Background: Hepatitis delta virus (HDV) infection therapy is unclear. This systematic analysis aimed to clarify the evidence on the efficacy of interferon (IFN)-α-based therapy in HDV.

Methods: We performed a systematic search on electronic databases including MEDLINE (1970 to January 2011), Web of Science, The Cochrane Library and ClinicalTrials.gov. Randomized clinical trials (RCTs) comparing IFN-α-based therapy with either another drug, placebo or no intervention were included. We excluded paediatric studies. We calculated relative risks (RRs) for comparison of treatment options on the primary outcome measure, which was defined as undetectable levels of HDV RNA and normal alanine aminotransferase at end of treatment (EOT; 1 year).

Results: Nine RCTs were included. Seven trials evaluated the treatment with IFN-α (n=132). The remaining two trials evaluated treatment with pegylated (PEG)-IFN-α (n=45).

We found that 1-year treatment with high-dose IFN-α achieved better primary outcome rates than with PEG-IFN-α (RR=4.14, 95% CI 1.00, 17.14). Data for 1-year treatment with low-dose IFN-α compared with PEG-IFN-α were similar (RR=2.83, 95% CI 0.65, 12.40), as were low-dose IFN-α versus high-dose IFN-α (RR=0.68, 95% CI 0.31, 1.50). High-dose IFN-α and PEG-IFN-α reached similar HDV RNA suppression 24 weeks after EOT (RR=1.00, 95% CI 0.51, 1.97). None of the 55 patients assigned to no intervention obtained undetectable levels of HDV RNA and only one patient achieved normalization of alanine aminotransferase level.

Conclusions: Based on available RCTs, 1-year high-dose IFN-α monotherapy appears to be more effective than PEG-IFN-α for treatment of HDV patients, with efficacy rates of approximately 30%. There is a lack of head-to-head comparisons. Combination therapies and longer treatment duration need to be investigated.

Introduction

Hepatitis delta virus (HDV) was first identified in 1977 in serum of hepatitis B surface antigen (HBsAg) carriers [1]. HDV is a parenterally transmitted RNA virus that requires HBV surface proteins to form the viral coat and to infect hepatocytes. There are eight genotypes, which each have a unique geographical representation [2–10]. HDV infection occurs as coinfection or superinfection. Coinfection of HBV with HDV is usually acute and self-limiting, with a clinical picture that ranges from mild to severe fulminant hepatitis. Chronic liver disease is seen in <5% of these patients [11,12]. Superinfection of HDV in HBV carriers is associated with severe acute hepatitis that leads to chronic HDV infection in up to 80% of patients [11–16]. Overall, an estimated 10% of chronic HBV-infected patients have a concomitant HDV infection, with considerable differences between countries, regions and risk groups [12,17]. Eventually, this may lead to chronic liver disease and progression to cirrhosis in 80% of patients [13,15,16,18–21].

Treatment of chronic HDV remains under debate. Clinical trials dating from the mid-1980s and early 1990s used interferon (IFN)-α-based therapy to inhibit HDV replication [22–27]. Response with IFN-α was not high, but therapeutic efficacy seemed to increase with higher IFN-α dosages [28,29] and prolonged therapy [22,23,30,31]. The addition of polyethylene glycol to IFN-α, which enhances the half-life of IFN-α, greatly increased the therapeutic efficacy in hepatitis C [32–34]. The effect of pegylated (PEG)-IFN-α in HDV treatment has not been fully explored [35,36]. In addition, several oral agents have been proven to be ineffective in HDV, including ribavirin, famcyclovir, lamivudine, levamisole and thymosin [37–42]. Since there is an important therapeutic role of IFN-α therapy in the...
treatment of HDV, an in depth assessment of the evidence that supports safety and efficacy of IFN-α based strategies in HDV is warranted. Our primary objective was to explore the published literature and clarify the evidence on the effects of IFN-α in HDV. Therefore, we performed a systematic review and examined all randomized clinical trials (RCTs) for IFN-α-based treatment of HDV from 1970 until present.

