Management of patients with chronic hepatitis C failing repeated courses of interferon-free direct acting antiviral combination therapy

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Summary

Background: Only few chronic hepatitis C patients treated with interferon (IFN)-free direct acting antiviral (DAA) combinations fail to clear the virus. Most patients can be cured by retreatment with another DAA combination; however, some still fail to eradicate the virus. So far, little is known about how to best retreat these patients. In this study we summarise our real world experience of re-retreatments.

Methods: One hundred and two patients who completed a DAA-retreatment after virological failure to an IFN-free DAA therapy and reached at least follow-up 12 were included in this study.Twenty-one (20.6%) of them relapsed again after retreatment (mean age 50.0 ± 10.6, 18 male, three female, GT1a:8, GT1b:4, GT1c:1, GT3a:7; GT4:1; cirrhosis:15; resistance associated substitutions [RAS]: 17/19; relapse after:SOF/SMV:2; 3D ± RBV:4; SOF/DCV ± RBV:4; SOF/LDV ± RBV:6; SOF/VEL:3; SOF/VEL/VOX:1; EBV/GZV:1).Treatment duration and addition of RBV were at the discretion of the treating physician. These 21 patients were studied in detail.

Results: Seventeen of the 21 patients finished a third DAA therapy: 13 achieved SVR12, three relapsed again (cirrhosis:2; SOF/VEL/RBV:GT3a; SOF/LDV/RBV:GT1a; EBV/GZV/SOF/RBV:GT1b), one was lost to follow-up. One (GT1a, cirrhosis) achieved SVR12 after the third retherapy with 24 weeks of 3D/SOF/RBV, and one (GT3a, cirrhosis) achieved SVR4 after 24 weeks of glecaprevir/pibrentasvir, but died shortly thereafter. Overall, 95 (93.1%) of 102 patients achieved SVR12 after one or more retreatments. Sex, cirrhosis, genotype, RAS or baseline viral load were not associated with retreatment failure.

Conclusion: Most patients with failure to a DAA therapy achieved SVR after retreatment with a different regimen; however, 13.7% of patients required multiple retreatments.
1 | INTRODUCTION

More than 95% of patients with chronic hepatitis C can be cured successfully with direct acting antivirals (DAA) within a few weeks. However, for the remaining patients with virological failure retreatment is needed. Until mid of 2017 no DAA had been licensed for patients who had failed an interferon (IFN)-free DAA pre-treatment, and only few clinical studies investigated retherapies in DAA failures others than relapers to pegylated IFN-α (PEG) and ribavirin (RBV) or PEG/RBV in combination with either telaprevir or boceprevir. Most retreatment regimens were combinations containing sofosbuvir (SOF; due to its high barrier to resistance) with a different DAA class than the one the patient had relapsed to. Further possibilities to optimize the retreatment were to extend treatment duration or to add RBV. In the meantime glecaprevir/pibrentasvir (G/P) and voxilaprevir (VOX) in combination with SOF/velpatasvir (SOF/VEL/VOX) were approved with certain restrictions by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for retreatment of patients failing the first IFN-free DAA combination therapy. SOF/VEL/VOX was licensed for patients with genotypes (GT) 1-6 who had previously been treated with a DAA regimen containing an NS5A inhibitor and for patients with GT1a or 3 who had previously been treated with a regimen containing SOF without an NS5A inhibitor. Although the FDA approved G/P in the US for GT1 patients with treatment experience to a NS5A inhibitor or a NS3/4A protease inhibitor (not both), the EMA approved this combination only for GT1-6 patients with treatment experience to (pegylated) interferon, RBV and/or SOF (but no prior treatment experience with an NS5A inhibitor or NS3/4A protease inhibitor). A further restriction is that due to the protease inhibitor containing G/P combination it is contraindicated in decompensated liver cirrhosis (Child-Pugh Score C, CPS-C), and is not recommended in CPS-B cirrhosis.

