

Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Esmat G. et al. (2014) Optimizing treatment for HCV genotype 4: PEG-IFN alfa 2a vs. PEG-IFN alfa 2b; the debate continues. Liver International, 34(Suppl 1):24-28.			
Date of Review:	February 9, 2015			
Reviewer(s):	Christine			
Part A				
Category:	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
Best Practice/Intervention:	Focus: Hepatitis C <input checked="" type="checkbox"/> Hepatitis C/HIV <input type="checkbox"/> Other: _____ Level: Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ Target Population: <u>patients with HCV genotype 4 infection in Peg-IFN trials</u> Setting: Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ Country of Origin: <u>Egypt</u> Language: English <input checked="" type="checkbox"/> French <input type="checkbox"/> Other: _____			
Part B				
	YES	NO	N/A	COMMENTS
<i>Is the best practice/intervention a meta-analysis or primary research?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Review of Peg-IFN trials to compare Peg-IFN a-2a and Peg-IFN a-2b in HCV patients with genotype 4
<i>The best practice/intervention has utilized an evidence-based approach to assess:</i>				
<i>Efficacy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Effectiveness</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention has been evaluated in more than one patient setting to assess:</i>				
<i>Efficacy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Effectiveness	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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	YES	NO	N/A	COMMENTS
<i>The best practice/intervention has been operationalized at a multi-country level:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Reviewed all peg-IFN trials performed worldwide for HCV genotype 4 since 2004
<i>There is evidence of capacity building to engage individuals to accept treatment/diagnosis</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>There is evidence of outreach models and case studies to improve access and availability</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Are the best practices/methodology/results described applicable in developed countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Are the best practices/methodology/results described applicable in developing countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Similar analysis results could be made with the same review criteria
<i>Evidence of manpower requirements is indicated in the best practice/intervention</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Juried journal reports of this treatment, intervention, or diagnostic test have occurred</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Liver International</i>
<i>International guideline or protocol has been established</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention is easily accessed/available electronically</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Free for download on http://onlinelibrary.wiley.com/
<i>Is there evidence of a cost effective analysis? If so, what does the evidence say?</i> Please go to Comments section	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>How is the best practice/intervention funded?</i> Please go to Comments section	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not funded
<i>Other relevant information:</i> _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

REVIEW ARTICLE

Optimizing treatment for HCV genotype 4: PEG-IFN alfa 2a vs. PEG-IFN alfa 2b; the debate continues

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Keywords

HCV genotype 4 – PEG-IFN alfa-2a – PEG-IFN alfa-2b

Abbreviations

EVR, early virologic response; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PEG-IFN, pegylated interferon; RBV, ribavirin; RVR, rapid virologic response; SOC, standard of care; SVR, sustained virological response.

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Chronic hepatitis C virus (HCV) infection is one of the most challenging global health problems (1, 2). It is the main cause of cirrhosis, hepatocellular carcinoma and the most common indication for liver transplantation worldwide (2–4); it also enhances the morbidity of other diseases such as metabolic diseases (5). Optimizing treatment strategies and options is a priority to obtain better results to decrease disease related complications. In the past decade, pegylated interferon (PEG-IFN) in combination with ribavirin has been the standard of care for HCV in all international guidelines. These guidelines do not discriminate between the two available forms of PEG-IFN: alfa-2a (40KD) (Pegasys[®]; Hoffmann-LaRoche, Basel, Switzerland) and PEG-IFN alfa-2b (12KD) (Peg-Intron[®]; MSD, Whitehouse Station, NJ, USA) (2, 6, 7). Although PEG-IFN alfa-2a and alfa-2b have many differences in pharmacokinetic and pharmacodynamic properties (8, 9), previous non-comparative studies have suggested that efficacy and safety profiles are similar (10, 11). The results of head to head comparative studies are discrepant. The similar efficacy and safety results were repeated in some recent large randomized controlled studies despite being exclusively conducted on genotype 1 HCV in western world countries (12) and this was also repeated in a study enrolling patients with HIV co-infection (13). Different

Abstract

Hepatitis C virus (HCV) remains one of the leading causes of morbidity and mortality worldwide. Combined therapy with pegylated interferon (PEG-IFN) and ribavirin is the current standard of care treatment for HCV genotype 4. Two types of PEG-IFN are commercially available. The limited number of trials that were conducted for HCV genotype 4 and the few head to head comparisons make it impossible to know which is the best option? In this article we review all available PEG-IFN trials performed worldwide for HCV genotype 4 since 2004. Unless another molecule is developed as a stand-alone for the treatment of HCV, PEG-IFN will continue to be a source of debate.

results were obtained from two different randomized head to head Italian studies (14, 15) which showed that results with PEG-IFN alfa-2a were better than (PEG-IFN alfa-2b) for sustained virological response (SVR). In Asia, a large multicenter Korean study rekindled the debate because it did not show any difference in response and safety between the two types and this suggested a possible difference in response to IFN based on ethnicity and genotype (16) which was also found in a recent Turkish study (17).

