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Management of hepatitis C virus genotype 4: Recommendations of An International Expert Panel

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HCV has been classified into no fewer than six major genotypes and a series of subtypes. Each HCV genotype is unique with respect to its nucleotide sequence, geographic distribution, and response to therapy. Genotypes 1, 2, and 3 are common throughout North America and Europe. HCV genotype 4 (HCV-4) is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections. It has recently spread to several European countries. HCV-4 is considered a major cause of chronic hepatitis, cirrhosis, hepatocellular carcinoma, and liver transplantation in these regions. Although HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world, it has not been the subject of widespread research. Therefore, this document, drafted by a panel of international experts, aimed to review current knowledge on the epidemiology, natural history, clinical, histological features, and treatment of HCV-4 infections.

Introduction

Hepatitis C virus (HCV), a member of the Flavivirida family of RNA viruses, is characterized by a high spontaneous mutation rate with an estimated frequency of $1.4–1.9 \times 10^{-3}$ mutations per nucleotide per year [1,2]. As a result, HCV exists as a heterogeneous group of viruses sharing approximately 70% homology. On the basis of nucleotide sequence homology, HCV has been classified into no fewer than six major genotypes and a series of subtypes [3]. Each HCV genotype is unique with respect to its nucleotide sequence, geographic distribution, and response to therapy [4]. Genotypes 1, 2, and 3 are common throughout North America and Europe. HCV genotype 4 (HCV-4) is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections. It has recently spread to several European countries [5,6]. HCV-4 is considered a major cause of chronic liver disease and cirrhosis, which leads to liver failure and is the root cause of hepatocellular carcinoma. Because of these complications, extended cirrhosis during chronic infection is a primary cause of liver transplantation in these regions. Although HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world, it has not been the subject of widespread research. Therefore, this document, drafted by a panel of international experts, aimed to review current knowledge on the epidemiology, natural history, clinical, histological features, and treatment of HCV-4 infections.

Epidemiology

Approximately 34 million people are chronically infected with HCV-4. The Iinfection is common in the Middle East and Africa, where it accounts for more than 80% of all hepatitis C cases [5–8]. The risk factors for HCV-4 transmission are determined by the geographical distribution of this genotype.

Egypt has the highest prevalence of HCV worldwide (15%) and the highest prevalence of HCV-4, which is responsible for 90% of infections, with a predominance of subtype 4a (55%) [5–9]. Epidemiological and molecular evolutionary analysis on Egyptian genotype 4a isolates suggest the origin of the HCV-4 epidemic arises from the antischistosomal campaign, which was administered parenterally, and only stopped in the mid-1960s [10,11]. However, other risk factors, mostly related to prevailing social and cultural conditions, are responsible for maintaining the high

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rates of HCV-4 transmission even after the treatment campaign was stopped. Currently, the major route of transmission appears to be health-related procedures with inadequately sterilized instruments. Procedures performed by non-medical professionals and traditional healers have been identified as important risk factors for HCV transmission in Egypt [12–14]. Intrafamilial and sexual transmissions also play a role in the high prevalence of HCV-4 in this country [15,16].

The prevalence of HCV in Saudi Arabia is 1–3%, [17] with a predominance of genotype 4 (62%). Unlike the predominance of subtype 4a in Egypt, subtypes 4c/4d are the most prevalent subtypes among Saudis, followed by subtypes 4h, 4e, and 4a, suggesting that the origin and transmission of HCV-4 is different from that in Egypt [17]. Similarly, studies from other parts of the Middle East also suggest a high prevalence of HCV-4. For example, 36–46% of HCV-infected Lebanese patients have HCV-4 [18], 59% of Syrian patients [19] and 27% of HCV-infected Jordanian patients on dialysis have HCV-4 [20].

HCV-4 is also endemic throughout Central and West African countries such as the Congo, Liberia, and Uganda (where it accounts for 100% of HCV infections), as well as Gabon, Tanzania, and Cameroon (97%, 50%, and 36% of HCV infections, respectively) [21–25]. Scarification, circumcision practices, and sexual transmission may contribute to the persistence and propagation of HCV transmission in these countries [21,25].

Recently, HCV-4 has become increasingly prevalent in some southern European countries on the Mediterranean Sea, particularly Italy, France, Greece, and Spain, where prevalence rates of 10–24% have been reported in some areas [26–31]. HCV-4 infection is frequent among intravenous drug users (IVDUs) (European and non-European), HCV/HIV-coinfected patients, and immigrants from North and sub-Saharan Africa [26–31]. HCV-4 was probably introduced into Europe through immigration and the movement of IVDUs across European borders [31].

HCV-4 infections are uncommon in the United States, Canada, South America, and Asia. The prevalence of HCV-4 in the United States is about 1% [32]. Most HCV-4 cases reported from the United States were clustered among IVDUs or immigrants from countries where subtype HCV-4 is known to be most prevalent or among individuals who acquired the infection in these countries [32,33]. There are no reliable data on the prevalence of HCV-4 either in Australia or in South East Asia. However, HCV-4 appears to be rare in these regions.

Natural history

There are few data on the natural history of HCV-4. It is likely that the course of genotype 4 infection is similar to that of other genotypes [25,34].

HCV-4 represents more than 30% of the annually reported acute hepatitis cases in Egypt [35]. Very few studies address the outcome of acute HCV-4 infection. Indeed, prospective studies have shown 20–50% rates of spontaneous resolution in acute HCV-4 infections [36–38]; whereas those rates are reduced in patients with a coinfection with HIV or *Schistosoma mansoni*, as frequently occurs in Egyptians [34,37]. The presence of schistosomiasis is a negative predictor of outcome, being associated with accelerated progression of hepatic fibrosis among HCV-4 patients. In fact, the fibrosis progression rate of 0.1 ± 0.06 fibrosis units/year observed in HCV-4 patients (similar to that of patients infected with other genotypes) increased up to 0.6 ± 0.13 in patients with associated schistosomiasis [39–43]. An Egyptian origin was independently associated with severe fibrosis in two French studies, however the higher fibrosis scores in these studies might be attributed to concomitant schistosomiasis in these Egyptian patients rather than ethnicity or HCV subtype [39,40]. Insulin resistance was also found to be correlated independently with severity of fibrosis [40]. The known association between hepatocellular carcinoma (HCC) and HCV needs to be weighed against other potential risk factors for HCC like schistosomiasis and exposure to aflatoxins or pesticides [44–47].

