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Management of hepatitis C genotype 4 in the directly acting antivirals era

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ABSTRACT

Genotype 4 chronic hepatitis C (G4 HCV) accounts for 13% of worldwide HCV infections; with 10 million people infected with the virus across the world. Up to the end of 2013, the only treatment option for G4 HCV was treatment with pegylated interferon and ribavirin for 24–48 weeks. Since late 2013, treatment of G4 HCV has been transformed by the licensing of many directly acting antiviral agents (DAA). It is an exciting time to be involved in the management of HCV generally and G4 particularly. Interferon-free DAA regimens are now a reality for G4 HCV. This review will highlight these developments and discuss the data behind the use of these drugs. It will also highlight future regimens that are likely to be available over the coming years.

INTRODUCTION

The introduction of directly acting antiviral agents (DAAs) in the treatment of infections with hepatitis C virus (HCV) has revolutionised the field.[1] Whereas even 5 years ago our clinics were full of patients with no prospect of successful treatment, DAA therapy now means that the majority of patients can be successfully cured with ever decreasing durations of well tolerated regimens.[2] The use of interferon (IFN) will continue to decrease if not cease all together especially in countries with well-resourced healthcare systems.[3] Second-generation and third-generation DAA combinations promise to provide pan-genotypic regimens that will cure >95% of patients with as little as 6 weeks of treatment.[4] Whether or not even shorter regimens of 4 weeks could be used has recently been brought into question, although it remains a goal that some wish to pursue. The pace of pharmaceutical development in the field is unprecedented, and it is therefore inevitable that reviews such as this one are almost certainly out of date as soon as they are written. Nevertheless, this review will attempt to summarise the current available evidence for the optimal management of genotype 4 (G4) HCV. It is important to state from the outset that this genotype has perhaps not attracted as much attention in large scale clinical trials as that afforded to some of the other HCV genotypes, and this will be highlighted below.[5]

Epidemiology of G4 HCV Worldwide

There have been a number of comprehensive reviews recently published on the epidemiology of HCV infection worldwide.[6–9] It is estimated that G4 accounts for 13% of all HCV infections which translates into an estimated 10.4 million patients living with active G4 infection.[6] The bulk of the G4 disease burden resides in the Middle East, Northern Africa and Sub-Saharan Africa with the largest single G4 population (and arguably the best characterised cohort) residing in Egypt where 15% of an estimated population of 80 million are HCV positive, of which 93% are infected with G4.[6 10] The cause of these high seroprevalence rates are likely multifactorial; however, the widespread use of parenteral antihelminthics to combat schistosomiasis is believed to be predominately responsible for the scale of the epidemic. In 55–59 year olds (a population that is likely to have a higher burden of fibrosis due to the length of infection), the prevalence rate approaches 40%. Indeed, a recent study that screened 6600 participants aged between 17 and 58 years of age found 1018 (15.42%) participants positive for HCV, and among these, 62.4% had evidence of liver cirrhosis.[10] Other estimates put the numbers of compensated and decompensated cirrhotics in Egypt at 630 000 and 138 000, respectively.[11] Such a large burden of advanced disease puts a considerable strain on the already overstretched health resources of the country.

Other countries with a high prevalence of G4 HCV include Saudi Arabia (60% of infected individuals), Iraq (52.9%), Kuwait (54.2%), United Arab Emirates (46.2%) and Syria (59%).[6] Sub-Saharan African countries have estimated rates of G4 infection similar to Egypt with 82.8%, 96.8% and 91.9% in the Central African Republic, Democratic

Republic of Congo and Gabon, respectively, with Central African countries lagging closely behind (13.8% HCV seroprevalence of which 76% G4).[12 13] In contrast, while the prevalence rates of HCV infection in Asia are low (0.2% in Taiwan for example), the dense population of some of these countries means that the absolute numbers of patients with G4 HCV in this continent is high.[6] India is estimated to have around 6 million viraemic HCV patients; and with a G4 prevalence of 5.8%, there are likely to be ~350 000 patients living with G4 HCV in this country alone.[6] In Pakistan, the equivalent figure is around 112 000.[6] Australasia and Latin America have low rates of G4 infection (<2%, where the data are available) as does the USA (6.3% of HCV infection) and Canada (2.3%).[6]

Rates of G4 HCV within Europe appear more variable. Nonetheless, with up to 14% of viraemic patients infected with G4 in Western Europe (eg, 3.8% of 768 000 viraemic patients in Italy; 8% of 472 000 in Spain; 14% of 69 000 in Belgium), these patients are not uncommon within most European HCV centres.[6] Transmission risk and patterns of distribution are not well defined in Europe but may be influenced by drug use, HIV coinfection and population migration.

