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Supplementary information

Breakthroughs in hepatitis C research: from discovery to cure

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Supplementary Table 1: Selected landmark treatment studies that established (Peg-)Interferon and Ribavirin as the standard of care in HCV infection

Study/Authors	Year of publication	Study Design	Treatment	Key Results	Major Contribution
Hoofnagle et al. [1]	1986	single-arm pilot study n=10 patients with NANBH	0.5 to 5 million units IFN alfa either daily, every other day, or three times weekly up to 12 months of therapy	n=8/10 patients showed a substantial decrease in ALT levels IFN therapy associated with an improvement of liver histology	Proof-of-principle for the value of IFN in NANBH (HCV infection)
Di Bisceglie et al. [2]	1989	randomized, double-blind, placebo-controlled trial n=41 patients with NANBH	Two treatment arms: A: 1 million units IFN per day for seven days followed by 2 million units three times a week for 23 weeks B: Placebo	ALT decrease and histological improvement in the treatment but not in the placebo arm Relapse of ALT levels in the majority of patients after the end of treatment Sustained response in only 10% of IFN treated patients	The first randomized, placebo-controlled trial regarding IFN in HCV infection
Davis et al. [3]	1989	A multicenter randomized, controlled trial n=166 patients	Three treatment arms: A: no treatment	Substantial ALT decrease to or near to normal values in 8% (A), 23% (B) and 46% (C)	Established IFN monotherapy as the standard of care in chronic HCV infection

		with chronic HCV infection	B: 1 million units IFN three times a week --- C: 3 million units IFN three times a week --- Treatment duration 24 weeks	Relapse after the end of treatment in 44-51% of patients	Demonstrated a higher efficacy of 3 million units of compared to 1 million units IFN
Reichard et al. [4]	1991	single-arm pilot study n=10 patients with chronic HCV infection	RBV at a dose of 1000-1200mg for 12 weeks	Significant decrease in ALT levels during treatment Relapse to pretreatment levels within 6-12 weeks after the end of therapy	Proof-of-principle for the efficacy of RBV in HCV infection
Di Bisceglie et al. [5]	1992	single-arm study n=13 patients with chronic HCV infection	RBV (increasing dosage from 600mg to 1200mg per day) for six months	A slight decrease of HCV RNA during treatment No patient lost HCV RNA during treatment	Demonstrated the insufficient antiviral efficacy of RBV monotherapy
Jäckel et al. [6]	2001	single-arm, multicenter study n=44 patients with acute HCV infection	5 million units IFN three times per week Treatment duration: 24 weeks	SVR in 98% of patients	Established IFN monotherapy as the standard of care for acute HCV infection Demonstrated the higher efficacy of IFN therapy in the acute phase of HCV infection

Kakumu et al.[7]	1993	A randomized, controlled study n=27 patients with chronic HCV infection	Three treatment arms: A: RBV (800-1000mg per day) B: IFN beta (3 million units three times per week) C: IFN beta (3 million units three times per week) + RBV (800-1000mg per day) Treatment duration: 24 weeks	SVR rates: A: 0% B: 22% C: 33%	Providing valuable data for a synergistic antiviral effect of RBV with IFN (beta)
Brillanti et al.[8]	1994	A randomized, controlled study n= 20 patients with chronic HCV infection and previous relapse (n=10) or null-response (n=10) to IFN	Two treatment arms: A: IFN (3 million units three times per week) B: IFN (3 million units three times per week) + RBV (800mg per day) Treatment duration: 6 months	SVR rates: A: 0% B: 40%	The first randomized study demonstrating a synergistic value of IFN alfa and RBV
Poynard et al.[9]	1998	A randomized, multicenter, double-blind, placebo-	Three treatment arms: A: IFN (3 million units three times per week) +	SVR rates: A: 43%	Established IFN + RBV as the standard of care in chronic HCV infection

		controlled trial n=832 patients with chronic HCV infection	RBV (1000-1200mg per day) for 48 weeks B: IFN (3 million units three times per week) + RBV (1000-1200mg per day) for 24 weeks C: IFN (3 million units three times per week) + placebo for 48 weeks	 B: 35% C: 19%	Demonstrated the higher efficacy of a 48-weeks compared to a 24-weeks regimen
McHutchison et al.[10]	1998	A randomized, multicenter, double-blind, placebo-controlled trial n=912 patients with chronic HCV infection	Four treatment arms: A: IFN (3 million units three times per week) + placebo for 24 weeks B: IFN (3 million units three times per week) + placebo for 48 weeks C: IFN (3 million units three times per week) + RBV (1000-1200mg per day) for 24 weeks D: IFN (3 million units three times	SVR rates: A: 6% B: 13% C: 31% D: 38%	Established IFN + RBV as the standard of care in chronic HCV infection Demonstrated the higher efficacy of a 48-weeks compared to a 24-weeks regimen