Utility of liver biopsy and noninvasive fibrosis tests

The biopsy is assessed for grade and stage of the liver injury, but also provides information on other histological features that might have a bearing on liver disease progression [48]. The two more common non-HCV conditions that might affect disease progression and possibly impede treatment response are steatosis [49,50] and excess of hepatocellular iron [51]. The pathological findings in chronic HCV-4 are in general similar to other types of viral hepatitis C. However, certain features may be prominent in this genotype, one of which is the presence of moderate to severe steatosis [50,52,53] with no associated sinusoidal fibrosis [53]. Host and viral factors contribute to the development of steatosis in hepatitis C, but their relative importance varies with genotype [54–56]. Hepatic steatosis in patients infected with HCV-4 is mainly associated with metabolic factors and follows the same pattern as those infected with genotype 1 [50,54]. Steatosis, in particular moderate-to-severe steatosis was detected in similar proportions of patients with genotype 1 and 4 [50,52,54]. Several studies have shown that steatosis in chronic HCV-4 is macrovesicular [50,52,53] and is seen without any prominent zonal preference [53]. More detailed studies are needed to determine if there is a characteristic histological pattern that might distinguish chronic HCV-4. Efforts are ongoing to seek alternative means focusing on noninvasive blood marker panels. In a recent study, the combination of hyaluronic acid, YKL-40, platelet count and serum aminotransferases provided information about the amount of hepatic inflammation and steatosis in Egyptian patients and achieved this cost-effectively [57].

Hepatocellular carcinoma

HCC is a major cause of cancer death worldwide [58], with evidence that its incidence has sharply increased in many countries as a consequence of the accumulation of patients with chronic liver disease caused by viral hepatitis or alcohol abuse [58,59]. The incidence of HCC in Egypt is also increasing [60–62] and is now the second most frequent cause of cancer and cancer mortality among men [63]. Hospital based studies have reported an increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from ~4.0% in 1993 to 7.3% in 2003 [60–62].

Data from the National Cancer Registry of Egypt, the National Cancer Institute and the Middle East Cancer Consortium recently reported that the incidence rate among males was 7 times greater than the next highest rate (among Israeli Jews) and more than 3 times that reported in the United States Surveillance Epidemiology and End Results summary [63,64].

A possible association has been suggested between HCV-4 and HCC based on the similarity of distribution of HCC and HCV-4 in

Table 1. Summary of studies of PEG-IFN-α in patients with chronic HCV-4.

Sample size	Study design	Treatment and duration	Country	EVR (%)	ETR (%)	SVR (%)	Ref.
12	Open-label, uncontrolled pilot study	PEG-IFN-α-2b (1.5 mcg/kg/wk) + RBV (15 mg/kg/d) x 48 wk	Kuwait	83	83	75	[76]
226	Prospective	PEG-IFN-α-2a (180 mcg/wk) or PEG -IFN-α-2b (1.5 mcg/kg/wk) + RBV (1000 mg or 1200 mg/d if ≤ or >75 kg, respectively) x 48 wk	Egyptians 40%, Europeans 35%, Africans 24%	74	64	54	[40]
131	Prospective	PEG-IFN-α-2b (1.5 mcg/kg/wk) + RBV (800 mg for <50 kg, 1000 mg for 50-65 kg, 1200 mg for 65-80 kg, 1400 mg for >80 kg) x 48 wk	Egypt	RVR: 34.3 cEVR: 64.8	NA	60.3	[77]
97	Prospective, randomized. PEG-IFN + RBV+ pioglitazone in patients with HOMA-IR >2	Arm A: PEG-IFN-α-2b (1.5 mcg/kg/wk) + RBV (1000 mg or 1200 mg/d) if ≤ or >75 kg respectively + pioglitazone 30 mg/d Arm B: PEG-IFN-α-2b (1.5 mg/kg/d) + RBV (1000 mg or 1200 mg/d) if ≤ or >75 kg respectively x 48 wk	Egypt	RVR: 271 vs. 6.1 EVR: 68.7 vs. 48.9	66.6 vs. 44.89	60.4 vs. 38.7	[78]
95	Prospective open-label	PEG-IFN α-2a (180 mcg/wk) + RBV ≥11 mg/kg/d x 48 wk	Egypt	NA	69.5	61.1	[79]
240 82 (34%) HCV-4	Retrospective	PEG-IFN α-2a (180 mcg/wk) or PEG-IFN-α-2b (1.5 mcg/kg/wk) + RBV (1200 mg/d) x 48 wk	Saudi Arabia	NA	NA	64	[80]
58	Retrospective	PEG-IFN-α-2b (1.5 mg/kg/wk) + RBV (1000 mg or 1200 mg/d) if ≤ or >75 kg respectively x 48 wk	Greece	63.8	NA	53.4	[81]
30	Prospective open-label	PEG-IFN-α-2a (180 mcg/wk) + RBV (1000 mg or 1200 mg/d) if ≤ or >75 kg respectively x 48 wk	Middle East	83.3%	NA	63.3	[82]
96	Prospective, randomized. PEG-IFN + RBV + nitazoxanide (NTZ)	PEG-IFN-α-2a + RBV x 48 wk (n = 40); NTZ monotherapy x 12 wk followed by NTZ + PEG-IFN-α-2a x 36 wk (n = 28); NTZ monotherapy x 12 wk followed by NTZ + PEG-IFN-α-2a + RBV x 36 wk (n = 28)	Egypt	RVR: 38, 54, 64 cEVR: 70, 68, 86	75, 71, 82	50, 61, 79	[83]
66	Prospective, response-guided therapy	PEG α-2a (180 μg/wk) + RBV 1000 or 1200 mg/d according to virological response at wk: 4 x 24, 48, 72	Austria	RVR: 45	NA	87	[84]
84	Prospective	PEG-IFN-α-2a (180 mcg/wk) + RBV (1000-1200 mg/d) if ≤ or >75 kg respectively x 48 wk	Qatar	NA	77	67.9	[85]
308	Prospective, response-guided therapy	PEG-IFN-α-2b (1.5 mcg/kg/wk) + RVB 10.6 mg/kg/d for either a fixed duration of 48 wk (control group) or a variable duration at 24, 36, 48 wk	Egypt	22 RVR, cEVR 26, pEVR 52	90 : 24 W 86 : 36 W 70 : 48 W	88 : RVR 87 : cEVR 64 : pEVR	[53]