HISTORICAL SUCCESS WITH DUAL THERAPY

Prior to the advent of DAAs, the only treatment option for G4 HCV infection was pegylated IFN (PEG-IFN) 2a or 2b with ribavirin (RBV). Patients with G4 HCV were under-represented in the registration trials, and it is difficult to infer sustained virologic response (SVR) rates from these.[14 15] Table 1 provides a summary of outcome data for patients with G4 HCV treated with PEG-IFN. One of the largest experiences came from the real-life PROPHESYS cohort of 7163 treatment-naïve patients of all genotypes reported in 2012.[16] In total, 317 of these patients with G4 infection were treated with either PEG-IFN α2a or PEG-IFN α2b and RBV and achieved SVR rates of 41% in those without and 27.5% in those with bridging fibrosis or cirrhosis. A larger albeit retrospective review performed in Egypt suggested that treatment with PEG-IFN α2a was associated with a significantly higher rate of SVR (59.6% vs 53.9% with PEG-IFN α2b, p<0.05) and fewer significant dose reductions (27.3% with PEG-IFN α2a vs 35.3% with PEG-IFN α2b; p<0.01).[17] While this may be explained by confounding factors such as patient body mass index (BMI), it has been a consistent finding across studies.[18]

Many of the traditional determinants of response to dual therapy such as interleukin-28 (IL-28) genotype, BMI, fibrosis stage, presence or absence of insulin resistance and vitamin D deficiency have also been shown to be of importance in the treatment of G4 infection.[5] In a large well-designed study from Egypt using PEG-IFN α2b, viral response at 4 and 12 weeks was used to tailor length of therapy to 24, 36 or 48 weeks.[19] Patients who achieved viral negativity at week 4 were treated for 24 weeks and achieved SVR rates of 86% compared with a rate of 76% for those negative at week 12 who were treated for 36 weeks. SVR rates fell to 56% if negativity was not achieved at either time point. This study population was highly selected (young, median BMI 28, few patients with cirrhosis) and treatment response may further be overestimated in Egyptian cohorts due to the predominance of the G4a subtype in this country. Data from a French study reported SVR rates of 54.9% in patients of Egyptian origin (predominance of G4a infection) compared with 40.3% and 32.4% in those infected in France or Africa (over 80% G4f, G4h, G4j, G4k and

Table 1 Efficacy of pegylated interferon and ribavirin in the treatment of G4 HCV infection

Trial	Treatment history	Number of patients treated—suffering from G4 HCV	Patient characteristics	Treatment	SVR rate
Marcellin *et al*[16]	Naïve	317	51 bridging fibrosis/ cirrhosis 214 no bridging fibrosis/cirrhosis	PEG-IFN α2a or PEG-IFN α2b+RBV (clinician discretion)	27.5% 41%
El Raziky *et al*[17]	Naïve	3718	6.3% cirrhotic 5.9% cirrhotic	PEG-IFN α2a+RBV (n=1985) PEG-IFN α2b+RBV (n=1733)	59.6% 53.9%
Kamal *et al*[19]	Naïve	358	Highly selected, few cirrhotic	Virus negative week 4–24 weeks PEG-IFN α2b Virus negative week 12–36 weeks PEG-IFN α2b Virus positive week 4+12–48 weeks PEG-IFN α2b	86% 76% 56%
Poynard *et al*[22]	Experienced	68	Fibrosis stage 2, 3 and 4	PEG-IFN α2b+RBV	28%

PEG-IFN pegylated interferon; RBV ribavirin; SVR sustained virologic response.

G4r subgenotypes), respectively.[20] It is possible, therefore, that subtyping of patients with G4 HCV may become important in determining duration of treatment with new DAAs; akin to the current differentiation between G1a and G1b.[21]

It is noteworthy that there are limited data on the efficacy of dual therapy in treatment-experienced patients with G4 in the literature; an overall SVR rate of 28% was reported in a cohort of 68 patients with relatively advanced fibrosis (patients split almost equally between F2, F3 and F4).[22]

IFN CONTAINING DAA REGIMENS

The first-generation protease inhibitors telaprevir and boceprevir came into widespread clinical use in 2012.[1] These agents have minimal activity against G4 HCV, and it has only been since the introduction of the nucleotide polymerase inhibitor sofosbuvir, the second-generation protease inhibitor simeprevir and the first-generation non-structural protein 5A (NS5A) inhibitor daclatasvir, that PEG-IFN/DAA combinations have been tested in patients with G4 HCV.[1 5 23] These agents all have good in vitro activity against G4 virus.[23]