Unfortunately some patients still fail to eradicate the virus after retreatment. However, this group of patients has never been studied before. In this study we summarise our real world experience of retreated patients who had failed an IFN-free DAA containing therapy up to three times.

2 | PATIENTS AND METHODS

One hundred and two patients were retreated after virological failure to an IFN-free DAA therapy at the participating Austrian therapy centers (male: 77, female: 25; GT1: 73, GT2: 2, GT3: 25, GT4: 2; IFN-experienced: 57; cirrhosis: 60; CPS-A: 47, CPS-B: 13; hepatocellular carcinoma [HCC]: 6). Further demographic data are summarised in Table 1. Some patients had participated in the AURIC registry before (Austrian Interferon/Ribavirin-free Cohort; ClinicalTrials.gov, NCT02628717), which recorded the treatment of patients with cirrhosis or advanced fibrosis with IFN/RBV-free DAA combinations. The choice of drugs, the use of RBV as well as the treatment duration were at the discretion of the treating physician and were restricted to the availability of drugs at certain time points. In general, patients who had failed a SOF-free regimen received a SOF-containing regimen, those without a NS5A-inhibitor a NS5A containing regimen and those after SOF/NS5A received SOF/protease inhibitor ± another NS5A-inhibitor ± RBV. Patients’ adherence and response to the therapy was monitored by monthly HCV PCR controls at our department when also subsequent drug prescriptions were issued.

Resistance associated substitution testing (RAS) was performed before retreatment, or, if available, from stored samples retrospectively. Sequencing of drug resistance relevant HCV regions in NS3, NS5A and NS5B were performed using BigDye Terminator v1.1 Cycle Sequencing Kit (Thermo Fisher Inc, Darmstadt, Germany) and ABI Prism 3130XL Genetic Analyser (Applied Biosystems, Foster City, CA). The resulting nucleotide sequences were analysed with SeqScape version 2.7 (Applied Biosystems). For determining drug resistance mutations the sequences were analysed using the web-based interpretations tool HCV Gen2pheno (http://hcv.geno2pheno.org). This study was approved by the local ethics committee of the Medical University of Vienna.

3 | RESULTS

3.1 | First retreatment

Overall, out of 102 patients who received an IFN-free DAA retreatment and reached follow-up 12 (FUP12) 81 (79.4%) achieved SVR12 and 21 (20.6%) failed (see Figure 1). Detailed SVR rates after first DAA retreatment are shown in Table 2.

RAS analyses before first retreatment were available in 71 (69.6%) patients and were detected in 58 patients: 30 (42.3%) patients had isolated RAS (NS5A RAS: 25, NS3 RAS: 3, NS5B RAS: 2), 21 (29.6%) had resistance to two classes (NS3 + NS5A:12, NS5A + NS5B:5, NS3 + NS5B:4) and seven (9.9%) patients to all three classes. Overall, NS5A RAS were found in 49 (69.0%) patients: in 31 of them only at one position, in 18 patients at two or more positions (30H/K/R/S:...
NS3 RAS were found in 26 (36.6%) patients (174N/S: 13; 168A/E/V: 11; 36M/V: 5, 80K/L/R: 4, other: 13) and NS5B RAS in 18 (25.4%) patients (316C/N: 9; 159F: 7; 556G: 7). The NS5A RAS 30H/K/R/S was found in patients with GT1a (n = 15), GT1b (n = 3) and GT3 (n = 4) after DAA therapy with 3D (n = 10), SOF/DCV (n = 4), SOF/LDV (n = 4), EBV/GZV (n = 2) and SOF/RBV (n = 2). It occurred in combination with other NSSA RAS in nine patients. 93H was found in GT1b (n = 11), GT1a (n = 7) and GT3 (n = 4) after DAA therapy with SOF/LDV (n = 7), SOF/DCV (n = 4), 3D (n = 6), EBV/GZV (n = 3), SOF/SMV (n = 1) and SOF/VEL (n = 1).