Methods

Literature search
We performed a systematic literature search using a set of electronic databases: MEDLINE (from 1970 to January 2011), Web of Science, The Cochrane Library and ClinicalTrials.gov. We identified all published articles, abstracts and ongoing studies in all languages from 1970 until January 2011. Searches were performed by using the official Medical Subject Headings (MeSH): ‘hepatitis’, ‘HDV’, ‘delta’ and ‘clinical trial’. Additional articles were obtained through citation snowballing to locate primary sources that were referred to in the initial document where necessary.

Selection of studies
We included all articles irrespective of language. We included any study that met the following criteria: RCT, comparing IFN-α-based therapy with another drug, placebo, or no intervention, outcome measures include levels of HDV RNA and alanine aminotransferase (ALT), and treatment duration of ≥1 year. All duplicates and paediatric trials were removed. Subsequently, we screened all remaining articles on the basis of title and abstract. Studies not evaluating the treatment of chronic HDV were removed from the analysis. Case series, cross-sectional studies, cohort studies, review articles and letters were excluded. Thereafter, we subjected the remaining studies to full-text screening.

Two reviewers (MHL and OOK) independently evaluated the eligibility of all studies retrieved from the databases on basis of the predetermined selection criteria. Disagreements were resolved by discussion with a third party (JPHD). In order to determine whether our search included all published articles, we manually searched the reference sections of included articles. Quality of the included studies was assessed, using a domain-based evaluation, where critical assessments were made separately for different domains [43].

Outcomes
The primary outcome measure was undetectable levels of HDV RNA at EOT, both at end of treatment (EOT; 1 year of treatment). The secondary outcome measures included undetectable levels of HDV RNA at EOT, normal levels of ALT at EOT, both variables at 24 weeks after EOT, mortality and occurrence of adverse events. All outcomes were extracted from the included trials and assessed at maximum follow-up.

Data extraction
We developed an electronic data extraction form in Microsoft Excel and used this for data entry. Extracted data included characteristics of trials, patients and interventions, as well as all outcome measures. Trial characteristics comprised the first author’s name, year and journal of publication, study design, type, dose and duration of applied therapy and length of follow-up. Patient characteristics included inclusion and exclusion criteria, mean age, number of patients randomized, number of and reasons for dropouts and withdrawals.

Synthesis of data and analysis
For each separate study, a brief overview of the interventions and number of patients was generated. We pooled patient data from all studies and stratified results in different subgroups according to applied intervention. Thereafter, we determined the primary and secondary outcome measures to assess the efficacy of the different applied interventions. We calculated relative risks (RRs) for comparison of treatment options on the primary and secondary outcome measures.

Results

Literature search and selection of studies
The search of our systematic literature and subsequent selection of articles is summarized in a flow diagram (Figure 1). The initial search identified 419 different articles. We excluded 356 articles on the basis of different study aims and 48 papers were rejected because the study design did not meet the inclusion criteria. Full-text screening was applied for 15 articles and ultimately 8 full papers met the selection criteria. We checked the reference lists of the first set of eight articles, and this strategy resulted in one additional article. Thus, a total of nine RCTs were included for further analysis [23,28,29,31,36,38,44–46]. Seven studies evaluated treatment with IFN-α (n=132 patients receiving monotherapy) [23,28,29,31,38,44,45] and another two studies evaluated treatment with PEG-IFN-α (n=45 patients receiving monotherapy) [36,46].