Sofosbuvir containing regimens

The efficacy of sofosbuvir-based triple therapy was assessed in the NEUTRINO study in which 27 out of 28 (96% SVR rate) patients with G4 infection were cured following 12 weeks of treatment.[24] Only 18% of the total study population were known to have cirrhosis, and it is unclear from the supplementary data of this paper what proportion of the G4 cohort had advanced fibrosis or cirrhosis. A slightly lower SVR rate (82% on intention to treat (ITT)) was reported from the phase II ATOMIC trial which provided 24 weeks of triple therapy to 11 patients with G4 infection.[25] Further real-life data on the efficacy of this regimen in a large, real-life cohort should become available as Gilead Sciences have agreed to provide 12 weeks of treatment for 75 000 patients with F3 and early F4 disease in government healthcare facilities in Egypt starting in September 2014 (Professor Imam Waked, National Liver Institute, Menoufia University, Egypt). However, the data will need to be interpreted with caution given the favourable profile of PEG-IFN in patients with G4 HCV of Egyptian ancestry.[20]

Simeprevir containing regimens

The RESTORE study recruited 107 treatment-naïve (n=35) and treatment-experienced (n=72) patients from France and Belgium.[26] The study population was predominately males (79%) with subtype 4a infection (42%) and without advanced fibrosis (14% F3 disease, 28% cirrhosis). Treatment naïve (n=35) and prior relapsers (n=22) were treated with 12 weeks of PEG-IFN, RBV and simeprevir, followed by either 12 or 36 weeks of dual therapy with PEG-IFN and RBV. Criteria used for response-guided therapy were HCV RNA<25 IU/mL (detectable or undetectable) at week 4 and HCV RNA <25 IU/mL (undetectable) at week 12. The total duration of treatment was 24 weeks if patients achieved both of these parameters or 48 weeks if not. Partial responders (n=10) or null responders (n=40), all received 12 weeks of triple therapy followed by 36 weeks of dual therapy. The overall SVR rate was 65% (83% treatment naïve; 86% prior relapsers; 60% partial responders; 40% null responders) but 96% in treatment-naïve and 95% in prior responder patients who achieved the response guided criteria. These response rates are comparable to those seen in the registration studies for simeprevir in genotype 1 (G1) HCV.[27 28]

The addition of simeprevir to standard dual therapy seems to confer a significant advantage in the treatment of G4 HCV infection particularly in patients that are treatment naïve or prior responders. A subsequent analysis conducted to assess the efficacy of a shortened 12-week course of simeprevir in addition to PEG-IFN and RBV in treatment-naïve patients with F0–F2 fibrosis has subsequently reported an overall SVR rate of 90% (97% 12-week treatment group; 82% 24-week treatment group) and may reduce total treatment duration to 12 weeks in patients that display a very rapid virological response.[29]

Daclatasvir containing regimens

The NS5A inhibitor daclatasvir in combination with PEG-IFN and RBV has been studied in 30 patients with G4 HCV in a phase IIb study.[30] Patients that received daclatasvir and achieved an HCV RNA lower than the limit of quantification at week 4 and undetectable at week 10 (protocol-defined response (PDR)) were then rerandomised at week 12 to continue triple therapy or switch to PEG-IFN and RBV for a further 12 weeks. Patients without a PDR and placebo patients continued PEG-IFN and RBV for a total of 48 weeks. SVR rates were daclatasvir dose dependent; 67% (8/12) with 20 mg daclatasvir and 100% (12/12) with 60 mg daclatasvir compared with 50% in the six patients who received standard dual therapy.

The HALLMARK-QUAD study, an open-label phase III study, subsequently treated 44 G4 prior partial (n=6) or null (n=34) responders with 60 mg daclatasvir, 100 mg of the protease inhibitor asunaprevir, PEG-IFN α2a and RBV for 24 weeks.[31] In total, 20 patients were cirrhotic and only 3 had the favourable CC genotype of IL-28. SVR rates in this difficult to treat cohort were 97.7% (43 out of 44; 1 patient lost to follow-up at SVR of 12 weeks (SVR12) but subsequently achieved SVR of 24 weeks (SVR24)). While it would appear that this regimen including an NS5A inhibitor and protease inhibitor in combination with dual therapy is highly effective, the acceptability (financial and to the patient) remains questionable.

IFN-FREE DAA REGIMENS

The era of IFN-free therapy is now achievable with a number of regimens licensed and many more in the

development pipeline.[32–33] While the bulk of these regimens are currently being licensed for G1 infection, most of them exhibit good activity against G4. This section and table 2 will attempt to summarise the major players in this field. It is important to note in advance that the side effect profiles of all these regimens are excellent and even RBV appears to be better tolerated when not combined with PEG-IFN.