Table 1 (*continued*)

Sample size	Study design	Treatment and duration	Country	EVR (%)	ETR (%)	SVR (%)	Ref.
242	Retrospective non randomized study	PEG-IFN-α-2b (1.5 mcg/kg/wk) + RBV(1000-1200 mg/d) x 48 wk	French, Egyptian, African	NA	NA	Egyptian: 48 French: 37 African: 25	[39]
73	Randomized (patients with history of bilharziasis)	PEG-IFN-α-2a (180 μg/wk) + RBV 1200 mg/d x 48 wk, (n = 38); IFN-α-2b 3 MU/tiw + RBV 1200 mg/d x 48 wk (n = 35)	Qatar	NA	Peg-IFN vs. non-peg-IFN (76.3 vs. 40; p = <0.002)	Peg-IFN vs. non-peg-IFN (65.8 vs.25.7 p <0.05)	[86]
180	Prospective non randomized	Peg-IFN-α-2b (100 μg/wk) RBV (1000-1200 mg/d) x 48 wk (n = 40); Peg-IFN-α-2b (100 μg/wk) + RBV 1000-1200 mg/ d x 24 wk (n = 70); IFN-α-2b 3 MU + RBV 1000-1200 mg/d + amantadine 200 mg/d, x 24 wk (n = 70)	Egypt	72.5, 72.9, 54.3	65.0, 65.7, 47.1	55.0, 48.6, 28.6 I and II: (p = 0.517), I and III: (p = 0.006), II and III: (p = 0.015)	[87]
260	Prospective, double-blind, randomized	PEG-IFN-α-2 b (1.5 mcg/kg/wk) + RBV (1000-1200 mg/d) for 24, 36, 48 wk	Egypt	69, 68, 69	48, 68, 70	29, 66	[88]
66	Prospective, open-label	PEG-IFN-α-2 b (1.5 mcg/kg/wk) + + RBV (1000-1200 mg/d) x 48 wk	52% Egyptian; remainder Kuwaiti and Syrian	78	77	68	[73]
100	Open-label	PEG-IFN-α-2a (180 μg/wk) + RBV 1200 mg/d x 48 wk (n = 51) IFN-α-2a 3 MU + RBV 800-1000 mg/d (n = 49) x 48 wk	Egyptian	NA	NA	69	[89]
98	Post hoc analysis of HCV-4 patients from two large RCTs	Study 1: PEG-IFN-α-2a (180 mcg/wk) + RBV 1000-1200 mg/d x 48 wk (n = 13) Study 2: PEG-IFN-α-2a (180 mcg/wk) + RBV 800-1200 mg/d x 24 or 48 wk High -dose RBV (n = 24) Low-dose RBV (n = 8) High-dose RBV (n = 12) Low-dose RBV (n = 5)	International	NA	NA	79, 63, 67, 0	[90]
59	Randomized, parallel-group	PEG-IFN- α-2b (100 mcg/wk) + RBV 800 mg/d x 48 wk (n = 28) , IFN-α-2b 3 MU+ RBV 800 mg/day x 48 wk (n=31)	Saudi Arabia	NA	67.9 54.8	42.9 32.3	[91]
180	Open-label multicenter	PEG-IFN-α-2a (180 μg/wk) + RBV (800 mg/d) PEG-IFN-α-2a (180 μg/wk) IFN-α -2a 4.5 MIU tiw + RBV (800 mg/d) x48 wk	Saudi and Egyptian	77, 60, 43	67, 59, 37	50, 28, 30	[74]
190	Prospective, open-label RCT	IFN -α-2b 3 MU tiw or PEG -IFN-α-2b (100 mcg/wk) + RBV (800 or 1000 mg for both groups) x 48 wk	Egypt	NA	NA	55 40	[75]

Abbreviations: Wk: week, d: day, *x*: for treatment duration, HOMA-IR: homeostasis model assessment index NA: no available data, EVR, early virologic response; RVR: rapid virologic response, ETR: end of treatment response, PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response.

Table 2. Outcome by virological response at weeks 4 and 12 in genotype four patients treated for 48 weeks with peginterferon alfa-2 plus ribavirin.

Study	N	Week 4		Week 12	
		RVR, n (%)	SVR, n (%)	EVR, n (%)	SVR, n (%)
Kamal [53]	387	77 (19.9)	66 (86) *	275 (71)	170 (64) **
Ferenci *et al.* [84]	66	30 (13.3)	26 (96) *	28 (56)	13 (46) **

Abbreviations: EVR = early virological response (HCV RNA < 50 IU/ml or 2 log drop in viral load); RVR = rapid virological response (HCV RNA < 50 IU/ml); SVR = sustained virological response (HCV RNA < 50 IU/ml); *Patients were treated for 24 weeks; **Patients were treated for 48 weeks or longer.

