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Commentary

The beginning of the end: What is the future of interferon therapy for chronic hepatitis C?

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ABSTRACT

Interferon has been the backbone of therapy for hepatitis C virus (HCV) infection for over 20 years. Initial response rates were poor, however they have slowly but steadily improved, such that with the addition of the nucleotide analogue ribavirin and the pegylation of interferon, over 50% of infected individuals could be cured with a course of therapy. However, interferon therapy is not ideal, requiring up to a year of weekly injections and associated with numerous systemic side effects. Advances in understanding of the HCV lifecycle have led to the development of numerous highly effective, well-tolerated oral direct acting antivirals (DAAs). Although the first DAAs were combined with peginterferon and ribavirin, with the rapid progress in the field, it is likely that interferon-free therapy will be available for most patients in the relatively near future. In the short term, peginterferon will be required with either the protease inhibitor simeprevir, or the nucleotide analogue polymerase inhibitor, sofosbuvir, for the treatment of genotype 1 infection. Peginterferon also appears to be a useful adjunct to sofosbuvir and ribavirin for patients with genotype 3 infection, particularly those with cirrhosis. In the future, once combination DAA therapies are available, peginterferon will serve a smaller and smaller role. Peginterferon may be useful as part of QUAD therapy with 2 DAAs and ribavirin in prior null responders or in patients who fail DAA regimens with multi-drug resistant HCV. Peginterferon may also have a role in resource-limited regions to reduce the number and/or duration of DAAs required. Ultimately, although peginterferon will remain a salvage therapy, its days as a mainstay of therapy are definitely numbered.

The identification and subsequent cloning of human interferon, a major component of the innate antiviral immune response, raised the prospect of treating chronic viral infections, and hepatitis C virus (HCV) was targeted with this therapy even before the virus had been identified. Early trials confirmed that interferon could suppress HCV replication and normalize liver tests in some patients (Hoofnagle et al., 1986). Although the early results were relatively disappointing, slow but steady progress over many years showed that effective interferon-based therapy could lead to a sustained virological response (SVR), effective viral eradication, in over half of treated patients (Fried et al., 2002; Manns et al., 2001). This progress was tempered by the fact that interferon therapy requires injections for up to a year and is associated with numerous systemic side effects, precluding treatment in many infected individuals (Hoofnagle and Seeff, 2006). Studies to understand the incomplete response to interferon demonstrated that the sensitivity of both the virus and the host cells to interferon were important determinants of treatment outcome (Hoofnagle and Seeff, 2006).

The recent discovery of numerous well-tolerated oral agents that can directly suppress HCV replication, so called direct-acting antivirals (DAAs), has heralded a new era in the treatment of HCV. Although the first DAAs must be combined with interferon, it is likely interferon-free therapy will be a reality for most patients in the not too distant future. As the backbone of HCV treatment for over 20 years, it is worthwhile to consider the future of interferon as a therapeutic for HCV infection.

1. Background

Direct-acting antivirals inhibit very specific events in the HCV lifecycle and thereby limit viral replication. In contrast, interferon has a very different mode of action. Rather than targeting a specific process in the viral lifecycle, interferons act by creating an antiviral state within the host cell (Feld and Hoofnagle, 2005). There are three major classes of interferons, which differ by their receptor distribution and their site of production. Type I interferons are produced upon viral infection by many cell types, with the greatest

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production occurring in specialized immune cells such as plasmacytoid dendritic cells (Feld and Hoofnagle, 2005). Type I interferons (interferon-α, -β, -ω), which have served as the main interferons used clinically for HCV, bind to the interferon-alpha receptor, present on the surface of every cell in the body. This interaction leads to a signaling cascade through the JAK–STAT pathway to activate the expression of a large number of genes, collectively known as interferon-stimulated genes or ISGs (Feld and Hoofnagle, 2005).

