) or lose response (Figure 1B) to infliximab over time is provided as a part of our reply. These findings did not achieve statistical significance; however, they suggest that not everyone benefits from infliximab combination therapy and that more targeted strategies need to be studied and applied.

Additionally, we respectfully correct Professor Amiot in his report of infliximab anti-drug antibody rates in our study population. The rate of infliximab anti-drug antibody formation was 25.4% in variant carriers vs 4.5% in wild-type individuals. Multivariable analysis revealed that variant carrier status was highly associated with antibody formation independent of other relevant variables including combination therapy.[2]

Lastly, we agree that a drug-sensitive ELISA may underestimate the incidence of anti-drug antibodies in our population; however, this is the test available to clinicians in practice and thus most closely mimics the real-world situation.

Ultimately, *HLA-DQA1*05* genotyping appears to be an important predictor of infliximab immunogenicity and other outcomes. There may be benefit for its use for the application of combination therapy or for the withdrawal of the immunomodulator as Professor Amiot suggests. As outlined in our paper, further study is needed to determine the utility of *HLA-DQA1*05* genotyping as a clinically actionable tool.

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The authors' declarations of personal and financial interests are unchanged from those in the original article.[2]

LINKED CONTENT

This article is linked to Wilson et al and Amiot papers. To view these articles, visit https://doi.org/10.1111/apt.15563 and https://doi.org/10.1111/apt.15576.

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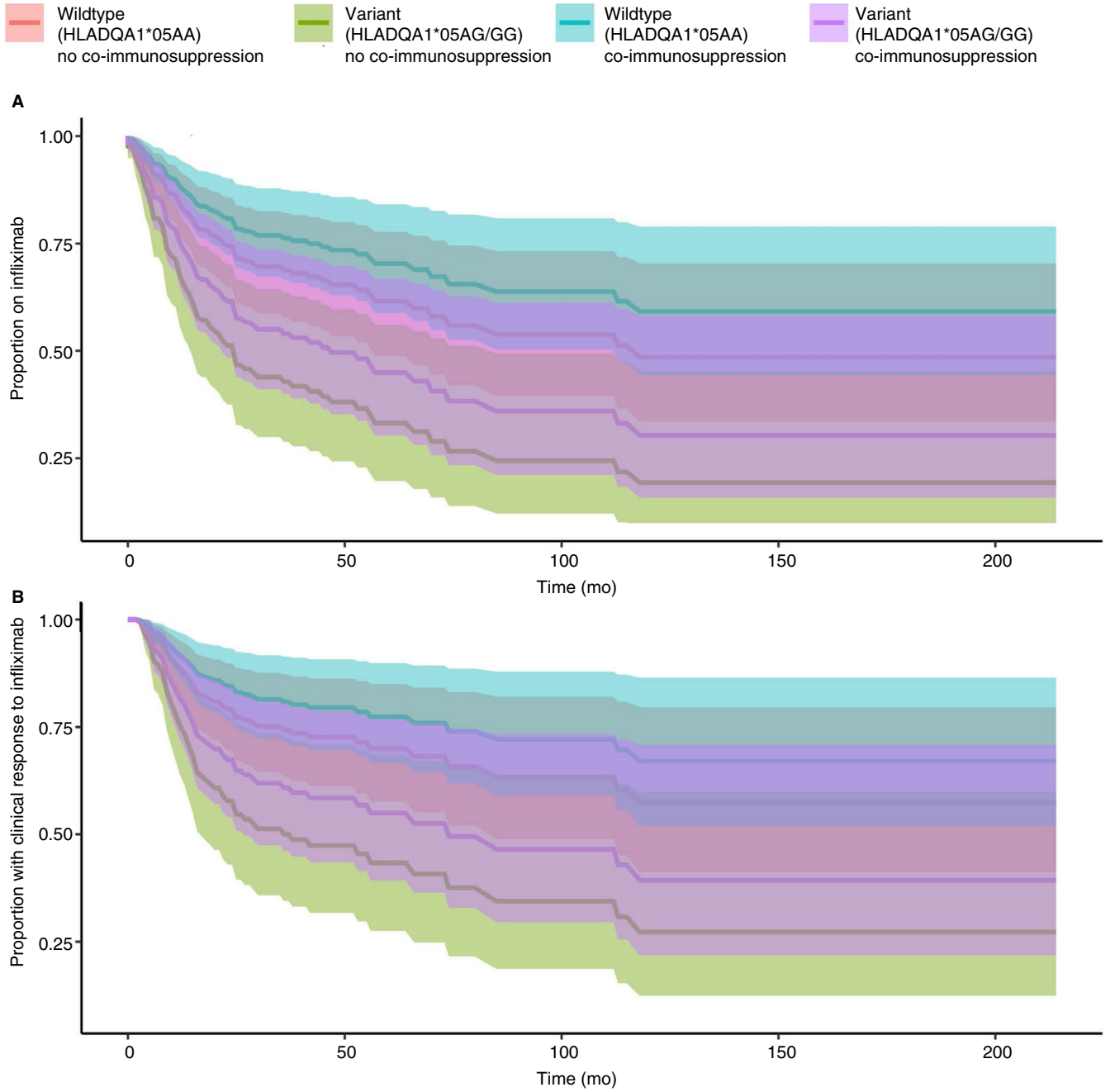

FIGURE 1 Adjusted survival curves of infliximab treatment discontinuation (A) and infliximab loss of response (B) according to *HLADQA1*05A>G* genotype and the presence or absence of co-immunosuppression with an immunomodulator (azathioprine or methotrexate) from a Cox Proportional Hazard Model. Data were *adjusted* for age, sex, weight and infliximab dose. 95% confidence intervals are represented by red (*HLADQA1*05* wild type and no co-immunosuppression), green (*HLADQA1*05* variant and no co-immunosuppression), blue (*HLADQA1*05* wild type and co-immunosuppression) and purple (*HLADQA1*05* variant and co-immunosuppression) shading

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