Sofosbuvir-based regimens

Sofosbuvir is a first in class nucleoside inhibitor of the HCV non-structural protein 5B (NS5B) polymerase.[34] It has good potency against the virus, a high barrier to resistance and minimal drug–drug interactions making it an excellent backbone for combination DAA regimens.[35] Its use has been widely investigated in IFN-free combinations for predominately HCV G1, but data on these regimens are emerging for G4.

Sofosbuvir and RBV

The efficacy of this combination for patients with G4 HCV was tested in a small single-centre randomised open-label trial of patients with G4 HCV of Egyptian ancestry.[36] The patients consisted of 23% cirrhotics and ~55% were treatment experienced. Patients were randomised to 12 or 24 weeks of treatment with this regimen. SVR12 rates were 79% (11 out of 14) for 12 weeks and 100% (14 out of 14) for 24 weeks in the treatment-naïve patients. The equivalent figures for the treatment-experienced patients were 59% (10 out of 17) for 12 weeks and 87% (13 out of 15) for 24 weeks.

A similar but slightly larger trial was also carried out in Egypt.[37] SVR rates for treatment-naïve patients overall were 84% (21 out of 25) for 12 weeks and 92% (22 out of 24) for 24 weeks. The equivalent figures for treatment-experienced patients were 70% (19 out of 27) and 89% (24 out of 27) for 12 weeks versus 24 weeks. Five out of the eight and seven out of the nine cirrhotic patients were cured in the 12-week and 24-week arms, respectively. Interestingly, even in the 12-week arm, treatment experienced non-cirrhotics had a 73% SVR12 rate.

These data suggest that this is a relatively effective regimen but that 24 weeks of treatment is necessary for treatment-experienced patients. The efficacy of 12 weeks for treatment-naïve patients is satisfactory, and given that no mutations were selected, it is possible that a strategy to then retreat those who failed 12 weeks with 24 weeks would make clinical and commercial sense. The role of intermediate lengths of therapy, for example 16 weeks, also deserves further study.

Sofosbuvir and ledipasvir

The fixed-dose combination of sofosbuvir and the first-generation NS5A inhibitor ledipasvir has been recently licensed throughout the Western world.[35] The registration ION trials were performed exclusively in G1 patients.[32] In a small phase IIa trial, the efficacy of this fixed-dose combination without RBV was tested in 20 patients with G4 HCV.[38] Eight patients were treatment experienced, seven had cirrhosis, seven were of Egyptian origin and seven were of African origin. Excellent results were obtained with 19 out of 20 (95%) patients achieving SVR12, with one patient not having got to this time point in the trial. These results need to be replicated in larger cohorts although, given the efficacy of this regimen in different G1 populations, there is no reason to suppose that such SVR rates will not be seen with a larger number of patients.[39 40]

Sofosbuvir and simeprevir

Simeprevir in combination with sofosbuvir has been shown to be highly effective in the treatment of G1 HCV infection including in historically hard-to-treat groups such as prior null responders and patients with cirrhosis.[41 42] Data on the use of this DAA combination in G4 disease have recently been presented from a phase II open-label study (OSIRIS) conducted in Egypt.[43] Non-cirrhotic patients were randomised to receive 8 or 12 weeks of treatment while all compensated cirrhotic patients received a 12-week treatment course. The overall SVR12 was 92.1% (58/63) with all patients treated for 12 weeks achieving viral clearance regardless of cirrhosis status. SVR12 rates were significantly higher than historical controls across all arms. While non-cirrhotic patients receiving 8 weeks of therapy achieved a higher rate of SVR12 than historical controls, the rate was lower than all other arms (only 72%) and is lower than that which is acceptable in the era of DAAs.

Sofosbuvir and daclatasvir

Both these agents have proven efficacy against G4 HCV and in combination, have proven efficacy in genotype 1–3 (G1–3) disease albeit in small numbers in a phase II trial.[44] The ongoing phase III ALLY-1, ALLY-2 and ALLY-3 studies continue to evaluate the role of this combination in larger numbers and across genotypes. However, a phase II study (IMPACT) has recently reported data on the use of this combination in addition to simeprevir for the treatment of G1 and G4 disease in DAA-naïve patients with evidence of portal hypertension or decompensated cirrhosis.[45] All patients achieved SVR12 after 12 weeks of therapy. Of interest, this high virological response was achieved despite the presence of baseline detectable resistance-associated mutations in 83% of patients.