While the gene products of some ISGs have been shown to have direct anti-HCV effects, it is likely the combination of many ISGs working in concert that leads to viral clearance (Schoggins et al., 2011). This combined action leads to a multi-pronged attack on the virus, making it difficult for resistant variants to emerge. It is very unlikely that a specific variant will be able to resist the effect of all of the different ISGs acting together and remain replication-competent. As a result, true interferon-resistant HCV has been extremely difficult to identify. Interferon non-response occurs because host cells do not respond to interferon, rather than because HCV is resistant to the effects of interferon (Hoofnagle and Seeff, 2006). In addition to activating intracellular antiviral genes, Type I interferons also up-regulate class I MHC leading to stimulation of the adaptive immune response (Rahman et al., 2004). It is not clear if the immunostimulatory effects of interferon are required for viral clearance, however immune activation can lead to flares or emergence of autoimmune conditions during therapy (Bockle et al., 2012). Although some ISGs have antiviral activity, others have less desirable therapeutic effects and likely account for the many systemic side effects that occur with Type I interferon-based therapy.

Type II interferon, interferon-γ, is produced by activated T cells and natural killer cells. Although interferon-γ also activates ISGs, it has not been shown to be an effective agent clinically against HCV (Soza et al., 2005). Most recently, Type III interferons, the interferon lambdas (also called interleukin (IL) 28a, IL28b and IL29) were identified (Ank et al., 2008). Type III interferons have similar antiviral activity to Type I interferons, however they bind to a distinct receptor complex with a limited tissue distribution. The interferon-lambda receptor is present on epithelial cells, including hepatocytes, but is not present on many cell types such as bone marrow-derived and neuronal cells. This limited receptor distribution has the potential to reduce systemic side effects, an observation that has been borne out in early studies of peginterferon lambda to treat patients with HCV infection (Ramos, 2010).

2. History of interferon use for treatment of HCV

Although 6 months of standard interferon monotherapy led to viral eradication in only 6% of treated individuals, investigators did not abandon interferon as a therapeutic (Davis et al., 1990) (Table 1). Initially therapy was extended to 12 months with only marginal improvement until the guanosine analogue ribavirin, which had minimal or no anti-HCV activity on its own, was added to the regimen (Fried et al., 2002; Manns et al., 2001). Ribavirin improved response rates by reducing the rate of relapse after stopping therapy (McHutchison et al., 1998). Although ribavirin continues to be of clinical importance, its mechanism of action remains poorly understood (Paeshuyse et al., 2011). The final improvement before the DAA era was the pegylation of interferon to create a longer lasting interferon with improved antiviral activity and improved tolerability, largely due to once weekly rather than three times weekly dosing (Hoofnagle and Seeff, 2006). Although these advances increased the rates of SVR, just over half of treated patients were cured with peginterferon alfa 2a or 2b and ribavirin alone.

Great efforts were put into understanding the reasons for treatment failure with interferon-based therapy. Numerous virological and host factors were identified that predisposed to treatment non-response. The viral genotype was recognized to be of major importance, with genotype 1 proving the least interferon responsive, for unclear reasons. Higher viral levels also proved less favorable. On the host side, hepatic fibrosis, particularly cirrhosis, race/ethnicity, body mass index, insulin resistance and HIV co-infection proved to be important predictors of treatment failure (Chevaliez and Asselah, 2011). More recently, genome-wide association studies identified single-nucleotide polymorphisms near the IL28B gene that are strongly associated with response to interferon-based therapy (Ge et al., 2009). Interestingly, some patients demonstrate activation of the interferon system with up-regulation of ISGs in liver cells prior to receiving interferon treatment. These ISG pre-activated patients respond less well to interferon and are much more likely to have the unfavorable IL28B genotype (Chen et al., 2010; McGilvray et al., 2012). How exactly the IL28B genotype drives the ISG pre-activation state remains unclear.

Table 1
Milestones of interferon-based therapy for HCV infection. *Genotypes 1, 4, 5 and 6. **Genotype 1 only. IFN – interferon; RBV – ribavirin; PegIFN – peginterferon alfa 2a/2b.

Therapy	Year	SVR rate (%)
IFN × 24 wks	1991	6
IFN × 48 wks	1995	16
IFN + RBV × 24 wks	1998	34
IFN + RBV × 48 wks	1998	42
PegIFN × 48 wks	2002	39
PegIFN + RBV × 48 wks	2002	55
PegIFN + RBV + telaprevir or boceprevir × 24–48 wks	2011	63–75
PegIFN + RBV + sofosbuvir × 12 wks*	2013	90
PegIFN + RBV + simeprevir × 12 wks + PegIFN + RBV × 12–24 wks**	2013	80

Interferon has also taught us a great deal about the innate antiviral immune response and the innate immune system in general. Studies to understand treatment response uncovered critical insights into how the body deals with viral infections from a better understanding of the pathogen-recognition receptors to identification of the IL28B genotypes (Ge et al., 2009; Suppiah et al., 2009) and now the discovery of interferon lambda 4 (Prokunina-Olsson et al., 2013). Studies of interferon's effects have also helped tease apart signaling between the innate and adaptive immune responses.

