



MM Mücke¹, E Herrmann², VT Mücke¹, C Graf¹, S Zeuzem¹, J Vermehren¹ ¹Department of Internal Medicine 1, University Hospital Frankfurt, Frankfurt am Main, Germany ²Institute of Biostatistics and Mathematical Modeling, Goethe University Frankfurt, Frankfurt am Main, Germany

INTRODUCTION

Historically, age has been a major limitation of interferon-based antiviral therapy for hepatitis C (HCV) due to poor tolerability, reduced efficacy and an increasing number of comorbidities. Since the introduction of direct-acting antivirals (DAAs), HCV treatment has been revolutionized and high sustained virologic response (SVR) rates can now be achieved in virtually all patient populations, even in those earlier considered difficult-to-treat.

AM

Aim of this systematic review and meta-analysis was to assess and compare the efficacy and safety of DAA therapy among elderly (≥ 65 years or ≥ 75 years) and younger (<65 years or <75 years) patients with chronic HCV infection.

METHOD

For this systematic review and meta-analysis, the PubMed MEDLINE, Embase and Cochrane databases were searched through July 2018. Two independent researchers extracted data and assessed quality and risk of bias. All phase 3 trial or post marketing studies were eligible for inclusion. The primary outcome was efficacy of DAA therapy with respect to age (<65 versus ≥65 years). To account for different study populations between studies and heterogeneous study designs/ protocols risk ratios (RRs) for non-SVR were calculated using random and fixed effect models and group comparison were performed. This study was registered with PROSPERO (CRD42018104392).

Efficacy and safety of direct-acting antiviral therapy for hepatitis C in the elderly: a systematic review and meta-analysis

RESULTS

Overall, we identified 63 studies including 34,082 patients treated with different DAAs. Risk for non-SVR was comparable in patients <65 and \geq 65 years of age (RR 1.00, 95% CI 0.86-1.15;p=0.979) and even lower in a subgroup analysis of cirrhotic patients ≥ 65 years of age (RR 0.59, 95% CI 0.35-0.99,p=0.044). Risk for non-SVR was similar between age groups in all other subgroup analyses. Elderly patients had a significantly increased risk of adverse events (RR 1.30, 95% CI 1.11-1.52,p=0.001), but not for serious adverse events (p=0.43) or treatment discontinuation (p=0.15). Risk for anemia if treated with additional ribavirin was 2.84 (95% CI 1.73-4.66,p<0.001) in elderly patients compared to patients <65 years.

Summary of search results and study selection.



Study

Ahn et al., Chuang et Dore et al. Feld et al. Foster et a George et Hézode et Isakov et Jacobson Kao et al., Kumada e Kumada e Kumada e Leroy et al Manns et Naggie et Nelson et Poordad (Rockstroh Roth et al. Saab et al Shah et al. Wei et al. Welzel et Wyles et a Zeuzem e Zeuzem e **Fixed effe**

Real Worl Akuta et a Atsukawa Backus et Bhattacha Conti et al Fox et al. Kanda et a Köklü et a Mangia et Mawatari Milazzo e Miyazaki Morisawa Ogawa et Ogawa et Ogawa e Omata et Pellicelli e Perello et Saab et al Sawinski Shiffman e Shin et al Sugimoto Taki et al., Vermehre Wei et al., Fixed effe Random e Heterogenei

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CONCLUSIONS

Our results show that DAAs are highly effective and safe in elderly patients. Ribavirin should be avoided in the elderly, as more AEs, and particularly anemia is observed. Further cost-effectiveness analyses are needed to evaluate the socio-economic benefit of treating elderly people without advanced liver disease.