Sofosbuvir and velpatasvir

Velpatasvir is a second-generation NS5A inhibitor with a higher barrier to resistance than either ledipasvir or daclatasvir.[46] It has been coformulated with sofosbuvir into a fixed-dose once-daily combination and phase III data comparing a 12-week course of treatment to matched placebo are now available.[47] The study included 116 patients with G4 disease that received active treatment versus 22 that received placebo. SVR rates were similar across genotypes in the sofosbuvir-

Table 2 Summary of trials of direct acting antivirals in G4-infected patients

Trial	Phase	Patient characteristics	Treatment history	Number of patients treated—suffering from G4 HCV	Treatment arms	SVR rate (%)
Lawitz *et al*[24] (NEUTRINO)	III	17% cirrhotic across genotypes	Naïve	28	SOF/PR 12 weeks	96
Kowdley *et al*[25] (ATOMIC)	II	Non-cirrhotic	Naïve	11	SOF/PR 24 weeks	82
Moreno *et al*[26] (RESTORE)	III		Naïve	35	SMV/PR 12 weeks, response guided PR	82.98
			Experienced	22		6.4
					SMV/PR 12 weeks, PR 36 weeks	
Hézode *et al*[30]	IIb		Naïve	30	DAC 20 mg+PR (RGT)	67
					DAC 60 mg+PR (RGT)	100
					Placebo+PR 48 weeks	50
Jenson *et al*[31] (HALLMARK-QUAD)	III	20 cirrhotic	Experienced	44	DAC/asunaprevir/PR 12 weeks	95
		24 non-cirrhotic			DAC/asunaprevir/PR 12 weeks	100
Ruane *et al*[36]	II	23% cirrhotic	Naïve or experienced	60	SOF/RBV 12 weeks	68
		38% diabetes			SOF/RBV 24 weeks	93
Esmat *et al*[37]	II		Naïve	25	SOF/RBV 12 weeks	84
			Naïve	24	SOF/RBV 24 weeks	92
			Experienced	27	SOF/RBV 12 weeks	70
			Experienced	27	SOF/RBV 24 weeks	89
Kapoor *et al*[38]	IIa	40% treatment experienced	Naïve or experienced	20	SOF/LDP 12 weeks	95
		40% advanced fibrosis				
		35% Egyptian origin				
		35% African				
El Raziky *et al*[43] (OSIRIS)	IIa	37% cirrhotic	Naïve or experienced	63	SMV+SOF 8 weeks (F0-F3)	75
					SMV+SOF 12 weeks (F0-F3)	100
					SMV+SOF 12 weeks (F4)	100
Feld *et al*[47]	III	19% compensated cirrhosis across genotypes	Naïve or experienced	116	SOF-VELPATASVIR 12 weeks	100
				22	Matched placebo 12 weeks	0
		32% treatment experienced across genotypes				
Pol *et al*[54] (PEARL-1)	IIb	Non-cirrhotic	Naïve	44	OMV/PTV/r	90.9
		Non-cirrhotic	Naïve	42	OMV/PTV/r/RBV	100
		Non-cirrhotic	Experienced	49	OMV/PTV/r/RBV	100
Hassanein *et al*[59]	IIa	Non-cirrhotic	Naïve	21	DAC/asunaprevir/beclabuvir 75 mg	100
					DAC/asunaprevir/beclabuvir 150 mg	100
Asselah *et al*[63]	II+III	36% treatment experienced	Naïve	56	GZR/EBR 12 weeks	96
		22% cirrhotic	Naïve	10	GZR/EBR+RBV 12 weeks	100
			Experienced	9	GZR/EBR 12 weeks	78
			Experienced	15	GZR/EBR+RBV 12 weeks	93
			Experienced	5	GZR/EBR 16 weeks	60
			Experienced	8	GZR/EBR+RBV 16 weeks	100

DAC, daclatasvir, GZR/EBR fixed-dose combination tablet Grazoprevir and Elbasvir; LDP, ledipasvir; OMV, ombitasvir; PR, pegylated interferon and ribavirin; PTV/r, paritaprevir/ritonavir; RBV, ribavirin; RGT, response-guided therapy; SMV, simeprevir; SOF, sofosbuvir; SVR sustained virologic response.

velpatasvir group with all patients with G4 HCV achieving SVR12. The combination tablet appeared well tolerated with no significant difference in the rates of adverse events between groups.