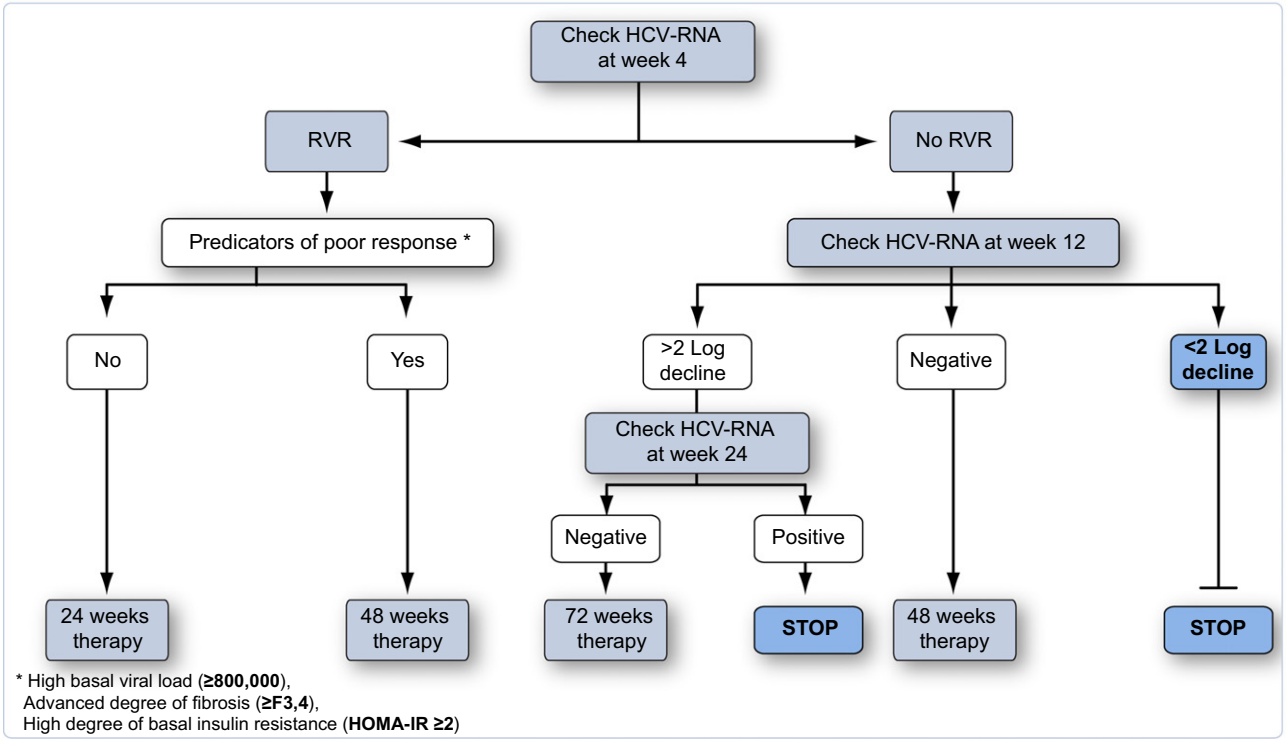

Fig. 1. A proposed algorithm for treating patients with chronic HCV-4 based on the kinetics of viral response (response-guided therapy). RVR, rapid viral response.

Egypt [63–68]. A recent meta-analysis showed that more than 84% of Egyptian patients with HCC are positive for HCV-4 [68].

A significant association seems to exist not only with the most prevalent subtype 4a, but also with subtype 4o [44] even though this association has not been confirmed by others [69]. Other factors related to HCC development may play a role, such as coinfection with schistosomiasis which is known to increase risk of HCC [4,66], exposure to pesticides [47], and dietary aflatoxins [70].

Evolution of treatment

Combination therapy with pegylated interferon alpha and ribavirin represents the current standard of care in chronic HCV-4. Interferon (IFN) based therapies were introduced in chronic hepatitis C in the 1980s and have improved dramatically over the subsequent years. With conventional IFN-α monotherapy the SVR rates were very poor, similar to those achieved in HCV genotype 1 infection, ranging between 5% and 25% [71,72]. However, with the addition of ribavirin to conventional IFN-α, SVR rates increased to 25–42% [73,74], about intermediate between those achieved in HCV-1 and HCV-2 or HCV-3. With the introduction of pegylated IFN compounds in combination with ribavirin, the efficacy of treatment in HCV-4 further improved significantly. In various studies from European and Middle Eastern countries, SVR rates ranging from 43% to 70% were reported [39,40,53,75–88,73,89–91] (Table 1). These results are indeed higher than those (42–46%) achieved in genotype 1 patients but still lower than those (76–82%) reported in chronic hepatitis C genotype 2 and 3.

Studies looking at predictive factors on HCV-4 patients are relatively scarce. Negative predictive factors at baseline include high viral load, presence of cirrhosis and steatosis, insulin resistance, IL-28B polymorphism TT, and HIV coinfection [75,86,73,91–93]; these factors are associated with a lower SVR. A rather unexpected finding of the therapeutic trials in HCV-4 has been that under the same treatment regimen, patients from Egypt and the Middle East experienced higher SVR rates than patients from Europe or Africa. In a French retrospective study, conducted in 242 HCV-4 patients from various geographical areas (40% Egyp-

Table 3. Summary of studies on combined therapy in HCV-4 patients with incomplete (F3) or complete (F4) cirrhosis.