At present there are six meta-analyses published in the literature comparing the two types of PEG-IFN. The results of these studies are heterogeneous. The first meta-analysis included retrospective studies only. This is the only study that found PEG-IFN alfa-2b to be better (18). Another study confirmed that both types of IFN were similar in the treatment of genotype 1 (19) while the four remaining studies showed that SVR was obtained more frequently with combination PEG-IFN alfa-2a in chronic HCV patients (20–23). The most recent of these meta-analyses mentioned that PEG-IFN alfa-2a is better especially in genotypes 1 and 4 (23).

Since 2004, HCV genotype 4 has been evaluated in PEG-IFN trials. Finding these trials is not difficult because they are relatively few. A Medline search

between 2004 and 2013 revealed 42 HCV genotype 4 clinical trials. We have harmonized the data by excluding the following trials:

1. Trials that didn't discriminate between PEG-IFN types in data collection (nine trials).
2. Trials including patients with combination HCV-HIV infection (three trials).
3. Trials performed in HCV genotype 4 patients along with other genotypes (three trials).
4. Trials that used additional drugs (three trials)
5. Only one trial that used PEG-IFN as monotherapy in treating acute HCV.

The 23 valid trials are summarized in Tables 1 and 2.

Three published Egyptian trials compared both PEG-IFN types in a head to head clinical trials including only patients with genotype 4. All these three trials showed that PEG-IFN alfa-2a was significantly better than PEG-IFN alfa-2b for SVR rates. The first study in 196 patients showed that the SVR in the PEG-IFN alfa-2a group vs. PEG-IFN alfa-2b group was 64.4% vs. 53.2%, respectively; $P = 0.04$ (24), the second study in 217 patients showed that the SVR was 70.6 vs. 54.6%, respectively; $P = 0.017$ (25). The third trial was a large retrospective cohort of 3718 Egyptian chronic HCV patients in a real life comparison and showed that the

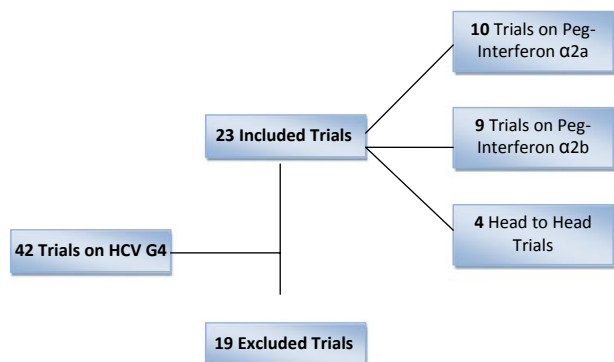
Table 1. Trials conducted for HCV genotype 4 using PEG-Interferon α 2a

Author	Study Country	Patients number	Description	Cirrhotics %	SVR %
Derbala <i>et al.</i> (28)	Qatar	73	–	Advanced fibrosis (F3–F4) in 34.2	65.8
Males <i>et al.</i> (29)	Egypt	100	–	14	61
Ferenci <i>et al.</i> (30)	Austria	30	All the enrolled patients achieved RVR and the total treatment duration was 24 weeks	–	86.7
Gad <i>et al.</i> (24)	Egypt	90	–	14.4	64.4
El Makhzangy <i>et al.</i> (31)	Egypt	95	–	14.7	61.1
Varghese <i>et al.</i> (32)	Kuwait	30	–	–	63.3
De Galocsy <i>et al.</i> (33)	Belgium	78	Sum of data from two randomized phase III trials BerNar-1 and BerNar-2, comparing (SVR) rates between G1, G4 patients	–	51.3
Dimitroulopoulos <i>et al.</i> (34)	Greece	60	Two groups: Group A: 30 European Group B: 30 Egyptians	–	36.7 in group A 26.7 in group B
Kamal <i>et al.</i> (25)	Egypt	109	–	0	70.6
Papastergiou <i>et al.</i> (27)	Greece	80	Multietnic (Greek-Egyptians)	–	47.5
El-Shazly <i>et al.</i> (35)	Egypt	40	Two groups: A: 20 patients with well controlled DM B: 20 patients without DM	0 (16 patients had no fibrosis assessment)	75 in group A 65 in group B
El Khayat <i>et al.</i> (36)	Egypt	102	87 patients achieved EVR randomized to group A (treated for 24 weeks, No = 43) and group B (treated for 48 weeks, No = 44)	26 in group A 18 in group B	70 in group A 73 in group B
Urquijo <i>et al.</i> (37)	Spain	198	–	–	52.7
El Raziky <i>et al.</i> (26)	Egypt	1985	–	6.3	59.6