Among the 21 patients with failure to the first retreatment 18 (85.7%) were male, eight (38.1%) had GT1a, four (19.0%) GT1b, one (4.8%) GT1c, seven (33.3%) GT3a and one (4.8%) GT4 (see Table 3). All eight patients with GT1a had RAS before retreatment: seven of them had NS5A RAS (most prevalent NS5A RAS: 58D/N/P and 30H/R/S conferring resistance or reduced susceptibility to all NS5A inhibitors), and six of them had NS3 RAS (most prevalent positions 174S and 168V/A). Isolated RAS were present in three patients (NS5A:2; NS3:1), the others had RAS against two or three classes. Among the four treatment failures with GT1b RAS analyses were available in three of them: each of them had at least one NSSA RAS. In two patients the NS5A RAS were combined with NS5B RAS, both of them at position 159F and additionally at position 316N in one of the two. Among the relapers with GT3a RAS analyses were available in six out of seven and were detected in four of them: only isolated NSSA RAS at positions 93H in three and 30K in one patient were detected.

Among the 21 relapers two patients had had discontinued the very first DAA therapy: one due to nonresponse to 3D (at week 12), and the other one due to liver transplantation (at week 6). In the
patient with nonresponse a retesting of genotype before the first retreatment revealed a genotype close to GT1c instead of GT1b. He had only NS5A RAS, however at three positions (30M, 31V, 93H). He achieved SVR after two further DAA therapies (see Table 3). Also the patient after liver transplantation relapsed again after 12 weeks of SOF/VEL. He had a NS5A RAS at position H58N and achieved SVR after two further DAA therapies (see Table 3). Also the first DAA treatment as well as the retreatments. Similarly, the in the described patients resulting in a considerable variation of both the first DAA treatment as well as the retreatments. Similarly, the first DAA treatment as well as the retreatments. Similarly, the management approach to relapers changed as first studies were presented at international meetings and more experience was available. Also RAS testing was not available from the beginning to help guide retreatment choices. Furthermore the assessment of adherence to therapy in a real-world study is also difficult, thus it is not sure whether adherence to monthly controls at our department correlated with the pill intake. Finally, we did not use ribavirin in about half of the patients. We tried to avoid ribavirin due to its substantial toxicities. The role of ribavirin in IFN-free DAA treatment is conflicting. Most studies have shown just a slight numerical benefit, if any, of adding ribavirin to treatments. Recent real world studies in GT3a patients with cirrhosis even showed a numerically worse outcome if ribavirin was added. The current EASL guidelines also suggest using RBV-free combinations. The recommendations for the length of retreatment are not based on well designed prospective studies either, and in this study treatment duration was determined by the treating physician and influenced by the availability of drugs at certain time points.

### 3.2 | Further DAA retreatments

Seventeen of the 21 relapers completed a second retreatment, two refused retherapy, one died and one got lost to follow-up. Thirteen of the 17 patients achieved SVR12 (76.5%), three relapsed again, one discontinued treatment after 8 weeks of treatment for no apparent reason (no RAS) and did not appear to follow-up. All three relapers had had RAS already before the first retherapy: one had only NS5A RAS (Y93H), one had RAS against NS5Aand NS5B (Y93H, L159F) and one had RAS against all three classes (R155K; M28T, Q30H; S556G). All three re-relapers received a third retreatment: two of them achieved SVR, one relapsed again. One of the patients with SVR had had received G/P, however, treatment was stopped after