It took major advances in the understanding of the molecular virology of HCV before direct-acting antivirals (DAAs) targeting different stages in the HCV lifecycle were finally developed (Lindenbach and Rice, 2005). Although clearly a major advance, the first DAAs could only be used in combination with peginterferon and ribavirin to prevent the immediate selection of resistant variants (Hezode et al., 2009; Kwo et al., 2010). It is hard to believe that just 2 years after the approval of boceprevir and telaprevir, highly successful, extremely well tolerated interferon-free regimens are on the immediate horizon. With the number of DAAs in development and the astounding rates of sustained virological response (SVR) reported, the era of interferon as a backbone of therapy is clearly nearing its end. However interferon will not disappear right away. It will still have a role to play, albeit a role that will continue to diminish over time (Table 2).

3. The immediate future

The most important determinant of the outcome of therapy with first-generation protease inhibitors (PIs) is the response to interferon (Pawlotsky, 2011a). Patients with poor interferon response characteristics and prior non-responders to peginterferon

Table 2
Future uses of interferon in the treatment of hepatitis C.

Immediate future	
Genotype 1	Combined with simeprevir or sofosbuvir
Genotype 2	Limited role–possibly used as first-line therapy in resource limited countries
Genotype 3	May combine with sofosbuvir and ribavirin in patients with cirrhosis
Genotypes 4–6	Combined with sofosbuvir or used alone with ribavirin
Medium to long-term	
QUAD therapy	Combined with 2 DAAs for prior null responders and/or those with multidrug resistant HCV
Multidrug resistant HCV	As above
Cirrhosis	Possibly used with QUAD therapy if lower response rates with interferon-free therapy in patients with cirrhosis – issues with safety and tolerability
Genotype 3	May be used with sofosbuvir and ribavirin long-term – ultimately likely to have interferon-free regimens with G3 active DAA combinations
Easy to cure	Regions with high prevalence of IL28B CC genotype may consider using peginterferon and ribavirin with or without DAAs as first-line therapy
Cost containment	May be used to reduce number or duration of DAA therapy to reduce overall costs of therapy
Interferon lambda	Similar antiviral activity and interferon alfa with reduced systemic toxicity. May prove to replace interferon alfa for many of above indications

and ribavirin do poorly with telaprevir or boceprevir-based therapy (Pawlotsky, 2011b). HCV replicates at an enormous rate with an error-prone RNA-dependent RNA polymerase, leading to a remarkable degree of diversity. The virus circulates as a swarm of closely related but distinct HCV genomes known as viral quasispecies. There is so much diversity within the quasispecies that every single and double nucleotide variant is produced every day (Rong et al., 2010). In the presence of drug pressure from one or more DAAs, pre-existing resistant variants are selected for and become the dominant viral population (Sarrazin and Zeuzem, 2010). Interferon and ribavirin 'protect' DAAs by controlling the replication of resistant variants, leaving wild-type virus to be controlled by the more potent antiviral effect of the DAAs. Triple therapy with a poor interferon-response is tantamount to DAA-monotherapy and leads to treatment failure with rapid selection for DAA-resistant variants (Pawlotsky, 2011a).

The first generation PIs, telaprevir and boceprevir, have a relatively low genetic barrier to resistance, with single nucleotide substitutions leading to high-level resistance (Sarrazin and Zeuzem, 2010). They therefore rely on the multipronged attack of interferon to inhibit resistant variants. This may be less important with future DAAs. Newer DAAs have a greater barrier to resistance for multiple reasons. With some DAA combinations, multiple substitutions are required for resistance making them less likely to occur, and with others, like the nucleotide analogue polymerase inhibitors (NUC), resistant variants replicate extremely poorly, markedly reducing their selective advantage in the presence of drug. In addition, the greater potency of the newer agents in development suppresses viral levels more rapidly, leaving less time for resistant variants to emerge (Sarrazin and Zeuzem, 2010). All of these factors will make interferon less important with future DAA-based therapy. Initially, the move will be to interferon-sparing regimens, which shorten the duration of but do not eliminate interferon. Ultimately interferon will be used in fewer and fewer clinical scenarios.