Paritaprevir/r/ombitasvir

Paritaprevir is a first-generation protease inhibitor that has been coformulated with ritonavir (as a boosting agent) and the NS5A inhibitor ombitasvir.[21 48] Both these drugs have activity against G1 and G4 HCV.[49] Along with the non-nucleoside NS5B inhibitor dasabuvir and RBV, this regimen is licensed for the treatment of G1 HCV in Europe and the USA, having shown SVR rates above 90% in phase II and III trials.[21 50–52] Dasabuvir has no activity against G4, however.[53] The combination of paritaprevir/r/ombitasvir with RBV for G4 HCV has been studied in the PEARL-1 trial.[54] There were a good number of patients including 135 in total, making it the largest DAA study in G4 HCV. None of the patients had cirrhosis. There were 86 treatment-naïve patients and 49 PEG-IFN and RBV-experienced patients. In total, 42 and 44 of the treatment-naïve patients were treated with and without RBV respectively and all treatment-experienced patients received RBV. SVR12 rates were very impressive with 100% of treatment-naïve patients receiving RBV and 100% of the treatment-experienced patients being cured. Out of 44 treatment-naïve patients treated without RBV, 40 achieved SVR12 giving a rate of 91%. This regimen could, therefore, become one of the cornerstones for the management of non-cirrhotic G4 HCV. The drug license suggests treating G4 cirrhotics for 24 weeks in combination with RBV;[55] however, data are emerging from the AGATE studies suggesting that 12 weeks therapy with RBV may be sufficient even for cirrhotic patients.[56 57]

Daclatasvir/asunaprevir/beclabuvir

The combination of the NS5A inhibitor daclatasvir, the protease inhibitor asunaprevir and the non-nucleoside NS5B inhibitor beclabuvir has been shown to be efficacious in the management of G1 HCV with overall SVR rates above 90%.[58] As all these drugs also have activity against G4. A small open-label phase IIa study was conducted in the USA to assess the efficacy of this combination in patients with G4 HCV. The full results of this study were recently published.[59] A total of 21 patients were recruited and all were treated with 12 weeks of 30 mg of daclatasvir and 200 mg of asunaprevir. In total, 11 patients were treated with 75 mg of beclabuvir and 10 were treated with 150 mg of beclabuvir. No patients received RBV. All patients were cured, although the SVR12 were compromised by one patient in each group not reaching that time point, one was confirmed cured at SVR24 and the other at SVR of 36 weeks (SVR36), implying that the SVR12 rate in this study was 100%. It is important to note that these were all treatment-naïve non-cirrhotic patients, and the results need to be replicated in larger cohorts with more advanced fibrosis.

Grazoprevir and elbasvir

Grazoprevir, a second-generation protease inhibitor, and elbasvir, a second-generation NS5A inhibitor, have demonstrated pan-genotypic activity.[60 61] Their use with or without RBV or in combination with a nucleotide polymerase inhibitor has been demonstrated in G1 infection.[61 62] An integrated analysis of 103 G4-infected patients who received a fixed-dose combination tablet of grazoprevir and elbasvir with or without RBV in a phase II or III clinical programme has recently been presented. This included treatment-experienced (36%) and cirrhotic (22%) patients.[63] All treatment-naïve patients received 12 weeks of treatment while treatment-experienced patients received either 12 or 16 weeks. The overall SVR12 rate was 97% in treatment-naïve and 86.5% in treatment-experienced patients. The inclusion of RBV provided little additional benefit in treatment-naïve patients (96% without RBV; 100% with RBV); however, it may improve outcomes when used in treatment-experienced patients particularly those who have experienced prior on treatment failure with PEG-IFN (78% 12 weeks without RBV; 93% 12 weeks with RBV; 60% 16 weeks without RBV; 100% 16 weeks with RBV).

THE NEXT GENERATION

While current DAA regimens have excellent efficacy, there are a number of practical issues that remain. Our understanding of drug resistance and its management, especially to protease inhibitors and NS5A inhibitors, remains in an early phase and retreatment strategies are not yet fully developed. Furthermore, DAA combinations, such as coformulated paritaprevir/r/ombitasvir, have potentially significant drug–drug interactions that may limit their rollout particularly in resource-limited healthcare settings. These challenges continue, in part, to drive drug development with the ultimate goal to create a pan-genotypic combination that can be given without RBV for as little time as possible and that can achieve SVR rates above 95% regardless of fibrosis stage.[2] In order to achieve this, drug companies are combining up to three different second-generation DAAs in single tablet regimens. For example, the combination of ABT-493 (a protease inhibitor) and ABT-530 (a NS5A inhibitor) has recently been shown to have pan-genotypic activity with a high barrier to resistance and has been taken forward to phase II studies across all genotypes.[64] Similarly, the aforementioned grazoprevir is being combined with either elbasvir or a different NS5A inhibitor MK-8408 as well as the nucleotide polymerase inhibitor MK-3682 in the C-CREST study programme.[65] The role of RBV in these combinations is likely to be limited, although it may allow treatment duration to be reduced. Such combinations will be of use for the

management of patients with G4 disease and may enable treatment to be extended to regions that do not have access to the diagnostic facilities required to genotype HCV infected individuals.