The RCTs evaluated IFN-α-based therapies in combination with lamivudine, ribavirin and adefovir. Outcome assessments in patients treated within the different treatment arms were made after an evaluation period of ≥1 year. The mean evaluation period was comparable between the different groups, and was approximately 1 year, except for one article that had a 2-year evaluation phase. Most trials used a 6-month follow-up period.
Interferon-α-based monotherapy
We retrieved seven studies, published between 1991 and 2008, which assessed our primary outcome of 1-year IFN-α therapy in chronic HDV patients. These seven trials evaluated 253 patients allocated to seven different intervention groups and 73% of participants were male (Table 1) [23,28,29,31,38,44,45]. Two studies compared IFN-α, in a dosage of 5 MU/m² three times per week, with no intervention [23,31]. Two studies performed a head-to-head comparison between high- (9 MU three times per week or 18 MU three times per week) and low-dose (3 MU three times per week or 3 MU daily) IFN-α, while one of the two trials used a non-treated control group [28,29]. One study compared IFN-α monotherapy (10 MU three times per week) with combination therapy of IFN-α (10 MU three times per week) and lamivudine (100 mg daily) [44]. Another trial studied the same drugs (IFN-α therapy [9 MU three times per week] and combination therapy of IFN-α [9 MU three times per week] with lamivudine [100 mg daily]) but included a third arm with lamivudine monotherapy (100 mg daily) [38]. One study performed a comparison between IFN-α monotherapy (9 MU three times per week) and IFN-α (9 MU three times per week) plus ribavirin (1,000–1,200 mg daily) combination therapy [45].

We identified two clinical trials that investigated the efficacy of PEG-IFN-α therapy in chronic HDV patients (Table 2) [36,46]. These studies included 128 patients (62% male) allocated to four different intervention
groups [36,46]. The first study compared PEG-IFN-α (1.5 µg/kg/week) with PEG-IFN-α (1.5 µg/kg/week) in combination with ribavirin (800 mg daily) [46]. The second study evaluated PEG-IFN-α (180 µg/week) and adefovir (10 mg daily) combination therapy, the combination of PEG-IFN-α (180 µg/week) and placebo, and adefovir monotherapy (10 mg daily) [36].

Primary outcome measure
In total, 122 patients were treated with IFN-α for 1 year [23,28,29,31,38,44], 72 patients were treated with low-dose (3–5 MU three times per week) IFN-α [23,28,29,31]. The combination of undetectable levels of HDV RNA and normal levels of ALT at EOT (1-year treatment) was observed in 20% of patients (Figure 2) [28,29,31]. We were not able to extract data on the primary outcome measure from one study as this manuscript contained only minimal information [23]. Overall, 29% of high-dose (9–18 MU three times per week) IFN-α-treated patients (n=42) reached both undetectable HDV RNA and normal ALT levels [28,29,44]. Patients on low-dose IFN-α had a similar response compared with high-dose IFN-α (RR=0.68, 95% CI 0.31, 1.50).

A total of 45 patients were treated with PEG-IFN-α [36,46]. Only 7% reached combined undetectable levels of HDV RNA and normal levels of ALT at EOT [36]. A 1-year treatment with low-dose IFN-α or with PEG-IFN-α was not significantly different (RR=2.83, 95% CI 0.65, 12.40). A 1-year treatment with high-dose IFN-α was better compared to PEG-IFN-α (RR=4.14, 95% CI 1.00, 17.14).

Secondary outcome measures
Overall, 16 of 72 (22%) patients treated with low-dose IFN-α reached undetectable levels of HDV RNA at EOT [23,28,29,31]. Similarly, 22% of PEG-IFN-α-treated patients (n=45) achieved HDV RNA negativity [36,46]. Overall 48% of high-dose IFN-α-treated patients (n=50) attained undetectable levels of HDV