However, in the immediate future, interferon will still have an important role and it will vary by viral genotype.

3.1. Genotype 1

Simeprevir and sofosbuvir have recently been approved for use in combination with peginterferon and ribavirin. Clinical trials with these agents are instructive. Simeprevir is a well-tolerated once daily, oral second-wave PI. However, like telaprevir and boceprevir, in patients with a poor response to interferon and ribavirin, SVR rates diminish due to the selection of simeprevir-resistant variants (Zeuzem et al., 2013). SVR rates dropped from 85% in the interferon-responsive prior relapser population to 45% in prior peginterferon/ribavirin null responders (Zeuzem et al., 2013; NDA, 2013). Similarly, in treatment naïve populations, patients with the treatment-responsive IL28B genotype achieved higher SVR rates (95%) than those with unfavorable IL28B alleles (74%) NDA, 2013.

The pattern with sofosbuvir is somewhat different. Sofosbuvir has a very high genetic barrier to resistance because the S282T mutant that confers resistance to this agent is very unfit, replicating at much lower levels than wild-type virus (Sarrazin and Zeuzem, 2010; Ludmerer et al., 2005). This high barrier to resistance means that even with a less than ideal interferon-response, the emergence of resistance is markedly limited. As a result, although the IL28B genotype was still predictive of response, SVR was still achieved in 87% of those with an unfavorable non-CC allele who completed 12 weeks of peginterferon, ribavirin and sofosbuvir (Lawitz et al., 2013). Furthermore, although not all patients achieved SVR, there was no breakthrough during treatment, with all treatment failures relapsing after stopping treatment and with no resistant variants detected in any patients (Lawitz et al., 2013). The resistant variants may still be present but at such low levels that they cannot be detected and likely do not persist very long once sofosbuvir is discontinued. Therefore, although interferon will still be a component of treatment with both agents for genotype 1 infection, the importance of the interferon response will differ between the two agents because of the difference in their resistance profiles.

In addition, it is important to remember that although simeprevir and sofosbuvir will be available in North America and Europe, there will be many areas of the world, including some parts of Europe, where there will be limited or no access to these drugs for many patients. Treatment will still rely on either triple therapy with first-generation PIs or, in many resource-limited settings, dual therapy with peginterferon and ribavirin. Hence interferon will still have a dominant role in the immediate future for genotype 1 infection.

3.2. Genotype 2

The FISSION, FUSION and POSITRON clinical trials showed that sofosbuvir plus ribavirin for 12 weeks is a very effective therapy for patients with genotype 2 infection, with SVR rates ranging from 82% in treatment-experienced patients to 93–95% in the treatment-naïve population (Lawitz et al., 2013; Jacobson et al., 2013). Although this all-oral combination proved superior to peginterferon and ribavirin and was much better tolerated, the SVR rate was a respectable 78% in patients in the control arm (Lawitz et al., 2013), which is actually somewhat lower than has been reported in previous trials. Given the expected high cost of

sofosbuvir, peginterferon and ribavirin may still be widely used globally to treat patients with genotype 2 infection. Some countries may opt to use sofosbuvir and ribavirin only for those who do not respond to peginterferon and ribavirin.

3.3. Genotype 3

The Phase 2 ELECTRON trial reported very high rates of SVR with sofosbuvir plus ribavirin in patients with genotype 3 infection (Gane et al., 2013). However, the results were less impressive with this interferon-free combination in the Phase 3 studies (Lawitz et al., 2013; Jacobson et al., 2013). In the treatment-naïve population, the SVR rate with 12 weeks of treatment was 56%, compared to 63% in patients treated with 24 weeks of peginterferon and ribavirin (Lawitz et al., 2013). The SVR rate dropped to 30% in patients with genotype 3 infection who had failed prior treatment with peginterferon and ribavirin (Jacobson et al., 2013). Extending treatment to 16 weeks increased the SVR rate to 62% in this population, raising the possibility that the issue was simply one of duration (Jacobson et al., 2013). To address this question, patients in the European VALENCE trial received 24 weeks of treatment with sofosbuvir and ribavirin. Although SVR rates increased in treatment-naïve patients, particularly those with cirrhosis (21% SVR with 12 weeks vs. 92% SVR with 24 weeks), there was no additional benefit in treatment-experienced patients with cirrhosis, with 24 weeks of therapy leading to an SVR rate of 60%, similar to the 61% reported with 16 weeks of therapy (Zeuzem et al., 2013). Clearly the treatment-experienced patients with genotype 3 infection and cirrhosis remain a challenge.

