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]

Financial support
The authors received no financial support to produce this manuscript.

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.

References
Author names in bold designate shared co-first authorship

[1] **Pape S**, **Snijders RJALM**, Gevers TJG, Chazouilleres O, Dalekos GN, Hirschfield GM, et al. Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. J Hepatol 2022;76:841–849.
[2] **Li Y**, **Yan L**, **Wang R**, Wang Q, You Z, Li B, et al. Serum immunoglobulin G levels predict biochemical and histological remission of autoimmune hepatitis type 1: a single-center experience and literature review. Clin Rev Allergy Immunol 2022;62:292–300.
[3] Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology (Baltimore, Md.) 2008;48:169–176.
[4] European Association for the Study of the L. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol 2015;63:971–1004.
[5] Pape S, Gevers TJG, Vrolijk JM, van Hoek B, Bouma G, van Nieuwkerk CMJ, et al. Rapid response to treatment of autoimmune hepatitis associated with remission at 6 and 12 months. Clin Gastroenterol Hepatol 2020;18:1609–1617 e1604.

You Li
Xiao Xiao
Qi Miao
Xiong Ma*
Division of Gastroenterology and Hepatology, NHC Key Laboratory of Digestive Diseases, State Key Laboratory for Oncogenes and Related Genes, Renji Hospital, School of Medicine, Shanghai JiaoTong University; Shanghai Institute of Digestive Disease; 145 Middle Shandong Road, Shanghai 200001, China
*Corresponding author. Address: Division of Gastroenterology and Hepatology, NHC Key Laboratory of Digestive Diseases, State Key Laboratory for Oncogenes and Related Genes, Renji Hospital, School of Medicine, Shanghai JiaoTong University; Shanghai Institute of Digestive Disease; 145 Middle Shandong Road, Shanghai 200001, China.
E-mail address: maxiongmd@hotmail.com (X. Ma)

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

Received 26 July 2022; accepted 28 July 2022; available online 17 August 2022
https://doi.org/10.1016/j.jhep.2022.07.025

initiation of treatment'.[1] Medas *et al.*[2] aimed to validate the IAIHG definition of non-response and the 'rapid response' definition from Pape *et al.*,[3] defined as a decrease of ≥80% in the level of aspartate aminotransferase (AST) after 8 weeks. They did so using a cohort of 60 patients with AIH and demonstrated that rapid response at 8 weeks predicts a higher probability of complete biochemical response than the IAIHG definition for (non-)response within 4 weeks.[1] The authors did not include relevant clinical outcomes such as liver-related death or liver transplantation. Although the endpoint of 'rapid response' was not formally assessed in the Delphi survey and differs from the endpoint 'non-response', we agree with the authors that it is interesting to examine whether 'rapid response' after 8 weeks better discriminates between disease courses than non-response within 4 weeks.

Ma *et al.*[4] validated the IAIHG response criteria, non-response, complete biochemical response, and insufficient response, in their large cohort of 650 Chinese patients with AIH. In contrast to the Portuguese study,[2] 4-week responders had a higher probability of achieving a complete biochemical response compared to non-responders (79.0% *vs.* 55.1%; p <0.001). In addition, they provided evidence on the prognostic value of non-response, and they reported that histological remission was more likely to occur in 4-week responders compared to non-responders (70.0% *vs.* 43.8%; p = 0.028).

In order to validate 'rapid response' at 8 weeks, we performed a retrospective analysis using our adult AIH cohort which includes patients possessing a simplified IAIHG score ≥6. Patients with variant syndromes or competing liver diseases were excluded. We included 289 patients who were eligible for the study (75% females). At diagnosis, the median age was 51 years (IQR 38–66), and 59 patients had evidence of cirrhosis at diagnosis. The median follow-up time was 7 years (IQR 3.8–10.0). Most patients (n = 177; 61.2%) were considered rapid responders at 8 weeks after initiation of treatment. Patients with a rapid response, *i.e.*, an ≥80% decrease in the level of AST after 8 weeks, had a similar risk of liver-related death and liver transplantation as patients with a disease course based on our IAIHG non-response definition (hazard ratio [HR] 0.143; 95% CI 0.031–0.656; p = 0.012 for rapid response at week 8 *vs.* HR 0.139; 95% CI 0.045–0.426; p <0.001 for the IAIHG non-response definition).