First Author, year [Ref.]	n	Therapeutic regimen	Duration (wk)	SVR, n (%)	Liver histology
Hasan, 2004, [73]	20	PEG-IFN-α 2b 1.5 mcg/kg/wk RBV 1000-1200 mg/d	48	30.0	F3-F4
Derbala, 2005, [104]	12	PEG-IFN-α 2b 1.5 mcg/kg/wk RBV 800-1200 mg/d	48	8.3	F4
Derbala, 2006, [86]	13	PEG-IFN-α-2a 180 mcg/wk RBV 1200 mg/d	52	38.5	F3-F4
Males, 2007, [105]	14	PEG-IFN-α-2a 180 mcg/wk RBV ≥11 mg/kg/d	48	35.7	F4
Kamal, 2007, [53]	27	PEG-IFN-α-2b 1.5 mcg/kg/wk Ribavirin 10.6 mg/kg/d	24-48	0	F4
Roulot, 2007, [39]	76	PEG-IFN-α-2b 1.5 mcg/kg/wk RBV 1000-1200 mg/d	48	31.6	F3-F4
Ferenci, 2008, [84]	4	PEG-IFN-α-2a 180 mcg/wk RBV 1000-1200 mg/d	48	75.0	F3-F4
Gad, 2008, [106]	78	PEG-IFN-α-2a 180 mcg/wk, PEG-IFN-α-2b 1.5 mcg/kg/wk, standard IFN-α-2b 3 MU thrice/wk, RBV 1000-1200 mg/d	48	37.2	F3-F4
El Makhzangy, 2009 [79]	33	PEG-IFN-α-2a 180 mcg/wk RBV ≥ 11mg/kg/d	48	45.5	F3-F4
Giannini, 2009, [107]	5	PEG-IFN-α-2a 180 mcg/wk, PEG-IFN-α-2b 1.5 mcg/kg/wk, RBV 800-1200 mg/d	48	0	F4 and portal hypertension

Abbreviations: Wk: week, d: day, *n* = number, PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response.

tians, 35% Europeans, and 24% Africans) the respective SVR rates were 54.9%, 40.3%, and 32.4%. Egyptian origin and the absence of severe fibrosis were found to be independently associated with SVR [39]. It remains unclear whether the difference in SVR is related to ethnicity, HCV-G4 subtype, the mode of transmission or IL-28B genotype [93].

Similar results have recently been reported in a prospective study of HCV-4 patients from Europe, France, and Africa with respective SVR rates of 63%, 51%, and 39% and an overall SVR percentage of 54%. Despite the presence of severe fibrosis in a large proportion of the Egyptian patients, Egyptian origin was again independently associated with SVR ($p = 0.001$); OR: 5.87 (95% CI: 2.75–12.55) ($p = 0.001$). SVR was also independently associated with insulin resistance measured by the homeostasis model assessment index (HOMA-IR)<2 ($p = 0.001$) and by non-severe fibrosis ($p = 0.001$) [40]. Moreover, in another trial from Egypt, HOMA-IR was found to be a predictor not only of SVR but also of rapid virologic response (RVR) ($p = 0.002$ and 0.0041; respectively) [77]. The use of insulin-sensitizing agents such as pioglitazone in conjunction with HCV-4 treatment increases both SVR and RVR rates [78]. HCV kinetics under therapy has been found to be extremely useful to predict SVR [53,88]. Other factors during treatment are patients' compliance and no dosage reductions or dose fulfilled with 80/80/80 [94].

IL28B polymorphism

A genome wide association study in patients infected with HCV-1 revealed a single nucleotide polymorphism (SNP)-rs12979860 in the IL-28B region on chromosome 19 (19q13.13), associated with a more than twofold increased rate of SVR [95]. In a multivariate analysis of HCV-4 patients, baseline viral load, fibrosis and the IL28 (rs8099917 T/T allele) (OR: 0.124, 95% CI: 0.030–0.505) were significantly associated with SVR [95]. The strongest predictor for the final outcome was RVR (OR: 26.00; 95% CI: 7.148–94.545, $p < 0.0001$). If RVR was included into the multivariate model, only the RVR and the fibrosis score remained significant. Thus, determination of IL28B polymorphism may not be useful to select patients with HCV-4 for abbreviated treatment schedules. However these data need further confirmation.

Duration of treatment

The duration of treatment is based on HCV genotype in current guidelines [96,97]. Forty-eight-week regimens are recommended for patients infected with HCV-1 and 4. This recommendation is based on the results of large randomized, international, phase III trials of peginterferon alfa-2 combined with ribavirin [98–100]. Unfortunately these studies included very few patients with HCV-4.

Measurement of the virological response at 4 and 12 weeks of therapy is a simple and reliable tool that allows the treatment regimen to be tailored to the individual. Patients who become HCV-RNA negative (<50 IU/ml by qualitative PCR assay) or have a $\geqslant 2 \log_{10}$ drop in serum HCV RNA level by quantitative PCR assay after 12 weeks of therapy are defined as having an early virological response (EVR). Failure to

achieve an EVR can predict which patients are unlikely to have a successful outcome with combination therapy. Those who are HCV-RNA negative after 4 weeks of treatment are defined as having a RVR. In contrast to EVR, RVR predicts which patients are most likely to have a successful outcome with combination therapy.

The probability of SVR increases with the speed of viral load decline. For example, a higher proportion of patients with HCV-1 who become HCV-RNA negative after 4 weeks of treatment will achieve an SVR than those who become HCV-RNA negative after 12 weeks of treatment [101]. SVR rates were much lower in patients who did not clear HCV RNA during the first 12 weeks of treatment. A completely negative test for HCV RNA at week 12 (complete EVR) is a better predictor of an SVR after 48 weeks of combination therapy than a partial EVR ($\geqslant 2\ \log_{10}$ drop in serum HCV RNA at week 12). Those who achieved an RVR had an SVR rate of 91%, those who achieved a complete EVR had an SVR rate of 75%, and among the 22% of patients with a partial EVR and virus negative by week 24 only 27% achieved an SVR [101].