To address this issue, patients in the LONESTAR2 study were treated with sofosbuvir, ribavirin and peginterferon for 12 weeks, with SVR rates of 83% reported in genotype 3 patients with or without cirrhosis (Lawitz et al., 2013). Although the numbers in the study were very small ($n = 24$), and only 50% were cirrhotic, the results suggest that there may still be a role for peginterferon in the treatment of genotype 3 infection. Ongoing larger studies will help clarify the utility of interferon but it is likely that at least in the immediate future, peginterferon will be used to treat patients with genotype 3 infection, particularly those with compensated cirrhosis.

3.4. Genotype 4, 5 and 6

A small number of patients with genotypes 4 ($n = 28$), 5 ($n = 1$) and 6 ($n = 6$) were included in the NEUTRINO trial of peginterferon, ribavirin and sofosbuvir for 12 weeks. All but one genotype 4 achieved SVR, suggesting that this regimen will be effective for these less well-studied genotypes (Lawitz et al., 2013). Although interferon-free regimens will likely be available for these patients as well in the future, interferon will remain part of the regimen for now. Furthermore, because of the high prevalence of these genotypes in resource-limited settings, it is likely that dual therapy with peginterferon and ribavirin will be used for many years to come. For genotype 6, treatment response rates to peginterferon and ribavirin are generally much better than for genotypes 1 and 4, possibly owing to the high prevalence of genotype 6 in Southeast Asia where the favorable IL28B genotype is common. For those who achieve a rapid virological response (RVR), HCV RNA negativity at week 4 of therapy, treatment can be truncated to 24 weeks, whereas those who do not achieve RVR should continue for a full year of therapy (Thu Thuy et al., 2012). Genotype 5 still requires a full 48 weeks of peginterferon and ribavirin therapy (Papastergiou et al., 2014).

4. The medium to long-term

Although peginterferon will remain part of the preferred regimen for all but genotype 2 infection in the short-term, what will happen once interferon-free regimens are approved for other genotypes in the relatively near future (Table 3)? Will there be any longer term role for interferon in the treatment of HCV infection? Interferon may have a role for treating certain distinct 'difficult-to-cure' populations.

4.1. QUAD therapy

An alternative to interferon-free regimens is the inclusion of 2 DAAs with peginterferon and ribavirin, so-called QUAD therapy. QUAD therapy may be an attractive strategy particularly in poor interferon responders, in whom there is a high risk of treatment failure with triple therapy due to breakthrough resistant virus that is not controlled because of the poor response to interferon. The addition of a second DAA, particularly one with a higher barrier to resistance, would reduce the chance of treatment failure. In addition to the lower chance of breakthrough with DAA-resistant virus, QUAD therapy may have an additional advantage; it may improve the response to interferon itself.

The strongest predictor of response to interferon-based therapy is the expression of ISGs in the liver prior to treatment. Paradoxically, patients who fail to respond to interferon have high expression of hepatic ISGs prior to receiving interferon (Chen et al., 2005). The interferon system is turned on or 'pre-activated' in the absence of interferon. With near maximal ISG expression at baseline, the addition of interferon has little effect, leading to treatment failure (Feld et al., 2007; Sarasin-Filipowicz et al., 2008). The cause for this pre-activated state remains unclear. The IL28B genotype is an important determinant, with patients with the unfavorable non-CC genotype showing higher baseline ISG expression, however other factors are also important (McGilvray et al., 2012; Honda et al., 2010). Patients with genotype 1 infection tend to have higher baseline ISG expression, as do those with other treatment-non-response characteristics such as advanced liver fibrosis, obesity and

Table 3
Treatment regimens in Phase 3 or later development with projected timelines for approval. Peg – peginterferon alfa 2a; RBV – ribavirin; PI – protease inhibitor; NNI – non-nucleoside polymerase inhibitor; NS5A – non-structural protein 5a inhibitor; Peg-lambda – peginterferon lambda.