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**TABLE 2** Outcome after first direct acting antiviral (DAA) retreatment

| Genotype       | Total | SVR—n (%) | Relapse—n (%) |
|----------------|-------|-----------|---------------|
| Overall        | 102   | 81 (79.4) | 21 (20.6)     |
| Male           | 77    | 59 (77.9) | 18 (22.1)     |
| Female         | 25    | 22 (88.0) | 3 (12.0)      |
| No cirrhosis (F1-F3) | 42    | 36 (85.7) | 6 (14.3)      |
| Cirrhosis (F4) | 60    | 45 (75.0) | 15 (25.0)     |

| Genotype       | Total | SVR—n (%) | Relapse—n (%) |
|----------------|-------|-----------|---------------|
| 1a             | 34    | 26 (76.5) | 8 (23.5)      |
| 1b             | 35    | 31 (88.6) | 4 (11.4)      |
| 2              | 2     | 2 (100.0)| 0 (0.0)       |
| 3              | 25    | 18 (72.0)| 7 (28.0)      |
| 4              | 2     | 1 (50.0) | 1 (50.0)      |

| HCV RNA        | Total | SVR—n (%) | Relapse—n (%) |
|----------------|-------|-----------|---------------|
| <800 000h      | 47    | 36 (76.6)| 11 (23.4)     |
| >800 000       | 50    | 40 (80.0)| 10 (20.0)     |
| IL28 non C/C   | 31    | 24 (77.4)| 7 (22.6)      |
| Diabetes       | 21    | 18 (85.7)| 3 (14.3)      |
| RAS            | 58    | 41 (70.7)| 17 (29.3)     |
| IFN containing pre-treatment | 57 | 45 (80.7) | 12 (20.3)

SVR: sustained virological response; RAS: resistance associated substitution; IFN: interferon.

*a One patient with GT1c.

*b Quantitative HCV RNA available in 97 patients.

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**DISCUSSION**

This study focuses on a yet uninvestigated group of patients with multiple treatment failures following repeated courses of retreatments with IFN-free DAA combinations. Clearly, this group of patients is very small and it is unlikely that a prospective controlled study could be performed in the near future. Our results indicate that patients with virological failure to treatment with IFN-free DAA combinations can be successfully retreated by a modified therapy regimen. However, in several cases more than one retreatment may be necessary. In our cohort of 102 patients with virological failure to the initial IFN-free DAA therapy, 81 (79.4%) achieved SVR after the first retreatment and overall 93.1% after multiple retreatments (in 14 patients at least two or more retreatments were necessary). A clear reason for multiple failures could not be found in this relatively small cohort of patients, however, 15 of the 21 retreatment failures had advanced liver disease and 12 already had failed to PEG/RBV previously.

Obviously, this is a real world study and not a controlled trial, thus several limitations need to be taken into account. Since IFN-free DAA therapy started in Austria in mid 2013 and up to 2017 several new DAAs became available, treatment choices changed accordingly in the described patients resulting in a considerable variation of both the first DAA treatment as well as the retreatments. Similarly, the management approach to relapers changed as first studies were presented at international meetings and more experience was available. Also RAS testing was not available from the beginning to help guide retreatment choices. Furthermore the assessment of adherence to therapy in a real-world study is also difficult, thus it is not sure whether adherence to monthly controls at our department correlated with the pill intake. Finally, we did not use ribavirin in about half of the patients. We tried to avoid ribavirin due to its substantial toxicities.

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TABLE 3  Characterization of relapsers to multiple direct acting antiviral (DAA) treatments (n = 21)