years versus <65 years.								treatment experience (A) and cirrhosis (B).							
	> 65 years	< 65 years		•••	Weight	Weight	^		≥ 65 years <65	5 years			Weight	Weight	
	non-SVR Total n	on-SVR Total	Risk Ratio	RR 95%-CI	(fixed) (random)	A	Study	non-SVR Total non-SV	R Total	Risk Ratio	RR	95%-Cl (fixed)	(random)	
								Ahn et al., 2016	0 8 0) 16			0.0%	0.0%	
d Studies	1 00	2 100		1 15 [0 10: 10 64]	0 10/	0.49/		Chuang et al., 2016	0 8 2	2 35	+	0.84 [0.04;	; 15.84] 2.8%	4.7%	
2016 t al 2017	1 29	3 100		1.15 [0.12; 10.64]	0.1%	0.4%		Isakov et al., 2018	0 2 1	1 25		3.40 [0.18;	; 63.37] 0.9%	4.8%	
al., 2017	0 15	28 500		0.20 [0.03, 1.40]	0.9%	0.3%		Manns et al., 2010	10 44 27	7 161	1 <u>6</u>	1.36 [0.71	: 2.58] 32.8%	0.0 <i>%</i> 37.6%	
. 2016	0 3	17 198		1.62 [0.12; 21.92]	0.1%	0.3%		Milazzo et al., 2017	0 2 0) 8			0.0%	0.0%	
2015	0 88	6 536		0.47 [0.03; 8.21]	0.2%	0.2%		Ogawa et al., 2016	7 72 5	5 72		1.40 [0.47	7; 4.21] 14.1%	22.5%	
al., 2015	3 21	64 531		1.19 [0.41; 3.46]	0.5%	1.7%		Omata et al., 2014	1 19 2	2 44 2 523			; 12.01] 3.4%	7.2% 0.1%	
al., 2018	2 26	16 224		1.08 [0.26; 4.42]	0.4%	1.0%		Sawinski et al., 2016	0 0 0) 12	-	0.47 [0.00	0.0%	0.0%	
al., 2017	0 5	7 102		1.24 [0.08; 19.07]	0.1%	0.3%		Vermehren et al., 2016	5 1 76 25	5 229 —		0.12 [0.02	2; 0.87] 35.2%	9.5%	
al., 2018	0 4	3 149			0.0%	0.3%		Wyles et al., 2015	0 3 1	1 49		4.71 [0.23;	; 95.78] 0.6%	4.5%	
2016	4 109	0 74		1.07 [0.39, 2.95]	0.7%	0.0%		Fixed effect model	331	1213		0.85 [0.53	• 1 361 100 0%		
t al., 2014	9 89	25 133		0.54 [0.26: 1.10]	2.2%	3.4%		Random effects model	el	1210	\checkmark	1.05 [0.53	; 2.05]	100.0%	
t al., 2015	10 154	7 209		1.94 [0.75; 4.98]	0.6%	2.1%		Heterogeneity: $I^2 = 23\%$,	$j^2 = 0.2009, p = 0.25$,		
t al., 2017	7 104	1 123	1 1 1	- 8.28 [1.04; 66.20]	0.1%	0.5%					0.1 0.51 2 10				
l., 2016	0 1	5 49		3.00 [0.27; 32.95]	0.0%	0.4%	P		> 65 years - 64	vears			Weight	Weight	
al., 2014	16 133	85 510		0.72 [0.44; 1.19]	3.8%	6.0%	D	Study	non-SVR Total non-SV	'R Total	Risk Ratio	RR	95%-CI (fixed)	(random)	
al., 2015	1 15	12 320		1.78 [0.25; 12.79]	0.1%	0.5%		,						()	
al., 2015	3 10	14 142		3.04 [1.04; 8.87]	0.2%	1.7%		Conti et al., 2017	15 244 24	4 214		0.55 [0.30	0; 1.02] 38.0%	32.3%	
etal.,2016	1 18	9 68 8 010		0.42 [0.06; 3.10]	0.4%	0.5%		Leroy et al., 2016 Milazzo et al., 2017		o 35 N Q		2.15 [0.20	<i>y</i> ; 23.48] 0.9%	4.4%	
2015	0 20	1 96		- 1.57 [0.12, 25.00]	0.1%	0.3%		Ogawa et al., 2017	5 52 5	5 38		0.73 [0.23	3: 2.35] 8.6%	14.9%	
2016	6 264	64 2029	+	0.72 [0.32: 1.65]	1.6%	2.7%		Ogawa et al., 2017	12 101 0) 26		6.53 [0.40;	; 106.71] 1.2%	3.3%	
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2018	1 13	12 142		0.91 [0.13; 6.46]	0.2%	0.5%		Poordad et al., 2016		3 37 —		0.26 [0.02	2; 4.07] 4.8%	3.4%	
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ıl., 2015	1 11	15 192	ł+	1.16 [0.17; 8.02]	0.2%	0.5%		Shiffman et al., 2015	1 24 22	2 96 -		0.18 [0.03	3; 1.28] 13.1%	6.4%	
t al., 2015	0 29	17 287		0.28 [0.02; 4.51]	0.4%	0.3%		Taki et al., 2018	1 62 1	I 14 —		0.23 [0.02	2; 3.40] 2.4%	3.5%	
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d Studies I., 2017 et al., 2017	62 563 6 127	37 281 2 143		0.84 [0.57; 1.22] 3.38 [0.69; 16.44]	5.3% 0.2%	8.6% 0.8%		Risk ra	tio for adv	0.01	0.1 1 10 10 events over	₀ all (A	and fo	or	
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Overall risk ratio analysis for non-SVR in patients ≥65





Subgroup analysis for non-SVR in patients with

CONTACT INFORMATION

- Marcus M. Mücke, MD
- **Department of Internal Medicine**
- Theodor-Stern Kai 7
- 60590 University Hospital Frankfurt a. M., Germany.
- marcus.muecke@kgu.de