The clinical consequence of these observations is that all endpoints may serve as predictors of the long-term disease course. As clinicians, we are continuously searching for parameters that predict the future of a disease with the hope that our management may change the clinical behaviour of that disease. However, this thinking confounds the debate on endpoints. We defined a set of endpoints needed for standard reporting of study results in AIH. To bolster credibility, we tested these definitions against (future) clinical outcomes and showed discriminatory predictive value. Our effort was not to design a tool to predict disease behaviour, as this requires the combination of many more (bio)markers to optimize the predictive value.[5] While a complete biochemical response is clinically a highly relevant endpoint, both clinicians and patients may want other (early) predictors in management algorithms for patients with AIH. We chose the 4-week period based on the best-published data at the time and after consensus within the IAIHG group, and we simplified the concept of non-responsiveness. Indeed, we could not distinguish between populations with a non-response or rapid response at 8 weeks with respect to the risk of liver-related outcomes, supporting the clinical relevance of the 4-week response.

The caveat is that our definitions help to compare AIH disease behaviour at a population level by implementing them in clinical studies. However, we think it is too early to use these definitions to guide individual management. It is important to consider that non-response does not necessarily imply that treatment should be changed, but it should alert the clinician since it is likely to have prognostic value, as we demonstrated above. It increases the transparency of the therapeutic pathway from the beginning of the AIH patient journey and can contribute to future clinical studies.

Financial support
No financial support was received for this letter.

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
RS: data analysis and manuscript drafting; TG, MH and JD: critical expert review and revision of the manuscript.

Acknowledgments
There are no additional acknowledgments.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.025.

References
Author names in bold designate shared co-first authorship

[1] **Pape S**, **Snijders R**, Gevers TJG, Chazouilleres O, Dalekos GN, Hirschfield GM, et al. Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. J Hepatol 2022;76:841–849.
[2] Medas R, Liberal R, Cardoso H, Macedo G. 2022 International Autoimmune Hepatitis Group non-response criteria in autoimmune hepatitis: a too early endpoint? J Hepatol 2022;77:1461–1462.
[3] Pape S, Gevers TJG, Vrolijk JM, van Hoek B, Bouma G, van Nieuwkerk CMJ, et al. Rapid response to treatment of autoimmune hepatitis associated with remission at 6 and 12 months. Clin Gastroenterol Hepatol 2020;18:1609–1617 e1604.
[4] Li Y, Xiao X, Miao Q, Ma X. Rapid response predicts complete biochemical response and histological remission in autoimmune hepatitis. J Hepatol 2022;77:1463–1464.
[5] Biewenga M, Verhelst X, Baven-Pronk M, Putter H, van den Berg AP, van Nieuwkerk K, et al. Development and validation of a prognostic score for long-term transplant-free survival in autoimmune hepatitis type 1. United Eur Gastroenterol J 2021;9:662–671.

Romée J.A.L.M. Snijders[1,4,*]
Tom J.G. Gevers[2,4]
Michael A. Heneghan[3,4]
Joost P.H. Drenth[1,4]
[1]*Department of Gastroenterology and Hepatology, Radboudumc, Nijmegen, the Netherlands*

[2]Department of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, the Netherlands
[3]Institute of Liver Studies, King's College Hospital, London, United Kingdom
[4]European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Germany

*Corresponding author. Address: Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, the Netherlands.
E-mail address: Romee.Snijders@radboudumc.nl (R.J.A.L.M. Snijders)

Liver stiffness, fatty liver disease and atrial fibrillation in the Rotterdam study: Some issues

To the Editor:

We read with great interest the recently published manuscript by van Kleef *et al.*[1] Based on the evaluation of atrial fibrillation (AF), hepatic steatosis and liver stiffness by 12-lead electrocardiogram (ECG), abdominal ultrasound and transient elastography, respectively, the authors concluded that liver stiffness but not non-alcoholic fatty liver disease (NAFLD) was significantly associated with atrial fibrillation. Having read the manuscript, we wanted to raise the following points:

First, AF was diagnosed based on a 10-second 12-lead ECG performed at regular visits in the present study. Although the ECG was assessed by the modular ECG analysis system and validated by 2 research physicians, the accuracy of the prevalent rate of AF has to be reconsidered. From a recent comprehensive evaluation of AF, the sensitivity of AF diagnosis by a 10-second ECG was less than 5%.[2] Using a 7-day Holter ECG to diagnose AF might yield around 50% sensitivity for detecting AF. According to guideline recommendations,[3] we suggest that the diagnosis of AF might be based on screening tools such as mobile/wearable devices, a single-lead ECG tracing of ≥30 seconds, long-term Holter and 1–2-week continuous ECG patches to prevent from the underestimation of AF prevalence. Furthermore, the prevalence of AF in those aged 65-69 years old was 3∼4.6% in the previous study.[4] With the average age around 69.5-year-old, the prevalence of AF was reported at around 7% in this study which seems to be higher than the previous data. Not to mention that this prevalence may possibly be underestimated, as mentioned earlier. The high prevalence rate of AF in the Rotterdam Study deserves further study and clarification.

Second, comorbidities such as obesity, thyroid disorder, valvular heart disease (mitral valve stenosis especially) and chronic obstructive pulmonary disease are well known to be the risk factors of AF,[5] which were not evaluated to clarify the relationship between liver disease and prevalent AF in the present study. It is a particular pity that the association between the available BMI data and AF was not studied.

Third, the authors assessed liver stiffness by transient elastography in the present study. It would be interesting to know the results of evaluating steatosis by controlled attenuation parameter (CAP). Recently published EASL Clinical Practice Guidelines[6] stated that there was insufficient evidence to recommend CAP as a first-line technique. Nevertheless, despite there being no consensual cut-offs, CAP values above 275 dB/m have high sensitivities and positive predictive value (>90%) for the identification of NAFLD. The addition of CAP data would solve several issues, enabling the: i) effective validation of the diagnosis of NAFLD by abdominal ultrasound; ii) assessment of the association between steatosis and AF; iii) assessment of the association between AF and non-alcoholic steatohepatitis (NASH) by the FAST (FibroScan-AST [aspartate aminotransferase]) score which has been reported to provide an efficient way to identify patients at risk of progressive NASH.[7] We believe that it will further add to the body of evidence regarding the association between AF and NAFLD/NASH.

Received 25 June 2022; accepted 30 June 2022; available online 08 July 2022
https://doi.org/10.1016/j.jhep.2022.06.027

Financial support

The authors received no financial support to produce this manuscript.

Conflicts of interest

CY Dai: Consultant of Gilead, Abbvie; Speaker of Gilead, Abbvie and Merck. ML Yu: Research support (grant) from Gilead and Abbott; Consultant of Gilead, Abbvie and Merck; Speaker of Gilead, Abbvie and Merck.

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

Authors' contributions

Chia-Yen Dai and Wei-Chung Tsai conceived of the presented idea. Chia-Yen Dai and Wei-Chung Tsai wrote the manuscript in consultation with Ming-Lung Yu. All authors discussed the results and contributed to the final manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.06.027.

References

[1] van Kleef LA, Lu Z, Ikram MA, de Groot NMS, Kavousi M, de Knegt RJ. Liver stiffness, but not fattyliver disease, is associated with atrial fibrillation: the Rotterdam study. J Hepatol 2022;77:931–938.
[2] Diederichsen SZ, Haugan KJ, Kronborg C, Graff C, Højberg S, Køber L, et al. Comprehensive evaluation of rhythm monitoring strategies in screening