| Nr. | Sex | Age | GT | Fibrosis grade | Pretreatment | Baseline HCV PCR (IU/ml) | 1st DAA Therapy (duration, wk) | NS3 RAS | NS5A RAS | NS5B RAS | 1st DAA Retherapy (duration, wk) | Response | 2nd DAA Retherapy (duration, wk) | Response | 3rd DAA Retherapy (duration, wk) | Response |
|-----|-----|-----|----|----------------|--------------|-------------------------|-------------------------------|--------|---------|---------|-------------------------------|----------|--------------------------------|----------|--------------------------------|----------|
| 1   | M   | 43  | 1a | F2             | TN           | 270 000                  | 3D (12) 168V                  | 93C, 58D | 0       |         | EBV/GZV (24)                   | SOF/VEL  | (12) SVR12                     |          |                                |          |
| 2   | M   | 56  | 1a | F4             | TN           | 600 000                  | 3D/RBV (12) R155K             | M28T, Q30H | 5556G   | SOF/SMV (12) | SOF/LDV/RBV (24) RL  | 3D/SOF/RBV (24) SVR12 |          |                                |          |
| 3   | F   | 74  | 1a | F4             | PR           | 17 000 000               | 3D (12) 168V, 174S 30S, 31V | 444D   | N444H   |         | SOF/DCV/ RBV (12)             | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 4   | M   | 61  | 1a | PR             | 5 000 000    | 3D/RBV (12) R155K M28T, Q30H | 5556G | SOF/SMV (12) | SOF/LDV/RBV (24) RL  | 3D/SOF/RBV (24) SVR12 |          |                                |          |
| 5   | M   | 63  | 1a | PR             | 180 000      | 3D/RBV (12) R155K M28T, Q30H | 5556G | SOF/SMV (12) | SOF/LDV/RBV (24) RL  | 3D/SOF/RBV (24) SVR12 |          |                                |          |
| 6   | M   | 57  | 1a | F4             | PR           | 1 650 000                | SOF/DCV (12) n.d. 31V, 58P   | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 7   | M   | 43  | 1a | F4             | TN           | 1 081 000                | SOF/DCV (12) 36L, 122G, 168A, 174S | 30R   | 444D, 556G |         | SOF/SMV (12) | SOF/LDV/RBV (24) RL  | 3D/SOF/RBV (24) SVR12 |          |                                |          |
| 8   | M   | 64  | 1a | F4             | TN           | 1 400 000                | SOF/DCV (12) 174S 30R, 31M, 58D, 93H | 0       |         |         | SOF/SMV (12) | SOF/LDV/RBV (24) RL  | 3D/SOF/RBV (24) SVR12 |          |                                |          |
| 9   | M   | 32  | 1c | PR             | 1 010 000    | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 10  | M   | 45  | 1b | PR             | 2 470 000    | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 11  | M   | 67  | 1b | F2             | TN           | 1 800 000                | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 12  | M   | 75  | 1b | F2             | PR           | 920 000                  | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 13  | M   | 52  | 1b | F4             | TN           | 1 000 000                | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 14  | F   | 60  | 3a | F4             | PR           | 1 130 000                | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 15  | M   | 42  | 3a | F4             | PR           | 415 000                  | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 16  | M   | 50  | 3a | F2             | PR           | 515 000                  | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 17  | M   | 52  | 3a | F4             | PR           | 6 260 000                | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 18  | F   | 57  | 3a | F4             | PR           | 98 000                   | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 19  | M   | 56  | 3a | F2             | PR           | 3 549 000                | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 20  | M   | 55  | 3a | F4             | TN           | 410 000                  | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |
| 21  | M   | 33  | 4a | F4             | PR           | 840 000                  | SOF/SMV (12) 30M, 31V, 93H | 0       |         |         | EBV/GZV/SOF/RBV (12)         | SOF/VEL/VOX (16) SVR12 |          |                                |          |

GT: genotype; M: male, F: female, RL: relapse, SVR: sustained virological response, n.d.: not done, n.a.: not applicable, TN: treatment naïve, P/R: pegylated interferon + ribavirin (RBV), 3D: dasabuvir + paritaprevir + ombitasvir + ritonavir, DCV: daclatasvir, LDV: ledipasvir, SMV: simeprevir, EVB: elbasvir, GZV: grazoprevir, VEL: velpatasvir, VOX: voxilaprevir, G/P: glecaprevir/pibrentasvir.

aOrthotopic liver transplantation (OLT) during 1st DAA therapy, early termination of therapy due to OLT.

bPatient died.

cNonresponse.

dPatient refused a further therapy.