Regimen	Includes IFN	Genotypes	Anticipated approval
Sofosbuvir + Peg/RBV × 12 wks	Y	1, 4,5,6	Approved
Sofosbuvir + RBV × 12 wks	N	2	Approved
Sofosbuvir + RBV × 24 wks	N	3	Approved
Simeprevir + Peg/RBV × 12 wks + Peg/RBV × 12 wks	Y	1, 4	Approved
ABT450 (PI), ABT-333 (NNI), ABT-267 (NS5A) ± RBV	No	1a and 1b	Late 2014 or early 2015
Sofosbuvir/ledipasvir) ± RBV × 12 wks	No	1a and 1b	Late 2014 early 2015
Daclatasvir (NS5A) + asunaprevir (PI) + BMS791325 (NNI)	No	1a and 1b	2015
Daclatasvir (NS5A) + asunaprevir (PI)	No	1b	2014 (Japan)
Peg-Lambda + Daclatasvir (NS5A)	Y	1b	Possibly 2015

insulin resistance (McGilvray et al., 2012). Importantly however, the ISG expression is dependent on the presence of viremia, returning to baseline with viral clearance. This is of particular relevance with DAA-combination therapy.

In an early study of interferon-free therapy, a NUC (mericitabine) and a PI (danoprevir), were combined for 14 days, followed by treatment with peginterferon and ribavirin (Gane et al., 2010). During the interferon-free period, HCV RNA levels declined by a mean of 4–5 logs. Accompanying the drop in HCV RNA, the level of interferon-gamma-inducible protein 10 (IP-1) also declined. IP-10 is an ISG and the level in the blood at baseline is strongly associated with treatment response to interferon-based therapy. Like hepatic ISGs, high levels of IP-10 at baseline are associated with treatment non-response (Romero et al., 2006; Lagging et al., 2006). In the INFORM trial, as viral levels declined during DAA therapy, IP-10 levels went down (Gane et al., 2010). This was most striking in the prior null responders in whom the markedly elevated IP-10 levels declined to levels seen in the treatment-naïve and prior relapser populations. This raises the possibility that potent DAA therapy may reduce IP-10 levels and presumably intrahepatic ISGs, 'resetting' the ISG set-point and thus potentially converting a non-responder to a responder. QUAD therapy may therefore be attractive in prior null responders or any population with poor interferon-response characteristics.

To date, Phase 2 studies of QUAD therapy in prior null responders have reported SVR rates of 95% (39 of 41) with asunaprevir (PI) plus daclatasvir (NS5A inhibitor) Lok et al., 2012 and 84% (62 of 74) with mericitabine (NUC) and danoprevir (PI) Feld et al., 2012, combined with peginterferon and ribavirin. Notably, both of these studies achieved these high rates of SVR in predominantly genotype 1a populations, who have a lower barrier to resistance to the DAAs used and in whom dual therapy (without peginterferon and ribavirin) was previously unsuccessful (Lok et al., 2012; Feld et al., 2012). These studies suggest that DAA therapy does improve interferon responsiveness, making QUAD therapy a possibly attractive approach for interferon-non-responsive populations. QUAD therapy may have a role to allow for use of somewhat less effective and thus potentially less expensive DAA combination regimens. However, it is important to note that more potent DAA regimens have proven highly effective in prior null responders suggesting that although QUAD therapy would likely be effective, it will not be necessary for most patients.

4.2. Multi-drug resistant HCV

Different classes of DAAs do not have overlapping resistance profiles. Therefore patients with resistance to a first generation PI should respond equally well to treatment with a polymerase or NS5A inhibitor as someone without prior DAA experience. It is precisely this lack of cross-resistance that has led to the development of combination therapy with DAAs from different classes. The results from these combination studies are very impressive, with >90% rates of SVR reported (Kowdley et al., 2014). However, in the patients who do not achieve SVR, multi-drug resistant virus may be an issue.

