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Conflict of interest

The authors declare that they have no conflict of interest relevant to the present study. LV has received speaking fees from MSD, Gilead, AlfaSigma and AbbVie, served as a consultant for Gilead, Pfizer, AstraZeneca, Novo Nordisk, Intercept, Diatech Pharmacogenetics and Ionis Pharmaceuticals, and received research grants from Gilead. SR has served as a consultant for AstraZeneca, Celgene, Sanofi, Amgen, Akcea Therapeutics, Camp4, AMbys, Medacorp and Pfizer in the past 5 years, and received research grants from AstraZeneca, Sanofi and Amgen.

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

Authors' contributions

LV, SR and GB conceptualized the study. GB performed the analyses. GB and LV drafted the manuscript. LV and SR reviewed the manuscript and supervised the study.

Supplementary data

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2022 International Autoimmune Hepatitis Group non-response criteria in autoimmune hepatitis: A too early endpoint?

To the Editor:

We have read with great interest the manuscript by Pape *et al.*[1] regarding an international consensus on response criteria and treatment endpoints in autoimmune hepatitis (AIH). The main goal was to standardize the criteria used among studies, enabling comparisons and the generation of more robust evidence. In this paper, the International Autoimmune Hepatitis Group (IAIHG) defined complete biochemical response (CBR) as normalisation of aminotransferases and IgG after no more than 6 months. The inability to achieve this endpoint was defined as insufficient response. Response was defined as ≥50% decrease of serum aminotransferases within 4 weeks after initiation of treatment.

Another recent paper from Pape *et al.*[2] had previously reported that patients with a significant decrease of aminotransferases after 8 weeks of treatment (rapid responders: defined as a decrease of ≥80% in level of aspartate aminotransferase [AST]) were more likely to achieve normalization of aminotransferases at week 26 and 52 (p <0.001).

Herein, we aim to validate the new IAIHG criteria and the 8-week response criteria in our cohort. We performed a

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retrospective analysis of a prospectively collated database including all adult patients with AIH diagnosed between 2004 and 2020. A liver biopsy was performed in all patients at the time of diagnosis; fibrosis was classified according to METAVIR scoring system. Clinical, biochemical and immunological parameters were assessed at baseline, 4, 8, 12, 26 and 52 weeks, and at last follow-up. Patients were included if the following criteria were met: 1. Age >18 years old at the time of diagnosis; 2. Definite diagnosis of AIH according to IAIHG simplified criteria[3]; 3. Induction therapy with oral steroids (prednisolone or budesonide) followed by introduction of azathioprine according to a well-established local protocol. Patients with variant syndromes or concurrent liver diseases or presenting with acute severe or fulminant AIH were excluded.

A total of 60 patients were eligible for the study (80% females). At diagnosis, the median age was 52 years (IQR 29-62). Type 1 AIH was predominant (86.7%). 23 patients had evidence of cirrhosis at diagnosis, 10 had advanced fibrosis (F3), while the remaining 27 patients had mild-to-moderate fibrosis (F1-2). Median follow-up time was 6.5 years (IQR 3.3-9.0).

Patients were initially treated per local protocol with prednisolone 40 to 60 mg/day (n = 55, 91.7%) or budesonide 9 mg/day (n = 5, 8.3%) for 2 weeks. The dose of prednisolone or budesonide was then tapered according to response; at the same time, therapy with azathioprine was commenced at 1 mg/kg/day, and then increased up to 2 mg/kg/day.

In accordance with IAIHG validation cohort, most of our patients were classified as responders after 4 weeks of treatment. Response (*i.e.*, decrease of >50% of AST levels after 4 weeks of treatment) was achieved in 50 (83%) patients. However, unlike in the original study, patients fulfilling response criteria had the same probability of cirrhosis at diagnosis (38.0% *vs.* 40.0%, $p = 0.9$).

CBR at month 6 was also achieved for most patients (n = 37, 61.7%). Despite a lower percentage of patients with CBR at month 6 having cirrhosis at diagnosis, this was not statistically significant (29.7% *vs.* 54.5%, $p = 0.1$).

We further evaluate the potential implications of IAIHG response criteria on the disease behaviour over time. In our cohort, IAIHG response criteria were not able to predict CBR at 6 and 12 months (66% *vs.* 60% $p = 0.72$; 65% *vs.* 50% $p = 0.36$, respectively). However, patients who achieved CBR at month 6 were able to maintain CBR over time (12-month CBR: 81% *vs.* 18% $p < 0.05$; last follow-up: 73% *vs.* 28% $p < 0.05$).

Lastly, we aimed to validate the impact of 8-week response criteria on the outcome of patients with AIH. Eight-week response criteria (*i.e.*, a decrease of more than 80% in the level of AST) was achieved in 50% (n = 30) of patients in our cohort. Rapid responders had a higher probability of CBR at 6 and 12 months compared to non-rapid responders (75% *vs.* 50%, $p = 0.05$; 79% *vs.* 54%, $p < 0.05$).

In conclusion, in our cohort, the 8-week response predicted a more favourable disease course, with higher probability of achieving and sustaining CBR, while the 4-week response as proposed by the IAIHG was not able to predict it. Assessment of CBR at 6 months performed well as an endpoint, since it was associated with maintenance of response over time. An early identification of non-response may enable the earlier identification of patients who would benefit from second-line therapies, but a 4-week assessment may be too early.

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Conflict of interest

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Authors' contributions

R.M. collected the patient data, planned the manuscript, performed the statistical analysis, did the literature review, and created the first draft. R.L. collected patient data, validated the statistical analysis and reviewed the manuscript. H.C. and G.M. did a critical expert review and revision of the manuscript.

Supplementary data

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