EVR, early virological response; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RVR, rapid virologic response; SVR, sustained virological response.

Table 2. Trials conducted for HCV genotype 4 using PEG-IFN α 2b

Author	Study Country	Patients number	Description	Cirrhotics %	SVR %
Alfaleh et al (38)	Saudi Arabia	28	–	0	42.9
Kamal et al (39)	Egypt	287	Three groups according to treatment duration: Group A: 24 weeks ($n = 95$) Group B: 36 weeks ($n = 96$) Group C: 48 weeks ($n = 96$)	–	29, 66 and 69 in groups A, B and C respectively
Derbala et al (40)	Qatar	30	–	26.7	33.3
Roulot et al. (41)	France	242	Multi-Ethnic study (French, Egyptians and Africans)	Advanced fibrosis in 24.2, 44.6 and 29 of French, Egyptians and Africans groups respectively	40.3, 54.9 and 32.4 in French, Egyptians and Africans groups respectively
Kamal et al (42)	Egypt	358	Two groups according to treatment duration: Control group: fixed duration 48 weeks ($n = 50$). Study group: variable duration ($N = 308$) [A: 24 weeks ($n = 69$). B: 36 weeks ($n = 79$). C: 48 weeks ($n = 160$)]	9.2	Control: 58 Group A: 86 Group B: 76 Group C: 56
Gad et al. (24)	Egypt	79	–	16.5	53.2
Elefsiniotis et al. (43)	Greece	58	Retrospective-Multi-Ethnic (Greek-Egyptians)	9.7	53.4
Ghaffar et al. (44)	Egypt	7	Children (8–15 years old)	–	28.6
Al Ali et al. (45)	Kuwait	12	Adolescent patients (14–17 years old)	0	75
Khatab et al. (46)	Egypt	131	Three groups according to steatosis prevalence in liver tissues: Group A: no steatosis ($n = 73$), Group B: mild steatosis ($n = 36$), Group C: moderate/severe steatosis ($n = 22$)	Advanced fibrosis in 40.4	Over all SVR = 50.0. 69.8 SVR in group A, 50 in group B and 40.9 in group C
Kamal et al. (25)	Egypt	108	–	0	54.6
Papastergiou et al. (27)	Greece	97	Multi-Ethnic (Greek-Egyptians)	–	38.1
El Raziky et al. (26)	Egypt	1733	–	5.9	53.9

**Fig. 1.** PEG-IFN trials on HCV G4 included in or excluded from the review.

SVR rates were 59.6% vs. 53.9% respectively (26). These data support a Greek trial also comparing both types of PEG-IFN in the treatment of 177 HCV genotype 4 patients and it also showed that PEG-IFN α -2a was better than PEG-IFN α -2b with SVR rates of (47.5% vs. 38.1%) for PEG-IFN α -2a & PEG-IFN α -2b respectively (27).

Conclusion

Pegylated interferon has improved the SVR results in a large proportion of patients with HCV. In an era when new oral antiviral drugs are becoming available thanks to the pharmaceutical industry and researchers, the two forms of PEG-IFN have been a key element in creating a

competition resulting in a reduction in prices, in many sponsored clinical trials and a gradual increase in access to treatment for many patients. Nevertheless, many of the head to head comparison trials have been designed and sponsored by the pharmaceutical industry with targets that are not only scientific. Thus, a careful analysis must be made when trying to decide which PEG-IFN provides better results, and in our opinion, the debate is still ongoing.

Disclosure

The authors do not have any disclose to report.

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