Multi-drug resistance will depend to some degree on the combinations used. There are currently a number of regimens using a PI, non-nucleotide polymerase inhibitor (NNI) and NS5A inhibitor with or without ribavirin. All 3 of these DAA classes have a relatively low genetic barrier to resistance, particularly for genotype 1a HCV (Sarrazin and Zeuzem, 2010). Because of the challenge of sequencing multiple regions of individual viral genomes, it is difficult to determine with certainty if patients who have failed these regimens have circulating virions resistant to each of the 3 classes of drugs, but this is the most likely scenario. Although these patients could presumably be retreated with a NUC-based regimen for which there is no cross resistance, an alternative approach would be to use interferon. Even with a NUC, another DAA would likely be necessary, which could be problematic if a patient began with virus resistant to PIs, NS5A inhibitors and NNIs. With careful selection, an agent without cross-resistance, such as a different type of NNI or a PI with a different resistance profile, could likely be selected, but alternatively one may opt for peginterferon and ribavirin with a NUC.

Of particular concern is NS5A inhibitor-resistance. These variants persist at high levels even when the NS5A inhibitor is stopped; likely because they are relatively fit viruses that compete reasonably well with wild-type virus (Sarrazin and Zeuzem, 2010). The development of NUC-NS5A combinations is promising but for a patient with NS5A resistance, this regimen may be inadequate and may lead to the selection of even NUC-resistant variants, leaving peginterferon as the only option (Lawitz et al., 2013). Because compliance will undoubtedly be less reliable in clinical practice than in clinical trials, multi-drug resistance will occur more frequently than seen to date. As the number of DAA combinations increases, it is likely that eventually there will be salvage interferon-free regimens for most patterns of resistance, but adding peginterferon will always likely remain a reasonable option.

4.3. Cirrhosis

Patients with cirrhosis have always proven to be a major challenge. They are the patients who require therapy most urgently to prevent complications but they also respond least well to treatment and suffer the greatest number of adverse events. The studies of interferon-free DAA combinations have largely excluded cirrhotics or included very well compensated patients with early Child A cirrhosis and minimal portal hypertension. It is therefore possible, and perhaps even likely, that results seen in clinical trials will not be replicated in clinical practice. This was certainly evident with the first generation PIs, in which lower SVR rates and much higher complication rates were seen in patients with cirrhosis in real-world studies (Hezode et al., 2013). The complications seen in the French early access program (CUPIC study) were largely related to prolonged interferon exposure in patients who might have met early stopping rules with peginterferon and ribavirin alone (Hezode et al., 2013). Therefore although DAAs combinations may be less effective in patients with cirrhosis, it is not clear that adding interferon will be any more effective and may impact on safety.

The precise reasons that patients with cirrhosis respond less well to treatment is not completely understood. It is likely multifactorial with different issues being more and less relevant in particular individuals ranging from variable drug delivery to hepatocyte populations due to shunting, a reduction in number and/or function of intrahepatic immune cell populations, alteration of the cytokine and chemokine milieu in the liver, as well as many other potential issues. With oral DAA therapy, another concern may be drug absorption in the setting of portal hypertension and intestinal permeability as well as impairment of drug uptake or metabolism, particularly for prodrugs like NUCs that require hepatic activation for their antiviral effect. In addition to reduced efficacy, there may also be greater issues with toxicity. This is probably of greatest concern with NUCs because of the reports of mitochondrial toxicity in NUCs used for other diseases, including HIV and hepatitis B, in which the presence of cirrhosis seems to increase the risk (Apostolova et al., 2011). This may also be a concern with host-targeting agents, if any ultimately make it to clinical use.

If DAAs are less effective in patients with cirrhosis, would peginterferon be a useful addition? The challenge is that peginterferon is also much less effective and much less safe in patients with cirrhosis, making it a less than ideal choice in this setting (Heathcote et al., 2000). Peginterferon seemed to improve response

