Reply. We thank Professor Liaw for his interest in our commentary on challenges with finite nucleos(t)ide analogue (NUC) therapy in patients with hepatitis B e antigen-negative chronic hepatitis B.[1]

In our commentary, we have argued that the one-size-fits-all approach to NUC therapy withdrawal underlying the clinical practice guidelines was too preliminary. Differences in methodology (retreatment criteria, monitoring frequency) and patient characteristics (ethnicity, HBV genotype) may confound results and therefore decrease external applicability. Liaw reasoned that most cohort studies with sufficient power and/or off-treatment follow-up have reported greater HBsAg loss rates, albeit to a lesser extent in Asian patients. Regarding HBsAg loss, 3 important points should be considered.

Even though our commentary was not a systematic review, we have highlighted all randomized controlled trials and the largest prospective and retrospective studies to date. Across these studies, HBsAg loss rates were not consistently increased, neither in Asian nor in Caucasian populations. For example, a recent international cohort study in 178 hepatitis B e antigen-negative patients (44% Asian, 49% Caucasian) reported that NUC therapy withdrawal did not influence HBsAg loss rates.[2]

The current data, which suggest a beneficial effect of stopping NUC, are largely based on observational studies, whereas the published randomized controlled trials show very little benefit. Most observational studies were not designed to investigate differences in HBsAg loss rates and should therefore be cautiously interpreted. Liaw mainly quotes Asian studies, of which the majority were from Taiwan, where the main reason for stopping was a lack of continued reimbursement by national health insurance after only a few years of NUC therapy. Even in studies with longer off-treatment follow-up, rates of HBsAg loss varied from 0% to 19%, which at best reflect that only highly selected patients have higher chances of achieving HBsAg loss.

As Liaw mentioned, in a previous observational study from our group we have indeed reported 14% HBsAg loss,[3] but we have also mentioned that the results required confirmation in a prospective randomized controlled trial, which we did. As is more often the case, this randomized controlled trial could not confirm the earlier findings, not even with prolonged follow-up.[4,5] All these discrepancies reveal that the data quality is insufficient to move on with widespread NUC cessation.

When discussing safety, Liaw claimed that adverse events after NUC cessation are rare and preventable by timely retreatment if patients adhere to adequate monitoring plans. Precisely these 2 concepts—when to retreat and how to monitor off-treatment—remain very contentious. The criteria for retreatment and definitions of monitoring plans differ in studies and the major clinical practice guidelines. Perhaps because of the lack of standardization, clinical relapse rates may be as high as 68%.[1] Furthermore, at a rate of 3%, hepatic decompensation after NUC withdrawal is not uncommon[6] and is not always limited to cirrhotics, as reported in our commentary.

Liaw suggested that shorter lengths of finite NUC therapy decrease complications compared with long-term therapy, which is hampered by nonadherence or loss to follow-up. The opposite might very well be true because consolidation therapy beyond 3 years leads to lower persistent virologic relapse and higher HBsAg loss rates.[3] Adherence issues to entecavir therapy among cirrhotics might not fully explain higher rates of hepatic complications, as well-known confounders (HBV genotype or higher HBsAg values) were not adjusted for.[7] Instead of limiting therapy, this merely reinforces the need to identify and address nonadherence, especially in at-risk groups such as cirrhotics.[6]

A controversial topic touched upon by Liaw is flare-induced HBsAg loss. Recent reviews have made this approach sound feasible, but the data only stem from small, nonrandomized studies in which some patients had to be rescued from hepatic decompensation.[8] This strategy is also difficult to apply in clinical practice.

We agree with Liaw that the road forward involves evaluating biomarkers shortly after, or preferably, before stopping NUC therapy to predict outcomes. Work on virologic (HBsAg, anti-HBc, HBcrAg, and HBV RNA) or immunologic biomarkers continues and may increase our predictive power for safely stopping NUC therapy. Thus far, no biomarker has proven robust through prospective, external validation, and several are not yet commercially available for clinical decision making.

To conclude, if a decade of investigating the potential for NUC therapy has taught us anything, it is that, first, no uniform NUC withdrawal approach exists, and, second, we still need better evidence to come to clinical recommendations. Until then, it seems that a careful walk on the road to finite NUC therapy, preferably in well-designed prospective studies, remains best practice.