			per week) + RBV (1000-1200mg per day) for 48 weeks		
Heathcote et al. [11]	2000	A randomized, multicenter study n=271 patients with chronic HCV infection and advanced liver fibrosis or cirrhosis	Three treatment arms: A: IFN (3 million units three times per week) for 48 weeks B: Peg-IFN-2a (90µg per week) for 48 weeks C: Peg-IFN-2a (180µg per week) for 48 weeks	SVR rates: A: 8% B: 15% C: 30%	Demonstrated the higher efficacy of Peg-IFN compared to IFN in patients with advanced liver disease Demonstrated the higher efficacy of the 180µg regimen
Zeuzem et al. [12]	2000	A randomized, multicenter study n=531 patients with chronic HCV	Two treatment arms: A: Peg-IFN-2a (180µg per week) for 48 weeks B: IFN (6 million units three times per week for 12 weeks followed by 3 million units three times per week for 36 weeks)	SVR rates: A: 39% B: 19%	Demonstrated the higher efficacy of Peg-IFN compared to IFN
Manns et al. [13]	2001	A randomized, multicenter study n=1530 patients with chronic	Three treatment arms: A: IFN (3 million units three times per week) + RBV (1000–	SVR rates: A: 47%	Established Peg-IFN + RBV as the standard of care in chronic HCV infection

		HCV infection	1200 mg per day) for 48 weeks B: Peg-IFN-alfa-2b (1.5 μg/kg per week) + RBV (800 mg per day) for 48 weeks C: Peg-IFN-alfa-2b (4 weeks 1.5 μg/kg and 44 weeks 0.5 μg/kg) plus RBV (1000–1200mg per day)	 B: 54% C: 47%	Demonstrated a slightly superior efficacy of Peg-IFN compared to IFN
Fried et al.[14]	2002	randomized, multicenter study n=1121 patients with chronic HCV infection	Two treatment arms: A: Peg-IFN-2a (180μg per week) + RBV (1000-1200mg per day) for 48 weeks B: Peg-IFN-2a (180μg/week) + placebo for 48 weeks C: IFN (3 million units three times per week) + RBV (1000-1200mg per day) for 48 weeks	SVR rates: A: 56% B: 29% C: 44%	Significantly contributed to establishing Peg-IFN + RBV as the standard of care in chronic HCV infection Confirmed a superior efficacy of Peg-IFN compared to IFN

ALT: Alanine transaminase; HCV: Hepatitis C Virus; IFN: Interferon-alfa; NANBH: Non-A, non-B hepatitis; Peg-IFN: pegylated-Interferon alfa; RNA: ribonucleic acid; RBV: Ribavirin; mg: milligram; SVR: sustained virological response; μg: microgram; kg: kilogram;

Supplementary Table 2: Important adverse events during Interferon-based antiviral regimens[a]

	Peg-IFN–RBV dual therapy	Peg-IFN–RBV–BOC	Peg-IFN–RBV–TLV
Fatigue	57-60%	53-57%	57-58%
Influenza-like illness	26-28%	23-25%	28-29%
Pyrexia	24-33%	32-33%	26-30%
Irritability	18-24%	22-23%	19-22%
Pruritus	27-36%	24-26%	45-50%
Rash	23-24%	24-25%	35-37%
Alopecia	20-27%	20-28%	22-23%
Nausea	31-42%	43-48%	40-43%
Diarrhea	22%	22-27%	28-32%
Headache	39-42%	46%	41-43%
Anemia	19-29%	[b]49%	[b]37-39%
Neutropenia	19-21%	25%	14-17%
Insomnia	31-33%	32-33%	32%
Depression	22%	19-23%	17-18%
Cough	21-24%	15-20%	17-21%
Myalgia	21-26%	21-25%	15-21%
Athralgia	18-19%	19-20%	13-15%
Dysgeusia	<10%-18%	[b]37-43%	<10%

[a]According to the phase 3 studies investigating telaprevir and boceprevir in previously untreated HCV patients. No head-to-head comparison between telaprevir and boceprevir has been performed.
[b]Adverse events that were more common in PI based regimens [15, 16].

PI: protease-inhibitor; Peg-IFN: pegylated-interferon alfa; RBV: Ribavirin; BOC: boceprevir; TLV: telaprevir

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