Response-guided therapy

There are only two randomized controlled trials in patients with HCV-4 reporting viral response at week 4 (Table 2). Patients with HCV-4 who achieve an RVR are potential candidates for abbreviated 24-week treatment regimens; provided that no other predictors of poor response (Fig. 1). [53,84]. Response rates are similar to those treated for 48 weeks [87]. The prospect of shorter treatment for these patients is appealing because the overall tolerability is likely to be better and the costs lower with an abbreviated treatment regimen; conversely, slow responders who do not achieve HCV RNA negativity by week 4 or 12 are potential candidates for prolonging treatment up to 72-weeks. Only one randomized study examined prolonged 72-week regimens in HCV4 patients [102] but the number of patients was too small to draw any conclusions.

Fig. 1 presents a proposed algorithm for treating patients with chronic HCV-4 based on the kinetics of viral response (response-guided therapy). In conclusion, measurement of RVR and complete/partial EVR is a simple and reliable tool that allows clinicians to estimate the likelihood of an SVR and to individualize the duration of treatment. Unfortunately, in contrast to patients with HCV-1 the concept of response-guided therapy has not been validated in patents with HCV-4. In the current absence of any firm data on HCV-4 patients, we suggest that similar response-guided approaches used in HCV-1 patients may be considered. Thus those with an RVR are highly likely to achieve SVR and are candidates for abbreviated, 24-week regimens. Patients with a complete EVR at week 12 have a high probability of achieving an SVR with a 48-week regimen. Patients with a partial (slow) EVR (no RVR and detectable HCV RNA but $>2\ \log_{10}$ drop at week 12 and virus negative at week 24) may be considered for treatment prolongation to 72 weeks, if they can tolerate this.

Treatment in special populations

Cirrhosis

Treatment of compensated cirrhosis is a relevant issue since sustained HCV clearance is associated with a better survival, reduced HCC occurrence and absence of decompensation [103]. However, severity of liver fibrosis and HCV genotype are the two major determinants of SVR. The published data on the efficacy of Peg-IFN and ribavirin in cirrhotic patients infected by HCV-4 are limited (Table 3) [39,53,79,84,86,73,104–107]. Overall the cumulative response rate is about 30% of treated patients, but this figure includes also incomplete cirrhosis, or F3, that probably overestimates the real treatment efficacy in cirrhotic patients.

HIV coinfection

It has been reported that the prevalence of HCV-4 among HIV-infected individuals is at least 15% of all anti-HCV positive subjects [108]. Data derived from two trials showed that among 75 HIV-infected patients with HCV-4 treated with Peg-IFN alfa-2a plus ribavirin, only 21 (28.0%) achieved SVR [92]. The major factor of low rate of response was related to premature treatment discontinuation due to severe adverse effects.

Hemodialysis

The prevalence of HCV infection in patients with end stage renal disease is highly variable ranging from 3% to 80% between different countries and centers [109]. HCV-4 infected subjects have a shorter graft survival after kidney transplantation due to increased risk of severe infection and liver disease deterioration. As a consequence, the current recommendation is to give antiviral therapy before transplantation with the aim to eradicate the infection. However the use of Peg-IFN and ribavirin in dialysis patients is hampered by fairly frequent side-effects [110]. Two recent meta-analyses have shown that the overall SVR after Peg-IFN with or without ribavirin was 40%, including 33% for genotype 1 [111]. No data on efficacy of combined therapy in patients infected by genotype 4 are available so far.

Children/adolescents

Combination therapy with Peg-IFN-alpha and ribavirin treatment is effective in children with chronic hepatitis C [112,113] with SVR rates across different genotypes comparable to adults. One study reported the results of Peg-IFN plus ribavirin treatment in 12 adolescents infected by genotype 4 [76]. Nine patients (75%) achieved SVR suggesting that combination therapy is effective in this clinical context.

Acute hepatitis C

Scant data are available about the optimal treatment regimen in acute HCV-4 and demonstrated a high SVR with IFN-based therapies compared with no treatment [37,114,115]. The available clinical trails showed that acute hepatitis patients infected with HCV-4 have higher rates of SVR compared with HCV-1 infections. In one study [116], an SVR was achieved in 60% and 88% of genotype 1 patients and in 93% and 100% of HCV-4 patients after 12 and 24 weeks of treatment, respectively [37].

Thalassamia major

Few data are available on the treatment of HCV-4 in patients with thalassamia. Current literature is lacking sufficient evidence about the use of PEG-IFN as monotherapy or in combination with ribavirin in thalassamic patients. Inati et al. evaluated in a randomized study [117] the safety and efficacy of PEG-IFN-α with

or without ribavirin therapy in 20 patients with thalassamia and HCV-4. An SVR was achieved in (30% and 62.5%; $p = 0.19$) in the monotherapy and combination groups, respectively. They reported an increase in the transfusion requirements by 34% in the combination group ($p = 0.08$). In another study, Kamal et al. [118] reported that the overall SVR rates were (46% and 64%) with PEG-IFN alfa-2b vs. PEG-IFN alfa-2b plus ribavirin combination therapy, respectively. However, the reported adverse events were more frequent with combination therapy than with PEG-IFN alfa-2b alone.

Liver transplantation

End-stage liver disease secondary to HCV infection is the major indication for orthotopic liver transplantation (OLT) worldwide [119]. The percentage of HCV-4 patients among recipients of OLT varies depending on the geographic location from around 29% in Saudi Arabia [120] to more than 90% in Egypt, [121] while it represents a relatively uncommon indication in the western world [122,123].

The natural history of HCV-4 re-infection after liver transplantation is inadequately described in the literature. Re-infection of the graft with HCV is universal after liver transplantation regardless of the genotype, leading to an accelerated course of liver injury in many cases [124]. Most studies conducted worldwide have investigated disease recurrence in HCV genotypes 1, 2, and 3 [119]. However, there are few reports on post-OLT recurrence of HCV-4.