### Table 1. IFN-α therapy in HDV patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Treatment duration, weeks</th>
<th>Patients, n</th>
<th>Undetectable HDV RNA and normal ALT, %</th>
<th>Undetectable HDV RNA, %</th>
<th>Normal ALT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosina et al. [23]</td>
<td>IFN-α2b, 3×/week, 5 MU/m² for 4 months, 3 MU/m² for 8 months</td>
<td>No intervention</td>
<td>– 30</td>
<td>Unknown</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Farci et al. [28]</td>
<td>IFN-α2a, 9 MU, 3×/week</td>
<td>No intervention</td>
<td>14</td>
<td>50</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Madejón et al. [29]</td>
<td>IFN-α2a, 3 MU, 3×/week</td>
<td>16</td>
<td>6</td>
<td>25</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 MU of IFN/day for 3 months</td>
<td></td>
<td>16</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and then 1.5 MU/day for 9 months</td>
<td></td>
<td>16</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 MU of IFN 3×/week for 6 months</td>
<td></td>
<td>16</td>
<td>6</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 MU 3×/week for 1 month, 6 MU 3×/week for 1 month</td>
<td></td>
<td>16</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 MU 3×/week for 4 months</td>
<td></td>
<td>16</td>
<td>6</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Gaudin et al. [31]</td>
<td>IFN-α2b, 5 MU/m² 3×/week for 4 months, 3 MU/m² 3×/week for 8 months</td>
<td>No intervention</td>
<td>11</td>
<td>36</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>Gunsar et al. [45]</td>
<td>IFN-α2a, 9 MU, 3×/week for 2 years</td>
<td>– 11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>IFN-α2a 9 MU 3×/week plus ribavirin 1,000–1,200 µg/day</td>
<td>–</td>
<td>21</td>
<td>Unknown</td>
<td>52</td>
<td>57</td>
</tr>
<tr>
<td>Canbakan et al. [44]</td>
<td>IFN-α2b 10 MU 3×/week</td>
<td>– 10</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>IFN-α2b 10 MU 3×/week plus lamivudine, 100 mg/day</td>
<td>– 14</td>
<td>50</td>
<td>64</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Yurdaydin et al. [38]</td>
<td>Lamivudine 100 mg daily</td>
<td>1</td>
<td>9</td>
<td>Unknown</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>IFN-α2a, 9 MU 3×/week</td>
<td>– 8</td>
<td>Unknown</td>
<td>50</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamivudine (2 months alone, 100 mg daily) plus lamivudine and IFN-α2a 10 months together</td>
<td>– 8</td>
<td>Unknown</td>
<td>50</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamivudine 100 mg daily</td>
<td>– 8</td>
<td>Unknown</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamivudine (2 months alone, 100 mg daily) plus lamivudine and IFN-α2a 10 months together</td>
<td>– 6</td>
<td>Unknown</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment-naïve patients (n=25). †Previously treated with interferon (IFN; n=14). ALT, alanine aminotransferase; HDV, hepatitis delta virus.

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RNA [28,29,38,44]. High-dose IFN-α was more effective than low-dose IFN-α (RR=2.16, 95% CI 1.28, 3.63) or PEG-IFN-α (RR=2.16, 95% CI 1.16, 4.01) to achieve undetectable HDV RNA. There was no significant difference between low-dose IFN-α or PEG-IFN-α (RR=1.00, 95% CI 0.50, 2.01).

Treatment with low-dose IFN-α resulted in normal levels of ALT in 25% of 72 patients [23,28,29,31]. Normalization of ALT was achieved in 25 of 50 high-dose IFN-α-treated patients [28,29,38,44]. A total of 31% of 45 patients achieved normal ALT levels with PEG-IFN-α [36,46]. High-dose IFN-α was more effective in reaching normal levels of ALT than low-dose IFN-α (RR=2.00, 95% CI 1.23, 3.25). Furthermore, the efficacy of low- (RR=0.80, 95% CI 0.45, 1.45) and high-dose (RR=1.61, 95% CI 0.96, 2.69) IFN-α was not different from that of PEG-IFN-α.

Because none of the articles contained information on the primary outcome measure after EOT (for example at 24 weeks after EOT) we were not able to extract these data. In total, 4 of the 72 (6%) patients treated with low-dose IFN-α had undetectable HDV RNA 24 weeks after EOT [23,28,29,31]. Overall, 29% of 38 high-dose IFN-α-treated patients maintained undetectable levels of HDV RNA at follow-up week 24 [28,29,38]. In total, 13 of 45 PEG-IFN-α-treated patients (29%) achieved negative HDV RNA levels [36,46]. High-dose IFN-α (RR=6.00, 95% CI 2.04, 17.65) and PEG-IFN-α (RR=5.99, 95% CI 2.08, 17.31) were better than low-dose IFN-α in reaching undetectable HDV RNA 24 weeks after EOT. High-dose IFN-α and PEG-IFN-α were similarly effective (RR=1.00, 95% CI 0.51, 1.97).

