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Rapid response predicts complete biochemical response and histological remission in autoimmune hepatitis

To the Editor:

We read with great interest the manuscript by Pape *et al.* entitled "Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group". In this paper, the International Autoimmune Hepatitis Group (IAIHG) presents a statement on 5 agreed response criteria and endpoints for autoimmune hepatitis (AIH).[1]

Herein, we want to validate the new IAIHG response criteria and endpoints in Chinese patients with AIH. We performed a retrospective analysis of patients with AIH recruited from Renji Hospital, Shanghai Jiao Tong University from 2008 to 2020. Details of this cohort have been previously described.[2] Adult patients with AIH and a simplified IAIHG score ≥6 were included, whilst patients with variant syndromes or competing liver diseases were excluded.[3,4] A total of 650 patients were eligible for the analysis. The mean age was 50.0 ± 12.7 years and 82.9% were female. Patients were initially treated with prednisolone and the prednisolone dose was gradually tapered after remission. Maintenance therapy consisted of prednisolone and/or azathioprine. Mycophenolate mofetil was required if patients developed unacceptable toxicity from azathioprine. According to Pape *et al.*, non-response was defined as <50% decrease of serum transaminases within 4 weeks after initiation of treatment; complete biochemical response (CBR) was defined as normalization of serum transaminases and immunoglobulin G after no more than 6 months of treatment; insufficient response (IR) was defined as lack of complete biochemical response.[1]

Most patients (n = 601; 92.5%) scored as responders within 4 weeks after initiation of treatment (Fig. 1). Responders were less likely to have cirrhosis at baseline compared to non-responders (21.5% *vs.* 36.7%; $p = 0.014$). Furthermore, 502 patients (77.2%) achieved CBR within 6 months. These patients were less likely to have cirrhosis at baseline (19.1% *vs.* 34.5%; $p < 0.001$). Additionally, CBR occurred more frequently in 4-week responders (79.0% *vs.* 55.1%; $p < 0.001$).

We further evaluated the prognostic significance of the predefined endpoints (non-response, CBR and IR) in histological remission. Liver biopsies were re-evaluated in 276 patients who