Four studies have been reported from liver transplant centers in Europe and Australia. Gane et al. reported on 14 patients with recurrent HCV-4 post-OLT and found that about 50% of these patients have progressive liver disease [125]. They also found that patients infected with genotypes 1b and 4 had the worst outcomes, while genotype 2 and 3 patients had less severe disease recurrence. Similarly, an analysis of 182 patients transplanted for HCV in Australia and New Zealand (16 of whom had HCV-4) found that among the many factors studied in univariate and multivariate analyses, genotype 4 was associated with an increased risk for re-transplantation and death [123]. By contrast, a study from another Australian center, including patients with HCV-4, showed that genotype 1b, but not 4, was associated with higher recurrence rates after transplantation [126]. In a more detailed study from the UK, 32 of 128 patients who underwent OLT for hepatitis C were infected with HCV-4 [122]. A statistically significant greater fibrosis progression rate was observed in HCV-4 patients compared to non-genotype-4, although their rates of survival were similar. The authors attributed the difference between these two groups to the significantly older donor age in the HCV-4 group and the ethnic background of these patients (predominantly Egyptian). On the other hand, studies from the Middle East show a more favorable outcome of HCV-4 patients. In a study from Saudi Arabia on biopsy proven recurrence HCV post-OLT there were no significant differences between genotype 1 and 4 patients in terms of epidemiological, clinical, and histological factors as well as outcome (patients and graft survival) [127]. Among many epidemiologic, laboratory, virologic factors included in that analysis, the only factor predictive of an advanced histological score was the HCV RNA level at the time of biopsy.

In Egyptian studies of living-related liver transplantation of HCV-4 patients a similar good outcome was observed. HCV clinical recurrence was observed in 31% of patients and was mostly mild, as 91% of patients had fibrosis scores less than F2 [128]. After 36 months of follow-up, 91% of patients were alive with good graft function. Similar to the study from Saudi Arabia, recurrent HCV was associated with pre-transplant and post-transplant viral load and to the presence of antibodies to hepatitis B core antigen.

Published studies on the response rates and outcome of antiviral therapy in patients with HCV-4 post-OLT are lacking. In an abstract from Saudi Arabia, 25 patients infected with HCV-4 were treated with PEG-IFN alfa-2a at a dose of 180 μg/week plus ribavirin 800 mg/day, (dose was adjusted as tolerated range 400–1200 mg) [129]. Fourteen patients (56%) achieved sustained virological response (SVR). The results of this study suggest that the post-transplant treatment outcome in HCV-4 is probably better then genotype 1 and less favorable than genotypes 2 and 3. This response pattern among the different genotypes parallels the response pattern in the immunocompetent population.

More studies are warranted to further understand HCV4 and OLT and to establish effective strategies for limiting the progression of liver disease post-OLT in HCV-4 patients.

Novel treatments

In spite of the improvement of chronic hepatitis C treatment over the last two decades, treatment with PEG-IFN and ribavirin is still associated with frequent and sometimes severe side effects and many patients cannot be treated because of contraindications [130]. A major step forward in the therapy of HCV infection is expected by the approval of new direct inhibitors of HCV replication. Several compounds, mainly inhibitors of the HCV NS3/4A protease and NS5B polymerase, are currently in phase II and III trials and the first HCV protease inhibitors will hopefully be licensed in 2011–2012. [131,132]. The large majority of the new antiviral drugs are currently developed only for HCV-1 infection. The most advanced compounds in clinical development are two protease inhibitors: telaprevir (VX950) and boceprevir (SCH503034). Telaprevir has shown an improvement of SVR rates in treatment naive HCV-1 patients to almost 70% and up to 40% in previously unresponsive patients [133,134]. In a proof of concept study, telaprevir has also shown activity against HCV-4 during 15 days monotherapy or combination with Peg-IFN and RBV compared to Peg-IFN, RBV and placebo [134]. Boceprevir is effective in HCV-1 patients [135], however, preclinical data suggests, that boceprevir might not be effective in HCV-4 with the currently used dosages [136], and data on boceprevir in HCV-4 patients haves not been published. R7128 is another nucleoside analog polymerase inhibitor that has demonstrated potent antiviral activity. In a recent interim analysis at week 12; the combination of R7128 (1500 mg twice daily) plus Peg-IFN α-2a and ribavirin in treatment-naive patients with HCV-1 and 4; R7 128 has show high rates of early viral response with promising safety profiles and low rates of resistance or breakthrough [137].

Further data haves been published for two other compounds with different mode of actions, nitazoxanide (NTZ) and Debio 025. NTZ, a synthetic antiprotozoal agent, is licensed in the United States for the treatment of infections with *Cryptosporidium parvum* and *Giardia lamblia*. Antiviral properties of this compound were discovered when patients with acquired immune deficiency syndrome (AIDS) coinfected with hepatitis B and C were treated for cryptosporidiosis. As a potential mechanism of action, NTZ activates the protein kinase activated by double-stranded RNA