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Conflicts of interest

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 **Most current article**

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The Nightmare Monitoring of JAKinhibs

Dear Editors:

We read the article published by Olivera et al[1] with a great interest. This review and meta-analysis focuses in particular on Janus kinase inhibitor (JAKinhib) safety. An important aspect of the safety of these molecules as well as their specificity lies in the doses used. We believe that it is crucial to improve the monitoring of these molecules to optimize their efficacy and safety profile.

Cytokines are key mediators involved in both normal homeostasis and various pathologic processes associated with inflammatory disorders. The biological effects of cytokines, including several implicated in the physiopathology of autoimmune diseases, occur as a result of receptor mediated signaling through the Janus kinase and Signal Transducer and Activator of Transcription (STAT) DNA-binding families of proteins. Until recently, anticytokine therapy with monoclonal antibodies that target only 1 or 2 single cytokines, such as tumor necrosis factor, IL-17, or IL-12/IL-23, have been approved for the treatment of inflammatory bowel diseases and rheumatoid inflammatory disorders. However, a significant proportion of patients experiences primary or secondary non-response to these drugs. Several JAKinhibs are in clinical development for the treatment of inflammatory disorders and have the potential to affect multiple proinflammatory cytokine-dependent pathways. Some of these molecules have demonstrated efficacy in early phase trials and to date, tofacitinib has been approved by the US Food and Drug Administration for the treatment of ulcerative colitis, psoriatic arthritis, and rheumatoid arthritis. Although the overall safety profiles of tofacitinib and other JAKinhibs have been favorable, the universality of JAK-mediated signaling may increase the potential for unexpected effects.[2]

Therapeutic drug monitoring can assist with making targeted dose adjustments in patients with low serum drug concentrations, monitoring of adherence, and assessment of patients who lose response, or who do not respond at all. Consensus has been achieved toward the usefulness of therapeutic drug monitoring of biologics in inflammatory bowel disease, particularly anti-tumor necrosis factor therapies, and predominantly in reaction to loss of response to therapy.[3–5] Despite the use of JAKinhibs in clinical trials, the lack of reliable predictive biomarkers pose a challenge to find the most effective regimen for each type of patient.

JAKinhibs such as tofacitinib, filgotinib, or upadacitinib have a pharmacokinetic half-life of a few hours, and were metabolized to form a major active metabolite with a half-life of about 1 day. The use of classical pharmacokinetic analysis does not predict the response to these molecules. In addition, these assays do not allow for the in vivo determination of active molecules on the JAK phosphorylation pathway. The half-life of these molecules is too short to predict their long-term efficacy in patients. In the numerous pivotal studies of the JAKinhibs, numerous and various cytokines were measured by ELISA/Luminex assays in patient plasma to predict efficacy and to identify a cytokine signature, but without great success. The detection of interferon-stimulating genes by NanoString or reverse transcriptase polymerase chain reaction has been proposed as an alternative for the detection of cytokine signatures, but the sensitivity, specificity, and predictive value of the assay have not been reported. Because the use of this simple test might represent a gold standard for the evaluation of various immune diseases, it could also be used to monitor patients treated with other drugs targeting the type I IFN pathway.[6]

Finally, the monitoring of target cells could be also a solution to predict clinical efficacy of JAK inhibitors. As JAK inhibitors mainly target B and T lymphocytes, it has been proposed to monitor JAK phosphorylation in vivo after administration. Owing to the lack of good antibodies to monitor JAK phosphorylation by flow cytometry, it has been proposed to look for STAT phosphorylation instead of JAK. Phosphospecific flow cytometry panels allow monitoring the activation of STAT3 and STAT5 by ex vivo whole blood analysis but require an in vitro stimulation of cells.[7–9] The technical difficulty of carrying out this type of assay makes its use in everyday practice complicated for therapeutic drug monitoring.

Interestingly enough, we also know that the binding of cytokines to cytokine receptors induce endocytosis.[10] Cytokine receptor endocytosis is required for activation of the JAK/STAT pathway as described for both IL-4 receptors[11] and IFNα/β receptors.[12,13] We also know that the re-expression of cytokine receptors after activation takes several days both in vitro and in vivo as described for IL-7 receptor.[14] Measuring the expression of these cytokine receptors not only by flow cytometry, but also by transcriptomic signature could be particularly interesting to predict the efficacy and safety of JAK inhibitors at baseline, but also during patient follow-up.

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