rates in patients with cirrhosis and genotype 3 infection treated with sofosbuvir and ribavirin (Lawitz et al., 2013). If these results are borne out in larger trials, there would certainly be rationale to evaluating the addition of peginterferon if it proves that certain DAA combinations are less effective in patients with cirrhosis. To date, although there are increasing numbers of cirrhotic patients being included in trials, most remain very well-compensated cirrhotics, limiting interpretation of the relevance of these results to the more advanced patients seen in clinical practice (Hezode et al., 2013). Unfortunately if patients with more advanced cirrhosis prove to be difficult to cure with all-oral DAA therapies, it is not clear that peginterferon would improve the situation. Studies of peginterferon and ribavirin in patients with even early hepatic decompensation have consistently shown a high risk of serious and even life-threatening toxicity (Hezode et al., 2013; Everson, 2005). In addition, these patients tend to have very low rates of response to peginterferon. It is possible that when combined with potent DAAs, interferon-responsiveness among cirrhotics will also improve because like null responders, patients with cirrhosis tend to have high baseline ISG expression, which may be reduced with viral suppression, making them more responsive to interferon. Ultimately it will likely require real-world data to determine if peginterferon is necessary, useful and safe as an adjunct to DAAs in patients with cirrhosis.

4.4. Genotype 3

As noted previously, the current interferon-free options for genotype 3 infection are suboptimal. Although there are combination DAA trials ongoing for genotype 3 and it is likely that one or more will be effective, it may be some time before these are approved and available, leaving an interferon-containing regimen as the preferred option for this group of patients, particularly for those with cirrhosis.

5. Other potential roles to consider using interferon

5.1. Easy-to-cure populations

Although it may seem counter-intuitive to use interferon in an 'easy-to-cure' population, this may be a reasonable approach, particularly if cost-containment is an issue. In patients with favorable interferon-response characteristics, particularly a favorable IL28B genotype, interferon-based therapy is likely to be extremely effective. Even with first-generation PIs, patients with the CC IL28B genotype have ~90% chance of response and almost all qualify for shortened therapy (Bota et al., 2013). In non-cirrhotic IL28B CC patients with genotype 1 infection, just 12 weeks of telaprevir, peginterferon and ribavirin led to an SVR rate of 89% in the CONCISE trial (Nelson et al., 2013). With more potent DAAs, it is conceivable that response rates would be even higher, possibly with even shorter therapy. In regions of the world with a high prevalence of the favorable IL28B genotype like Asia (Thomas et al., 2009), there may be a strong incentive to continue to use peginterferon, with the promise of high cure rates and the potential to use simpler and less expensive DAA regimens.

5.2. Cost-containment

Even beyond the IL28B CC population, it may be attractive to use peginterferon-based therapy in areas where cost is a major concern. It is very likely that peginterferon will remain considerably less expensive than most if not all DAAs. If triple or even QUAD therapy with peginterferon allowed one to reduce the number of DAAs or the duration of therapy, this may be an important cost-containment measure. Depending on the economic models, some countries may suggest that DAA-based therapy should only be used as salvage therapy for peginterferon-ribavirin failures, however given the toxicity of interferon, this is unlikely to be acceptable in most regions of the world. Lobbying and activism may well be required to pull together the resources necessary to treat most patients without interferon-based therapy.

5.3. Interferon lambda

As a Type III interferon, interferon lambda binds to a different receptor than interferon alpha to activate the same cascade of JAK–STAT signaling, ISG induction and viral suppression. The restricted distribution of the interferon lambda receptor may reduce systemic toxicity of interferon-based therapy. To date, small phase 2 studies have shown that peginterferon lambda has similar antiviral efficacy to peginterferon alfa 2a with reduced toxicity, particularly reduced bone marrow suppression (Ramos, 2010). Unfortunately, interferon lambda has shown some hepatotoxicity at high doses, which might limit its use in patients with cirrhosis, those who would benefit most from the reduced marrow suppression. However, overall, interferon lambda appears to be a better-tolerated equally efficacious interferon. Provided the early results hold up in larger trials, interferon lambda may serve a useful tool in settings where interferon may still play a therapeutic role.

6. Conclusions

Interferon has been the backbone of treatment for HCV for over 20 years. It has certainly posed significant challenges to both patients and physicians but it has also been an important stepping-stone on the way to HCV eradication. Even as interferon becomes less important therapeutically, understanding some of its mechanistic properties will still be relevant for other viral infections and possibly even for HCV. Peginterferon will still be around for a little while longer as a mainstay of treatment but will clearly largely be replaced by interferon-free DAA combination therapy in the not too distant future. Peginterferon lambda may have a role as a better tolerated, equally efficacious option. Interferon will likely remain a salvage therapy for DAA failures and a cost-containment option in resource-limited settings but it is fair to say that we can start preparing to say goodbye to a true and trusted, but rather difficult, friend.

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