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van Seyen, Minou; Smolders, Elise J.; van Wijngaarden, Peter; Drenth, Joost P. H.; Wouthuyzen-Bakker, Marjan; de Kegt, Robert J.; Honkoop, Pieter; El-Sherif, Omar; Colbers, Angela; Back, David J.

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Successful HCV treatment of patients on contraindicated anti-epileptic drugs: Role of drug level monitoring

To the Editor:
We read with great interest the Snapshot “Treatment of chronic hepatitis C” recently published by Forns and Sarrazin in the Journal of Hepatology. The authors defined several special populations which require special attention. We believe, that patients on strong inducing anti-epileptic drugs (AEDs) such as carbamazepine, phenytoin and phenobarbital are an additional population that requires special attention as treatment of individual cases remains a major challenge. Co-administration of direct-acting antivirals (DAAs) with these AEDs is contraindicated as plasma concentrations are markedly reduced potentially leading to loss of efficacy and virological failure. A recent study in Sweden showed that carbamazepine was prescribed in 2% of all patients diagnosed with HCV. Carbamazepine was the most commonly used contraindicated drug for the several DAA combinations.

The majority of drug-drug interactions (DDIs) with other drugs classes, an interacting drug can temporarily be stopped or substituted. However, it is our experience that in some cases, patients are not able or willing to stop or substitute AEDs, to prevent DDIs. Therefore, some patients on enzyme inducing AEDs, based on product labels, cannot be treated for HCV. As separate daclatasvir (DAC) and sofosbuvir (SOF) formulations are available, dose adjustment of individual agents is possible. We aimed to cure HCV patients on contraindicated AEDs and examine the feasibility of an adaptive dosing strategy of reduced DAC exposure, the dose was increased to 60 mg TID. We found no reduction in SOF exposure when combined with carbamazepine 400 mg/day and phenobarbital 100 mg/day. In contrast, a 3-fold lower SOF exposure was observed for carbamazepine ≥1,000 mg/day compared with reference values. For 2 patients SOF data were not evaluable.

We decided to study the combination of DAC/SOF because dose adjustments for individual HCV components might have been required, which was possible with DAC and SOF. This was not possible with fixed-dose tablets available at time of treatment initiation, which also applies to the currently preferred pangenotypic DAA combinations.

DAC extrapolated AUC$_{0-24h}$ was lower in all patients on carbamazepine compared to reference values. Exposure, efficacy and safety analyses from phase II studies support DAC doses ≥20 mg (33% of the licensed dose) to be effective in treatment-naïve patients. We found similar or higher DAC exposures compared to the mean (SD) AUC$_{0-24h}$ of 3.42 (1.33) h$^*$ mg/L in genotype 1b infected patients on 20 mg QD. The variability in DAC exposure relative to the DAC dose seen in this case series suggests that DAC exposure is dependent on the AED used and the AED dose. Unfortunately, no one size fits all strategy can be used, as for different AEDs different DAC doses may be required.

Recently, Lutz et al. demonstrated a decreased SOF AUC of 24% after co-administration of carbamazepine 300 mg BID with a single-dose SOF in healthy subjects. Our data showed even lower SOF exposures in patients using carbamazepine ≥1,000 mg/day, but no reduction for SOF when combined with carbamazepine 400 mg/day or phenobarbital monotherapy. Reduction in SOF exposure might also be AED and dose-dependent.

Despite the valuable data of intensive sampling in this study, less intensive monitoring might be sufficient for patients using AEDs. Since all patients achieved SVR12 on the standard SOF dose, drug monitoring of SOF might not be required in clinical practice. In contrast, adjustment of DAC dose might be required based on low or high drug exposure, guided by drug level monitoring.

In conclusion, this case series demonstrates a successful approach of treating patients on contraindicated AEDs for pharmacokinetic reasons in clinical practice with an SVR rate of 100%. We advise prescribers to be cautious prescribing DAAs with contraindicated AEDs until our data are confirmed by data from a larger cohort of patients. Drug monitoring is still required in patients on contraindicated AEDs, but monitoring of DAC drug levels might be sufficient.

We recommend more pharmacokinetic studies to aid clinicians in optimizing HCV treatment choice for this patient cohort.

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Conflicts of interest
JD declares that The Radboudumc, on behalf of JD, received honoraria or research grants from Novartis, Zambon, Ipsen, Otsuka, Falk, Merck, Janssen, AbbVie, and Norgine. JD has served as consultant for Gilead and Abbvie, and has been member of advisory boards of Otsuka, Gilead, BMS, Janssen and Abbvie. PH reports personal fees from Gilead, personal fees from Abbvie, outside the submitted work; DJB reports grants from Gilead, grants from BMS, grants from Merck and grants from Abbvie, outside the submitted work. MvS, ES, PvW, MWB, RdK, OES, AC and DMB have nothing to disclose.

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

Authors' contributions
Minou van Seyen: preparation and execution of the sampling day, analysis of data, interpretation of results, manuscript preparation. Elise J Smolders: preparation and execution of the sampling day, analysis of data, interpretation of results, critical revision of the manuscript. Peter van Wijngaarden: treating physician, critical revision of the manuscript. Joost PH Drenth: treating physician, critical revision of the manuscript. Marjan
Letters to the Editor

Wouthuyzen-Bakker: treating physician, critical revision of the manuscript. Robert J de Knecht: treating physician, critical revision of the manuscript. Pieter Honkoop: treating physician, critical revision of the manuscript. Omar El-Sherif: supervision of the case series. Angela Colbers: analysis of data, critical revision of the manuscript. David J Back: critical revision of the manuscript. David M Burger: interpretation of results, critical revision of the manuscript, supervision of the case series.

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8 weeks of sofosbuvir/ledipasvir is effective in DAA-naive non-cirrhotic HCV genotype 4 infected patients (HEPNED-001 study)

To the Editor:
In contrast to genotype 1, genotype 4 hepatitis C (HCV) infections are more often found in Central Africa and the Middle East with the highest prevalence in Egypt.1 As the initial budget impact of HCV treatment with direct-acting antivirals (DAAs) can be substantial for countries with a high HCV prevalence,2 shortening treatment duration could help in reaching the World Health Organization’s HCV elimination goals3 by lowering costs and expanding access.4 The most recent EASL guideline suggests 8 weeks of therapy with sofosbuvir/ledipasvir (SOF/LDV) as an option for treatment-naive non-cirrhotic patients with chronic HCV of the genotypes 1a and 1b.5

Although the first clinical trials with DAAs were primarily focused on HCV genotype 1 infections, the advent of pan-genotypic DAAs give us the opportunity to study new treatment options and even treatment shortening for genotype 4 infections.6 Indeed, LDV showed a high potency in a study that assessed the phenotypic susceptibility of various genotype 4 subtypes7 and in the study that led to the registration of 12 weeks of SOF/LDV for genotype 4, in which 41 of the 44 (93%) patients achieved a sustained virological response (SVR).8 Given the very comparable cure rates after 12 weeks of SOF/LDV for genotype 1 and 4, a treatment duration of 8 weeks may be appropriate for genotype 4 as well.8 Recently,