ePatient discontinued DAA therapy.

fPatient lost.
Most published data have focused on retreatment of patients who failed one IFN-free DAA therapy. The 21% failure rate in the present study is in the range of that reported in other studies. Before controlled trials with SOF/VEL/VOX and G/P have become available the evidence for retreatment of patients who had failed IFN-free DAA therapy was based on GT1 patients retreated with SOF/LDV plus RBV for 12 to 24 weeks after relapse to SOF containing IFN-free regimens in clinical trials. In the latter study patients without NS5A RAS obtained a SVR12 rate of 100%. However, among those with NS5A RAS this strategy was suboptimal, with an SVR12 rate of only 60%. In two other studies patients who failed SOF/SMV were successfully retreated (SVR12: 88%) with SOF/LDV ± RBV. The combination of EBV/GZV was also shown to be effective in relapsers. In an open-label phase 2a trial 34 HCV GT1 patients without cirrhosis who had failed after short time treatment (4-6 weeks) with SOF/LDV in combination with new protease inhibitors in a phase 2 study were retreated with 12 weeks of SOF/LDV and achieved a SVR rate of 91%. 85% had had NS5A-resistant variants before retreatment. The two latest approved pangenotypic combinations (SOF/VEL/VOX and G/P) seem promising, however, they are not available everywhere. SOF/VEL/VOX has been evaluated in four phase 3 studies; in two of them DAA-experienced patients were retreated with this combination: in POLARIS-1 patients with a prior NS5A-containing DAA regimen, and in POLARIS-4 non-NS5A inhibitor DAA-experienced patients achieved SVR rates between 93% and 100% in dependence of genotype and presence or absence of cirrhosis. In POLARIS-1 the presence of baseline NS3 protease inhibitor, NS5A inhibitor, and nucleoside analog NS5B inhibitor RAS did not affect the SVR rates. G/P was evaluated in the phase 3 MAGELLAN-1 trial for 12 or 16 weeks in patients with GT 1, 4, 5 and 6. Patients with treatment experience to NS3/4A inhibitors had SVR12 rates of 100% regardless of treatment duration, those with past experience to only NS5A inhibitors SVR12 rates of 88% and 94% for 12 and 16 weeks of treatment, respectively. Also the SURVEYOR-II, part 3 trial investigating 12 or 16 weeks of G/P in GT3 patients with prior treatment experience and/or compensated cirrhosis showed high SVR12 rates. Based on these studies the current EASL guidelines suggest a fixed-dose combination of SOF/VEL/VOX ± RBV or SOF/G/P ± RBV for 12 weeks for the first retreatment of DAA failures; also the latest AASLD recommendations suggest SOF/VEL/VOX or G/P for 12-weeks for retreatment of DAA failures. Unfortunately, none of the above mentioned studies included patients with repeated failures. Furthermore G/P has not been licensed for retreatment by the European Medicines Agency; and outside of North America, Europe, Japan and Australia G/P is not marketed yet.

So far, there are no systematic data and consequently no evidence-based recommendations how to retreat patients who had failed more than one DAA retreatment. The options include to retreat patients who had failed a SOF-free regimen with a SOF-containing regimen, those who were treated without a NS5A-inhibitor with a NSSA containing regimen and those after SOF/NS5A with SOF/protease inhibitor ± other NS5A-inhibitor ± RBV. However, most patients who failed two IFN-free DAA combinations usually were already exposed to all three available drug classes. A further possibility to improve response to a re-retherapy with SOF-containing DAA may be the addition of a ritonavir-containing regimen (2D or 3D), since pharmacokinetic investigations showed an increase of the concentration of SOF and its metabolite in combination with ritonavir.