Normal ALT levels 24 weeks after EOT were achieved in 6% of 72 patients treated with low-dose IFN-α [23,28,29,31]. Moreover, 32% of 38 high-dose IFN-α- and 38% of 45 PEG-IFN-α-treated patients reached normal levels of ALT [28,29,36,38,46]. High-dose IFN-α (RR=5.68, 95% CI 1.97, 16.43) and PEG-IFN-α (RR=6.8, 95% CI 2.44, 18.92) were more successful in achieving normal ALT levels than low-dose IFN-α at 24 weeks after EOT. High-dose IFN-α and PEG-IFN-α were similarly effective in this respect (RR=0.84, 95% CI 0.49, 1.52).

For comparison, none of the 55 patients who received placebo or no intervention obtained undetectable levels of HDV RNA and ALT levels normalized only in a single patient. There was no mortality in patients assigned to no intervention [23,28,31]. This contrasts with one patient in the high-dose IFN-α group who died due to liver decompensation in month 5 of therapy [44] and one patient in the low-dose IFN-α group who committed suicide [31].

![Graph: HDV RNA negativity and normal alanine aminotransferase at end of treatment](image)

**Table 2. PEG-IFN-α therapy in HDV patients**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Treatment duration, weeks</th>
<th>Patients, n</th>
<th>Undetectable HDV RNA and normal ALT, %</th>
<th>Undetectable HDV RNA, %</th>
<th>Normal ALT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niro et al. [46]</td>
<td>PEG-IFN-α 1.2 mg/kg/week</td>
<td>1.5</td>
<td>16</td>
<td>Unknown</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>PEG-IFN-α 1.2 mg/kg/week plus ribavirin 800 mg/day</td>
<td>–</td>
<td>22</td>
<td>Unknown</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Wedemeyer et al. [36]</td>
<td>PEG-IFN-α 1.2 mg/kg/week plus adefovir 10 mg daily</td>
<td>1</td>
<td>31</td>
<td>7</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>PEG-IFN-α 1.2 mg/kg/week plus placebo</td>
<td>–</td>
<td>29</td>
<td>7</td>
<td>24</td>
<td>28</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; HDV, hepatitis delta virus; PEG-IFN, pegylated interferon.

![Graph: Comparison of high-dose interferon (IFN-α) versus pegylated (PEG)-IFN-α](image)

"The comparison of high-dose interferon (IFN-α) versus pegylated (PEG)-IFN-α was clinically significant. Values above bars represent comparisons between the treatment groups with associated risk ratios. ALT, alanine aminotransferase; HDV, hepatitis delta virus; RR, relative risk."
MH Lamers et al.

Overall, 5 of the 10 patients who were treated for 2 years with high-dose IFN-α reached undetectable HDV RNA and normal ALT levels. One patient obtained normal ALT, but failed to reach undetectable HDV RNA [45]. IFN-α treatment for 1 or 2 years was not different (RR=0.45, 95% CI 0.17, 1.22). The article describing the trial gave no information on mortality [45].

IFN-α based combination therapy and other monotherapies

A total of 57% of 28 patients on IFN-α and lamivudine reached undetectable levels of HDV RNA [38,44], 61% achieved normalization of ALT levels [38,44] and 50% attained both [44]. IFN-α monotherapy and IFN-α in combination with lamivudine were similarly effective (RR=0.45, 95% CI 0.19, 1.07). Lamivudine monotherapy was investigated in 17 patients. Undetectable HDV RNA was seen in 12%, while 18% reached normal ALT levels [38].