(PKR), a key kinase that regulates the cell's innate antiviral response [138]. These observations could explain the clinical antiviral effect of NTZ. In this context, two clinical studies are of interest. A pilot trial explored NTZ monotherapy in Egyptian hepatitis C patients infected with HCV-4. HCV-RNA became undetectable in seven out of 23 patients who all had a rather low viral load before treatment (⩽400,000 IU/ml). Interestingly, four patients achieved SVR after 24 weeks of NTZ treatment [139]. A recent study by Rossignol et al. explored the combination of NTZ and standard PEG-IFN/RBV combination therapy in Egyptian HCV-4 infected patients [93]. The trial was conducted in two Egyptian centers and included 96 treatment-naïve patients – all were infected with HCV-4. Patients were randomized in one of three arms, a control arm with Peg-IFN alfa-2a and ribavirin for 48 weeks ($n = 40$), and two arms with a 12 week lead-in monotherapy with NTZ followed by a 36 week course of NTZ in combination with pegylated interferon with ($n = 28$) or without ribavirin ($n = 28$). SVR rates in the control arm were only 50%, which is relatively low as compared to most other previous HCV-4 trials [140]. Importantly, 79% of the patients receiving triple therapy with NTZ and PEG-IFN/RBV achieved a SVR that reached statistical significance although patients in the triple therapy arm were treated for only 36 weeks with PEG-IFN. Of note, patients receiving NTZ and PEG-IFN without RBV also showed a surprisingly high SVR of 61%. Although these data are promising, several issues need to be considered, for example the rather small overall number of patients with only five of the 96 patients having advanced fibrosis or cirrhosis (Ishak S F4-6) [141]. In addition, there were some differences in patient characteristics between the study arms as the body mass index (BMI) was significantly lower in patients who received PEG-IFN, RBV, and NTZ as compared to the control group. This also could have contributed to the better response in the triple therapy arm although the BMI was not an independent factor associated with SVR. Nevertheless, it is quite obvious that further studies are needed to investigate NTZ in genotype 4 patients. The antiviral efficacy of NTZ was confirmed during the 12 week lead-in phase when NTZ was administered alone. NTZ induced a modest but significant HCV-RNA decline of -0.27 $\log_{10}$, which is in line with the previous monotherapy study [93]. However, only two out of 53 patients treated with NTZ monotherapy had a decline of more than 1 $\log_{10}$ and just one patient achieved a complete response (HCV-RNA negative) after 12 weeks, which is in contrast to a previous trial where six out of 23 patients (26%) were HCV-RNA-negative after 12 weeks [141]. Thus, it is very unlikely that NTZ monotherapy will play any role in future treatment of chronic hepatitis C.

The cyclophilin inhibitior Debio 025 inhibits HCV replication by inhibiting endogenous cyclophilin and interaction with the NS5B polymerase, but without immunosuppressive activity. For treatment-naïve HCV-1 monoinfected patients a reduction of HCV-RNA of up to 4.75 $\log_{10}$ after 29 days of combination therapy with Debio 025, PEG-IFN alfa-2a, and ribavirin was shown [142]. Two HCV-4 patients were treated underin this study, one of them ose in a Debio 025 monotherapy arm. With a dose of 1000 mg per day the mean viral load reduction after 29 days was 2.2 ± 2.4 $\log_{10}$ for the 12 patients in that arm (11 patients with genotype 1, one with HCV-4). Importantly, the one genotype-4 patient also had a viral load decline of >2 $\log_{10}$ [142]. Finally, silibinin, for which the mechanism of action is not yet entirely resolved, administered intravenously (20 mg/kg/day) for 7 days, led to a mean decline of the HCV-RNA concentration by 3 $\log_{10}$ IU/ml. So far, mainly genotype 1 and single patients with genotype 2, 3, and 4 infections have been investigated and no data on differences of antiviral activities for the different HCV genotypes are available [143]. Recently, Beinhardt et al. reported a case that the use of silibinin IV are associated with prevention of graft re-infection in a patient infected with mixed genotype 1a/4. [144].

The available data on NTZ is are promising, but has need to be confirmed in larger studies. Other new compounds have been shown to suppress viral load in HCV-4 patients in proof-of-concept studies. Further larger trials on the combination of new compounds with PEG-IFN and RBV are needed to explore the beneficial effect in terms of SVR improvement in patients with HCV-4.

Conclusions

In recent years the study of HCV kinetics under therapy has been found to be extremely useful to guide the appropriate duration of therapy, motivate the patient and improve the cost/effectiveness of treatment. By the application of the RVR, as well as of the complete (cEVR) and partial early responses (pEVR), the duration of therapy can be individualized between 24 and 48 weeks. In this context it has become clear that in HCV genotype 4 – similar to genotype 1, 2, and 3 – a response guided duration of combination therapy is becoming the current standard of care.

The ongoing spread of HCV-4 to European and other countries is expected to facilitate further therapeutic studies including promising drugs like NTZ and direct acting antiviral agents specifically targeted to the proteins of HCV genotype 4.

Key points 1. Major facts about hepatitis C virus genotype (HCV-4)

- HCV-4 is responsible for more than 20% of worldwide HCV infections.
- Although HCV-4 is common in the Middle East and in Africa. recently, it has become increasingly prevalent in some southern European countries.
- The natural history of HCV-4 is likely similar to that of other genotypes.
- Moderate to severe steatosis with no associated sinusoidal fibrosis may be prominent in this genotype, which is mainly associated with metabolic factors and follows the same pattern as those infected with genotype 1.
- A possible association has been suggested between HCV-4 and HCC based on the similarity of distribution of HCC and HCV-4 in Egypt. A significant association seems to exist not only with the most prevalent subtype 4a, but also with subtype 4o.
- Scarce data are available on correlation between HCV-4 and extra hepatic manifestation of HCV, with no clear specific manifestation.

Key points 2. Treatment of HCV-4

- Combination therapy with pegylated interferon alpha and ribavirin for 48 weeks represents the current standard of care in chronic HCV-4
- Patients with HCV-4 who achieve an RVR are potential candidates for abbreviated 24-week treatment regimens; provided that no other predictors of poor response. However; slow responders who do not achieve HCV RNA negativity by week 4 or 12 are potential candidates for prolonging treatment up to 72-weeks
- Negative predictive factors at baseline include high viral load, presence of cirrhosis and steatosis, insulin resistance, IL-28B polymorphism TT and HIV coinfection.
- Determination of IL28B polymorphism may not be useful to select patients with HCV-4 for abbreviated treatment schedules. However these data need further confirmation before final conclusion can be extracted.
- Telaprevir has also shown activity against HCV-4, however, preclinical data suggests, that boceprevir might not be effective in HCV-4 with the currently used dosages.
- R7 128 has show high rates of early viral response with promising safety profiles and low rates of resistance or breakthrough.
- The available data on nitazoxanide (NTZ) and Debio 025 is promising, but has to be confirmed in larger studies.
- The use of insulin-sensitizing agents such as pioglitazone in conjunction with HCV-4 treatment increases both SVR and RVR rates.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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