A further important issue is the occurrence and impact of RAS in relapsers/nonresponders. Although it is likely that patients with failure to IFN-free DAA therapy may have more RASs, in a significant number of them no RAS were found. On the other hand most patients with baseline RAS in various studies achieved SVR. In our limited RAS analyses RASs were found only in 58 of the 71 tested patients who failed the first DAA therapy; the presence of RAS appeared to increase the likelihood of relapse after retreatment. Routine RAS testing in treatment naïve patients is not recommended by the recent AASLD and EASL guidelines. Nevertheless it may be useful in order to guide retreatment, although it is underlined that currently no specific algorithms can be derived if RAS are detected. In a large study of NS5A inhibitor naïve patients receiving SOF/LDV within several phase II and III clinical trials pretreatment NS5A RAS were found in 8%-16% of patients and resulted in lower SVR rates compared to those without, especially in treatment-experienced patients, patients with cirrhosis and with GT1a. Furthermore a recent observation from Italy revealed significantly higher prevalence of RAS in patients with breakthrough/nonresponse vs. relapse, in GT1a and GT3 vs. other genotypes, in patients with a viral load at baseline of >800 000 IU/mL. RASs in the NS5A position for genotypes 1a and 3 are of particular interest, especially as they may persist for years. Similar to other studies the most frequent NS5A RASs were found at amino acid positions 28, 30, 31 and 93, against which the efficacy of NS5A inhibitors varies. NS5B nucleotide RASs are detected only in about 1% of failures to nucleotide containing DAA therapies and thus can be re-used for retreatments after DAA failure. However, no correlation between RAS and SVR could be found in our study.

In summary, retreatment of IFN-free DAA combination failures is effective in the majority of patients. The choice of the best DAA combination for a particular patient is based on expert opinion rather than on evidence based recommendations. Multiple DAA combinations may be needed for selected patients. Nevertheless, there will be treatment failures even in these patients. These very few patients may need new approaches which are currently being explored.

**CONFLICTS OF INTEREST**

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REFERENCES

1. Drug Approval Package: VOSEVI (sofosbuvir, velpatasvir, and voxilaprevir). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209150Orig1s000SumR.pdf. Accessed March 11, 2018.
2. Drug Approval Package: MAVYRET (glecaprevir and pibrentasvir). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000SumR.pdf. Accessed March 11, 2018.
3. European public assessment report (EPAR) for Maviret. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004430/human_med_002151.jsp&xmlid=W-C00b1ac058001d124. Accessed March 20, 2018.
4. Kozbial K, Moser S, Al-Zoairy R, et al. Follow-up of sustained virological responders with hepatitis C and advanced liver disease after interferon/ribavirin-free treatment. Liver Int. 2018;38(6):1028-1035.
5. Kalaghatgi P. Geno2pheno[ HCV] - A web-based interpretation system to support hepatitis C treatment decisions in the era of direct-acting antiviral agents. PLoS One. 2016;11(5):e0155869.
6. Copegus® (ribavirin). Highlights of prescribing information [online], http://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/021511s023lbl.pdf. Accessed July 12, 2018.
7. Pasulo L, Gambato M, Spinetti A, et al. Treatment of genotype 3 cirrhotic patients with 12 weeks Sofosbuvir/Velpatasvir with or without ribavirin: Real life experience from Italy. Hepatology 2018;68 (Suppl. 1):S51A.
8. EASL Recommendations on Treatment of Hepatitis C 2018. European association for the study of the liver. Electronic address: easloffice@easloffice.eu; European association for the study of the liver. J Hepatol. 2018; 69(2):461-511.
9. Wyles DL, Pockros P, Morell G, et al. Ledipasvir- sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. Hepatology. 2015;61:1793-1797.
10. Osinusi A, Kohli A, Marti MM, et al. Re-treatment of chronic hepatitis C genotype 1 infection after relapse: an open-label pilot study. Ann Intern Med. 2014;161:634-638.
11. Lawitz E, Poordad F, Hyland RH, et al. Ledipasvir/sofosbuvir-based treatment of patients with chronic genotype-1 HCV infection and cirrhosis: results from two Phase II studies. Antivir Ther. 2016;21:679-687.
12. Modi AA, Nazario HE, Gonzales GR, Gonzalez SA. Safety and efficacy of ledipasvir/sofosbuvir with or without ribavirin in hepatitis C genotype 1 patients including those with decompensated cirrhosis who failed prior treatment with sofosbuvir/ledipasvir. Aliment Pharmacol Ther. 2018;47:1409-1415.
13. Tam E, Luetkemeyer AF, Mantry PS, et al. Ledipasvir/sofosbuvir for treatment of hepatitis C Virus in sofosbuvir-experienced, NSSA treatment-naïve patients: Findings from two randomized trials. Liver Int. 2018;38(6):1010-1021.
14. Lawitz E, Poordad F, Gutierrez JA, et al. Short-duration treatment with elbasvir/grazoprevir and sofosbuvir for hepatitis C: A randomized trial. Hepatology. 2017;65:439-450.
15. Wilson EM, Kattakuzhy S, Siddharthan S, et al. Successful retreatment of chronic HCV genotype-1 infection with ledipasvir and sofosbuvir after initial short course therapy with direct-acting antiviral regimens. Clin Infect Dis. 2016;62:280-288.
16. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med. 2017;376:2134-2146.