One trial studied the combination of IFN-α and ribavirin for 2 years; 52% of 21 patients achieved undetectable HDV RNA levels and 57% reached normal ALT levels [45]. PEG-IFN-α in combination with ribavirin resulted in undetectable HDV RNA levels in 9% (2/22 patients), and in 41% (9/41) of patients normal levels of ALT were obtained [46]. A total of 31 patients were treated with PEG-IFN-α and adefovir, 23% achieved undetectable levels of HDV RNA, 32% reached normalization of ALT levels and 7% reached both outcome measures [36]. Treatment with PEG-IFN-α or combination therapy with PEG-IFN-α and adefovir was not different (RR=1.07, 95% CI 0.16, 7.10). Thirty patients were treated with adefovir monotherapy, 7% reached normal ALT levels and none obtained undetectable HDV RNA levels [36].

Adverse events

Frequencies and percentages of reported adverse events were not always adequately documented. Patients receiving IFN-α-based therapy had a number of well-known adverse events, such as flu-like syndrome, leukopenia, thrombocytopenia and fatigue (Additional file 1). We found no differences in adverse events incidence between the different IFN-α-based therapies. Both in the low-dose [23,28,29,31] and high-dose IFN-α group [28,29,38,44] one patient died. None of the patients treated with PEG-IFN-α [36,46] or who received no intervention died [23,28,31].

Discussion

This systematic review evaluates the evidence that is available for IFN-α-based therapy in HDV. In order to offer accurate recommendations for optimal treatment in HDV, we performed a systematic analysis of the published RCTs. Results from our analysis show that 1-year high-dose IFN-α monotherapy is better than 1-year PEG-IFN-α therapy in achieving undetectable levels of HDV RNA and normal levels of ALT. A 1-year course of high-dose IFN-α therapy reached efficacy rates of 29%. In view of these data one might favour high-dose IFN-α for HDV, which unfortunately has the disadvantage of multiple weekly administration. A logical corollary is the suggestion that higher dosages of PEG-IFN-α might be better, but this has not been investigated. Another outstanding question is whether longer treatment improves treatment response rates. There is only one trial that studied the efficacy of 2 years of IFN-α therapy [45]. The response rate was higher than in trials evaluating shorter (that is, 1-year) IFN-α treatment regimens. Although this might suggest that longer treatment duration is more effective, formal proof is lacking. Trials exploring longer treatment with PEG-IFN-α are ongoing [47].

In general, we found efficacy rates of 10–30% in achieving both undetectable levels of HDV RNA and normal levels of ALT. These rates indicate that this is an area of clear unmet need. No specific HDV inhibitors have been developed so far. Based on our current knowledge of HDV replication, HBV therapies would be theoretically attractive only if they cleared HBV entirely or reduced levels of HBsAg, on which HDV depends.

The use of HBV inhibitors in HDV has been disappointing and these drugs appear to have no or little effect on HDV replication [48]. Combination of IFN-α with nucleoside or nucleotide analogues did not improve virological response rates. However, combination of PEG-IFN-α and adefovir was superior in reducing quantitative HBsAg levels and induces HBsAg seroconversion more often. As a consequence, combination therapies of PEG-IFN-α with more potent HBV polymerase inhibitors aiming to induce clearance of both HBsAg and HDV RNA should be explored in HDV [36].

There is a lack of RCTs in HDV treatment that are useful for the clinician in making evidence based decisions. The number of RCTs describing the clinical efficacy of different treatment strategies in HDV patients is low. We only found 13 RCTs published between 1970 and January 2011. Only 2 of them were RCTs evaluating the efficacy of PEG-IFN-α [36,46]. For comparison, between April 2010 and April 2011 alone, already some 20 RCTs in HBV were reported in the literature. An explanation for this difference could be a reduced interest in HDV therapy by pharmaceutical companies because of the relative low burden of HDV infection in western countries [49–51].

Obviously, new treatment strategies for HDV are needed. Future trials should be powered to detect meaningful differences in the primary outcome, which in this era will be tested with more reliable and optimal laboratory diagnostics. Furthermore, trials should differentiate
between treatment-naive and previously-treated patients and ideally a long-term follow-up is needed to evaluate different treatment outcomes of equal duration.

A new upcoming class of antiviral agents are prenylation inhibitors. These agents block hepatitis delta antigen prenylation, an essential step in the assembly of HDV [52]. Prenylation inhibitors clear HDV from experimental mouse models and are obviously agents that should be tested in a clinical setting [53]. Indeed, clinical trials with these agents have been started [54].