TREATMENT OF DECOMPENSATED CIRRHOTICS

The advent of IFN-free DAA combinations has provided patients with advanced Child's A, Child's B and Child's C cirrhosis with HCV treatment options that carry a lower risk of decompensation than seen with IFN.[66] In a proof of concept study, sofosbuvir and RBV were administered for 24 weeks to 25 patients with cirrhosis at Child-Pugh scores of 5–9 and portal hypertension and the outcome was compared with equivalent patients who were observed for the same time period prior to then also being treated.[67] There were two patients with G4 HCV in the treatment arm and one patient with G4 HCV in the observation arm. There was 100% on treatment viral suppression in the Child's A cirrhotic patients and 93% in the Child's B cirrhotic patients. More importantly, there were improvements in albumin levels, platelet counts, hepatic encephalopathy episodes and ascites. The SOLAR-1 study has recently reported similar results.[68] This compared 12–24 weeks of fixed-dose sofosbuvir–ledipasvir with RBV in decompensated Child's B and C cirrhotics. The trial included patients with G1 and G4 HCV, although the precise percentage of patients with G4 HCV is unclear. The SVR rates in all groups were above 86%. While treatment was associated with improvements in bilirubin, albumin, Model For End-Stage Liver Disease (MELD) and Child-Pugh scores, five patients decompensated and accounted for 83% of patients that discontinued treatment due to adverse events.

Preliminary real-world data are now emerging from patients with decompensated cirrhosis who have received early access to DAAs through compassionate use programmes across Europe. In England, the National Health Service (NHS) permitted the treatment of patients with decompensated Child's B and C cirrhosis with 12 weeks of either sofosbuvir and ledipasvir or sofosbuvir and daclatasvir from July 2014. To date, there are 28 patients with G4 HCV who have been treated in this scheme (Professor Will Irving, University of Nottingham, Personal Communication). SVR12 rates and outcome data are likely to be fully available over the next few months; however, data analysed for the first 23 patients suggest an SVR12 rate of 87% (20 achieved SVR12, 2 relapsed, 1 lost to follow-up). An extended treatment duration of 24 weeks improved the SVR12 rate in G4-infected patients with decompensated cirrhosis to 100% in the French programme but only when RBV was used in addition to sofosbuvir and daclatasvir (SVR12 75% (n=9/12) without RBV; 100% (n=5/5) with RBV)[69] supporting the ongoing beneficial role of RBV in this difficult-to-treat cohort.

The impact of viral clearance on these real-world cohorts has been assessed but the long-term effect on the demand for liver transplantation and risk of death and cancer remains unclear. While a reduction in incidence of decompensations was noted in the English programme from start of treatment and to untreated patients, 9 deaths (3%), 17 new liver cancers (5%), 39 transplantations (12%) and 52 serious decompensations (16%) were still observed over a 15-month period.[70]

TREATMENT IN THE PRESENCE OF SIGNIFICANT COMORBIDITY

Chronic kidney disease (CKD)

Sofosbuvir is excreted by the kidneys, and its use is therefore not recommended in severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min) or in patients on haemodialysis. However, the AbbVie 3D regimen has been successfully used in a small number of treatment-naïve, non-cirrhotic G1 infected patients with CKD stage 4 or 5 (including those on haemodialysis). All 20 patients completed 12 weeks of treatment with an SVR12 rate of 90% (one treatment-unrelated death and one relapse). There were no treatment-associated serious adverse events, although RBV was interrupted in nine G1a patients (69%) due to anaemia.[71] The combination of grazoprevir plus elbasvir (without RBV) has additionally been shown to be safe and effective in G1-infected patients with advanced and end-stage renal disease and may provide a RBV-free treatment option in G4-infected patients in the future.[72]

HIV coinfection

Progression of HCV-related liver disease in HIV coinfected cohorts is accelerated and while treatment has therefore been prioritised, viral clearance has been limited by the reduced efficacy and increased side effects observed with PEG-IFN and RBV in this group. However, DAAs have demonstrated comparable SVR rates across genotypes in coinfected cohorts and while the potential for significant drug–drug interactions needs to be considered, indications for IFN-free regimens and treatment options remain the same for coinfected and monoinfected patients.[73]