17. Struble K, Chan-Tack K, Qi K, Naeger LK, Birnkrant. Benefit-risk assessment for sofosbuvir/velpatasvir/voxilaprevir based on patient population and hepatitis C virus genotype: U. S. Food and Drug Administration’s evaluation. Hepatology. 2017;67:482-491.

18. Poordad F, Pol S, Asatryan A, et al. Glecaprevir/pibrentasvir in patients with hepatitis C virus genotype 1 or 4 and past direct-acting antiviral treatment failure. Hepatology. 2018;67:1253-1260.

19. Wyles D, Poordad F, Wang S, et al. Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: a partially randomized phase 3 clinical trial. Hepatology. 2017;67:514-523.

20. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America Present HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Last Updated: September 21, 2017. www.hcvguidelines.org. Accessed July 12, 2019.

21. King JR, Dutta S, Cohen D, et al. Drug-drug interactions between sofosbuvir and ombitasvir-paritaprevir-ritonavir with or without dasabuvir. Antimicrob Agents Chemother. 2016;60(2):855-861.

22. Sarrazin C. The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. J Hep. 2016;64:484-504.

23. Pawlotsky JM, Hepatitis C. Virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology. 2016;151:70-86.

24. Zeuzem S, Mizokami M, Pianko S, et al. NS5A resistance-associated substitutions in patients with genotype1 hepatitis C virus: prevalence and effect on treatment outcome. J Hepatol. 2017;66:910-918.

25. Di Maio VC, Cento V, Araghi M, et al. Frequent NS5A and multiclass resistance in almost all HCV genotypes at DAA failures: what are the chances for second-line regimens? J Hepatol. 2018;68(3):597-600.

26. Wyles D, Mangia A, Cheng W, et al. Long-term persistence of HCV NS5A resistance associated substitutions after treatment with the HCV NS5A inhibitor, ledipasvir, without sofosbuvir. Antivir Ther. 2018;23(3):229-238.

27. Gottwein JM, Pham LV, Mikkelsen LS, et al. Efficacy of NS5A inhibitors against hepatitis C virus genotypes 1-7 and escape variants. Gastroenterology. 2018;154(5):1435-1448.

28. Dietz J, Susser S, Vermehren J, et al. for the European HCV Resistance Study Group. Patterns of resistance-associated substitutions in patients with chronic HCV infection following treatment with direct-acting antivirals. Gastroenterology. 2018;154:976-988.

29. Gane EJ, Metivier S, Nahass R, et al. The emergence of NS5B resistance associated substitution S282T after sofosbuvir-based treatment. Hepatol Commun. 2017;1:538-549.