Another issue that requires further investigation concerns the length of treatment. As mentioned, 2 years of IFN-α treatment seems better than 1-year [45]. Recently, a Turkish study group retrospectively analysed standard (<18 months; n=47) or long-term (>18 months; n=34) conventional or PEG-IFN-α treatment. The primary end point of this study was ALT normalization for ≥6 months post-treatment and undetectable HDV RNA. Preliminary results suggested that standard 1-year course of treatment with IFN-α is most likely not enough to achieve ALT normalization in the majority of patients with HDV, and that prolongation of treatment is crucial. However, results have only been published in abstract form [55]. Moreover, in the reviewed trials most patients relapsed after stopping therapy, suggesting that longer treatment might be beneficial.

This review has some limitations. There is no standardized, universally accepted definition of remission in HDV patients. Each described trial used their preferred and own end points. For example, ALT was used as end point in all included trials [23,28,29,31,36,38,44-46]. One article described normalization of ALT as ‘normalization of ALT levels’ [28], whereas another trial described it as ‘a decrease of ALT that was ≥50% from baseline to <1.5x the upper limit of normal’ [23]. Furthermore, other end points of relevance to HDV, such as histological grading and staging, HBV DNA and HBsAg could not be investigated here. These variables should also be considered in treatment decisions.

One of the most important limitations of this study is the problem with HDV RNA assays. Earlier studies may have used less sensitive HDV RNA assays and thus overestimated virological response rates as compared to more recent trials investigating PEG-IFN-α [56]. The limit of detection used in the early studies varied between 10 and 100 viral particles per ml [29,31], compared to 1 to 10 viral particles per ml in the latest studies [36,46].

In addition, PEG-IFN-α may be associated with some increase in ALT levels despite virological response. This phenomenon has been described for HCV infection [57]. Therefore, the use of ALT levels as the only outcome measure might underestimate the effect of PEG-IFN-α.

Another limitation is the short follow-up duration. The majority of studies provided results at EOT and some also at 24 weeks after treatment discontinuation. To be sure that a virological response is achieved, a longer follow-up would be necessary, taking into account that HDV RNA concentrations fluctuate spontaneously [58].

Furthermore, the trials used various doses of IFN-α. Therefore, we were not able to extract the best dose needed for the most optimal response rates. Unfortunately, we were also not able to distinguish between treatment-naive and treatment-experienced patients. There is definitively a need for trials that distinguish between these two categories of patients. Moreover, variations in medication schemes, IFN-α-based therapy (for example, PEG-IFN-α2a or -2b), outcome measures, and validity of trials introduced heterogeneity between included studies. Although high-dose IFN-α seemed more effective than PEG-IFN-α, no formal head-to-head studies have been performed and results are based upon indirect comparisons. In addition, most studies include a small number of patients. Indeed, current therapy is based on 13 trials published since 1970 with only 457 patients, reflecting the paucity of evidence. We also noted some redundancy in the literature. There are a number of articles that report on a similar dataset and seem to reuse data from the same patient cohort in subsequent articles [23,24,31,59,60]. We have excluded these articles from our analysis. In the same context we note that there is also an absence of structured and systematic recording of adverse events in HDV therapy.

In conclusion, 1-year high-dose IFN-α monotherapy appears to be more effective than PEG-IFN-α for treatment of HDV patients. Unfortunately, efficacy rates are only approximately 30% at EOT. Ideally, a long-term follow-up is needed to evaluate different outcomes of equal duration for IFN-α and PEG-IFN-α with the same test used to detect HDV RNA and a comparable long-term histological evaluation. Alternative proposed strategies are very welcome to improve the current treatment armamentarium.

Disclosure statement

The authors declare no competing interests.

Additional file

Additional file 1: Supplementary table 1 displaying adverse events occurring in HDV patients can be accessed via http://www.intmedpress.com/uploads/documents/AVT-11-OA-2355_Lamers_Add_file1.pdf

References