ACCESS TO THERAPY IN RESOURCE-LIMITED SETTINGS

There are now strong data to support the efficacy of DAAs in the treatment of HCV and the impact of SVR on patient survival.[74] However, the cost of these new regimens may be prohibitive in allowing access to the vast number of people living with HCV in low-income and middle-income countries. This is especially the case for G4 HCV, the majority of infections occurring in the Middle East and Sub-Saharan Africa. Here, there are many parallels with the history of access to HIV therapy.[75] With simplification of highly active antiretroviral regimens and with the development of coformulated tablets, more people infected with HIV have

started therapy without the need for complex diagnostic and virological information required for initiation of treatment in the Western world. Indeed, similar considerations are now being addressed for HCV.[76] The development of combined point-of-care antibody and antigen testing may go some way towards allowing service delivery to be devolved from expensive centralised physician-based models of care to community-based non-physician-dependent models of care.

It is also encouraging to see that pharmaceutical companies have started to negotiate heavy discounts for some DAA combinations for countries in resource-limited settings.[5] The cost of sofosbuvir for instance is $900 for 12 weeks in Egyptian governmental organisations and a similar price has been agreed for India.[77] It is likely that other companies will follow suit in negotiating individualised prices for different countries; something which ultimately will enable more people to be treated and cured of HCV.

DAA RESISTANCE

Understanding of the emergence, fitness and clinical significance of resistance-associated variants (RAVs) that develop with suboptimal exposure to DAAs is in its infancy but should advance as treatment is expanded and more treatment failure is observed in real-world cohorts. However, DAA resistance appears to be a class-specific phenomenon. Sofosbuvir is known to have a high genetic barrier to resistance with no S282T substitutions in NS5B (the most common treatment-emergent NS5B mutation) detected across its phase III registration studies. Less common NS5B variants were detected at low levels (L159F 15%; V321A 5%) at the time of virological failure but had no impact on retreatment with sofosbuvir, PEG-IFN and RBV.[78] Sofosbuvir is, therefore, recommended as a core component of any retreatment strategy,[73] although it is worth acknowledging that G4-specific data are scarce.

The development of non-structural protein 3 (NS3) and NS5A mutations is better understood; phylogenetic and sequence analysis available for 132 G4-infected patients treated with AbbVie 2D in the PEARL-1 study.[79] The rate of NS5A variants at baseline was 57.6% (n=76/132), but their presence was not associated with a significant difference in SVR12 rate (96.1% NS5A variant present vs 98.2% without NS5A variant present; p=0.64). Two of three patients who did not achieve SVR12 (all subtype G4d, treatment naïve with no RAVs at baseline) had detectable treatment-emergent RAVs at the time of treatment failure; D168V the most common RAV in NS3 and L28V in NS5A. However, while the NS3 variant D168V persisted at week 24 post-treatment but was undetectable by week 48, NS5A variants persisted at resistance-associated amino acid positions at week 48.

In practice, baseline resistance testing is not currently advocated prior to treatment with first-line therapy as RAVs are not thought to significantly affect efficacy and therefore choice of regimen.[73] The role of resistance testing and its interpretation in the development of retreatment strategies remains less clear but second-generation DAA regimens with a greater therapeutic efficacy and higher barrier to resistance will be needed to overcome resistance in the long term.

CONCLUSIONS

It would be fair to say that the last 2–3 years have seen a transformation in the treatment landscape for HCV. Many of the new agents now licensed have efficacy against G4 HCV and there will be more data presented on this over the next few months and years. It will be important to learn lessons from real-life data that will hopefully be forthcoming from the national treatment programmes in places like Egypt. The days of PEG-IFN therapy may be limited, and it is certainly no longer recommended in some guidelines.[80]

While it is now possible to treat patients with decompensated cirrhosis relatively effectively, the goal must be to try and prevent the development of cirrhosis in the first place. Whereas even 5 years ago the goal of global eradication of hepatitis C looked impossible, this is achievable if enough political will is applied in the right places. Furthermore, with improvements in point-of-care diagnostics, simplification of treatment regimens and due consideration to the costs of these newer agents, premature deaths from HCV-associated liver failure and hepatocellular cancer should become a thing of the past.

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Competing interests AME has received lecture fees from Gilead Sciences, AbbVie, Merck Sharpe & Dohme, Bristol-Myer Squibb and Janssen. He has also been a consultant for Gilead and Janssen and has received research funding from Gilead Sciences. AME currently sits on the editorial board of BMJ Open Gastroenterology. EH has received educational support and fees from AbbVie.

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