of RVR in deciding whether genotype 2/3-infected patients should receive short-term treatment. Additionally, considering that sampling HCV RNA on day 7 entails only one sampling instead of the two suggested by Sarrazin et al., i.e. baseline and week 4, while identifying approximately as many suitable candidates for short-term therapy, sampling at day 7 is likely to be more cost-effective for patients infected with HCV genotype 2 or 3. Also, the suggested cut-off level of 1000 IU/ml is stably quantifiable by most currently available assays, and is not prone to re-definition as the limits of detection of HCV RNA analyses will further improve over time. Similarly, since it is important that the day 7 HCV RNA sample is drawn immediately prior to the second dose of pegylated interferon, this allows for an additional opportunity to directly observe the patient's injection technique as well as minimize the risk of sampling variations in relation to the previous dose as is often the case with week 4 HCV RNA determination. However, it is important to consider the intra- and inter-assay variability of real-time PCR based HCV RNA assays [6] as well as differences between methods that persist despite the introduction of WHO standardizations [7], which obviously affect all proposed algorithms based on quantitative HCV RNA determinations, including those at baseline or day 7.

Conflict of interest

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For the NORDynamIC Study Group

Viral kinetics for individualized treatment durations

Reply to Lagging et al.:
The shortening of treatment duration is the most important aim for improving antiviral therapy in patients with chronic hepatitis C. The new direct antiviral agents currently in development should allow an increasing number of patients to benefit from shortened treatment durations and consequently to significantly increase the number of patients who are willing and able to receive antiviral therapy. Algorithms for abbreviated treatment durations established for the current standard of care are mainly based on viral kinetics. In addition, while not visible in smaller studies [1,2] all large studies have shown that in patients with high baseline viral load, higher relapse rates were observed, although they become HCV RNA negative at time points that are identical to those reported in patients with a low baseline viral load [3,4]. Thus, in the NORDynamIC study reported by Lagging et al., baseline viral load may not be a significant predictor of relapse in patients with virologic response at day 7 because of the limited number of patients investigated [5]. However, it may also be that the selection of patients for shortened treatment very early on during therapy (i.e. day 7) and the application of a viral cut-off level (i.e. 1000 IU/ml) rather than undetectable HCV RNA, allow for a response to be predicted independent of baseline viral load. This has to be explored in future studies. However, while the assessment of virologic response very early during therapy may indeed have the potential of very high positive predictive values of sustained virologic response, the number of patients

benefitting may decline (i.e. 109 vs. 136 patients in the NORDynamIC trial). In addition, practical, pharmacokinetic, and technical problems may arise: (1) it is essential to take an early assessment of viral kinetic measurements of HCV RNA viral load from blood drawn exactly at day 7 and directly before the next PEG-interferon injection because viral load may fluctuate significantly during the initial phase of viral decline. This may be less of a problem 4 weeks after initiation of antiviral therapy. Indeed, in our study we found that when retesting a large number of samples at week 4, undetectable HCV RNA and viral levels below 15 IU/ml had identical predictive values for sustained virologic response in genotype 1 and 2/3 infected patients [6]. (2) Differences may be present between the two pegylated interferons alfa 2a and 2b because of different pharmacokinetics (65 vs. a 28 h elimination half-life, respectively). For pegylated interferon alfa 2b, a more step-wise viral decline is well known. After one week of therapy a flat or even slightly increasing viral load kinetics may be seen while a more continuous viral decline is observed with pegylated interferon alfa 2a. With identical rapid virologic response rates for both pegylated interferons at week 4 of treatment (IDEAL study 11.4% vs. 11.9% for pegylated interferon alfa 2a vs. 2b, respectively) [7] algorithms with later assessments of virologic response may be better applicable for these differences. (3) Finally, despite standardization of IU HCV RNA viral loads measured with different commercially available assays, these are not comparable and this is already a problem for the determination of low vs. high baseline viral load. For a measurement at day 7 as proposed by Lagging et al., for example 1000 IU/ml by the Cobas TaqMan assay in genotype 1, 2, 3 infected patients equals approximately 300, 1000, and 600 IU/ml by realtime HCV and 300, 600, and 500 IU/ml by the bDNA assay [8–11]. Moreover, a significant intra- and inter-assay variability especially for lower viral loads (0.04–0.13 log10 SD) may make it difficult to establish a general and precise rule with just one HCV RNA measurement taken early during therapy [10]. Herein, determination of undetectable HCV RNA levels with a highly sensitive assay may be superior because all new assays have lower detection limits between 5 and 10 IU/ml (Cobas TaqMan, realtime HCV, TMA).

All these parameters have to be taken into account for the current standard of care. In the era of direct antiviral agents that display strong antiviral activities, highly individualized and tailored treatment durations will be established. The determination of virologic response with or without additional parameters (baseline viral load, IL28B polymorphisms etc.) very early during therapy (i.e. between day 3 and week 4) will most likely be required for the selection of super responders that may benefit from very short treatments (24 weeks or shorter for genotype 1 and perhaps even below 12–16 weeks for genotype 2/3 infected patients).

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reactivation of autoimmune hepatitis during budesonide monotherapy, and response to standard treatment

To the Editor:

The large European trial of budesonide therapy suggests that budesonide might be better than prednisone in the treatment of newly diagnosed autoimmune hepatitis [1]. These results were based on the sensible combination of azathioprine and steroid, but already physicians have started using budesonide monotherapy, or combinations of budesonide and prednisone or prednisolone. We wish to report a case of autoimmune hepatitis (AIH), who experienced reactivation of disease activity during treatment with 3 × 3 mg budesonide per day and tapering doses