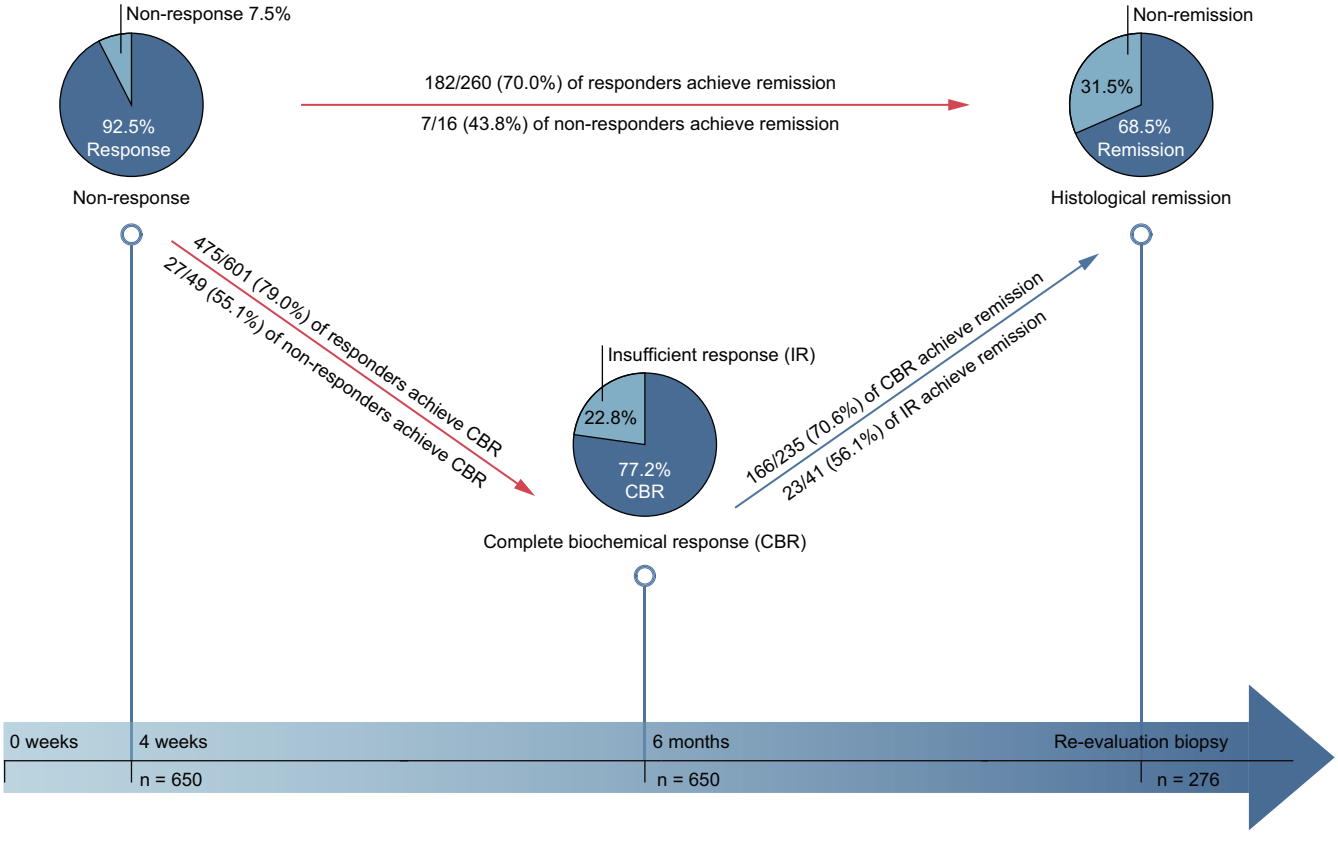

Fig. 1. Validation of the proposed surrogate endpoints in the Chinese AIH cohort. Statistical comparisons were performed using Fisher's Exact test or the chi-squared test. AIH, autoimmune hepatitis. (This figure appears in color on the web.)

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had received immunosuppressive therapy for at least 3 years, and histological remission (hepatic activity index <4) was achieved in 189 (68.5%) patients. Among them, 4-week responders were more likely to achieve histological remission than non-responders (70.0% *vs.* 43.8%; $p = 0.028$). Though the histological remission rate was higher in the CBR than the IR group, there was no statistical difference between the 2 groups (70.6% *vs.* 56.1%; $p = 0.064$). This finding could partly be explained by the limitation of the analysis that most patients with follow-up biopsies had already achieved biochemical remission.

In conclusion, we agree with Pape *et al.* that the 3 surrogate endpoints are reproducible and valid in AIH treatment and would be helpful to guide future clinical studies. More importantly, we provide further evidence of the predictive value of these surrogate endpoints in histological remission. Our data are in line with previous studies in which a rapid response to immunosuppressive therapy is a reliable predictor of biochemical and histological remission.[2,5]

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
YL: data analysis and manuscript drafting. XX: clinical diagnosis support and manuscript revision. QM: histological analysis support. XM: study concept and design.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.012.

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Author names in bold designate shared co-first authorship

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Reply to: "Correspondence on 'Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group'"

Defining endpoints that guide treatment in autoimmune hepatitis

To the Editor:
The focus point of our systematic review was to define endpoint criteria to allow interstudy comparisons. We performed a systematic review using a Delphi method process to provide a straightforward framework to define treatment response and endpoints in autoimmune hepatitis (AIH).[1] Endpoints can be used as reference points and as a standard that helps systematically report study results. This allows for a better comparison of outcomes across studies and facilitates data aggregation into systematic reviews to more accurately assess treatment efficacy.

The International Autoimmune Hepatitis Group (IAIHG) agreed that non-response in AIH should be defined as '<50% reduction of serum transaminases within 4 weeks after

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