Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Bota S. et al. (2013) Role of interleukin-28B polymorphism as a predictor of sustained virological response in patients with chronic hepatitis C treated with triple therapy: a systematic review and meta-analysis. *Clinical Drug Investigation*, 33(5):325-331
Date of Review:	March 10, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **HCV patients treated with triple antiviral therapy** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Romania** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Meta-analysis; to determine the role of reference single nucleotide 12979860 allele of interleukin-28B (IL28B) CC versus CT+TT genotype as a predictor of sustained virological response in patients with chronic hepatitis C treated with triple therapy (Peg-IFN + ribavirin + direct antiviral agents)
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Further studies are required to clarify the underlying mechanisms and the role of other factors on sustained virological response rate.

Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	Similar analysis could be done in developed countries.
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☐	☒	☐	Research of HCV triple therapy may be limited given the high cost of the direct acting agents
The research study/tool/data dictionary is easily accessed/available electronically	☐	☒	☐	Available to download with a purchase from http://link.springer.com
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☒	☐	No funding was received for the study
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- Genotype IL28B CC patients had significantly higher SVR rates than non-CC patients when only triple therapy patients were included in the randomized controlled trials - SVR rate significantly higher in patients with CC genotype than with the CT+TT genotype, though significant heterogeneity was present between the studies Limitations: - Small number of studies included - Small number of studies that

				analyzed SVR according to IL28B polymorphisms in naive and previously treated patients - Impossible to analyze the role of race and baseline viral load on SVR rate
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☐	☒	☐	Collected all relevant studies published until July 15, 2012
Are these data regularly collected at and/or below a national level?	☐	☒	☐	
Are these data collected manually or electronically?	☐	☐	☐	Electronically from various databases
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	*Clinical Drug Investigation*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Utilized existing data/surveillance information

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SYSTEMATIC REVIEW

Role of Interleukin-28B Polymorphism as a Predictor of Sustained Virological Response in Patients with Chronic Hepatitis C Treated with Triple Therapy: A Systematic Review and Meta-Analysis

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Abstract
Background and Objective Chronic hepatitis C represents an important health problem. The aim of our meta-analysis was to establish the role of reference single nucleotide (rs) 12979860 allele of interleukin-28B (*IL28B*) CC versus CT+TT genotype (the most researched allele of *IL28B*) as a predictor of sustained virological response (SVR) in patients with chronic hepatitis C treated with triple therapy.
Methods The PubMed, MEDLINE, Lilacs, Scopus, Ovid, EMBASE, Cochrane and Medscape databases as well as abstract books from important gastroenterology and hepatology meetings were searched for all studies published until 15 July 2012 that analysed the relationship between the polymorphism of *IL28B* and SVR in patients with chronic hepatitis C, genotype 1, treated with pegylated interferon + ribavirin + direct antiviral agents (telaprevir or boceprevir). The following keywords were used: *IL28B* polymorphism, chronic hepatitis C, sustained virological response, SVR, triple therapy, telaprevir, boceprevir.
Results Odds ratios (ORs) with 95 % confidence intervals were pooled from five study populations (1,641 cases) using a random–effects model. The SVR rate was significantly higher in patients with the CC genotype of *IL28B* than in those with non-CC genotypes (CT and TT): OR = 3.91 (95 % CI 2.11–7.28), $p < 0.0001$. Higher SVR rates were obtained in chronic hepatitis C patients with the CC genotype of *IL28B*, regardless of their therapeutic status (naïve patients: OR = 3.99 [95 % CI 1.67–9.51], $p < 0.0001$; and previously treated ones: OR = 2.15 [95 % CI 1.35–3.43], $p = 0.001$).
Conclusion *IL28B* polymorphism seems to influence the SVR rate in patients with chronic hepatitis C treated with triple therapy, but further studies are needed to clarify the mechanism and the influence of other factors on the SVR rates.

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1 Background

Chronic infection with hepatitis C virus (HCV) is an important public health concern worldwide. The World Health Organization has estimated the prevalence of chronic HCV infection at about 3 %, with approximately 170 million people affected [1]. In the last 8–10 years pegylated interferon (PegIFN) and ribavirin were the standard of care therapy in chronic HCV infection, with a rate of sustained virological response (SVR) ranging from 40 to 50 % in patients infected with HCV genotype 1 and 4, and from 70 to 80 % in patients with HCV genotype 2 or 3 [2–5]. In patients with liver cirrhosis the rate of SVR is even lower (approximately 20 % in genotype 1 and 4 patients and 50 % in genotype 2 and 3 patients) [6–8].

In recent years several studies, including two meta-analyses, have shown the influence of the genetic polymorphism of interleukin-28B (*IL28B*), encoding interferon-λ-3, on the SVR rate in patients with chronic hepatitis C treated with PegIFN and ribavirin [9–12].

In the meta-analysis by Li et al. [11] the SVR rate was significantly higher in patients with reference single nucleotide (rs) 12979860 CC allele than in those with the

CT genotype (odds ratio [OR] = 5.22, 95 % CI 4.37–6.23) or those with the TT genotype (OR = 7.97, 95 % CI 6.20–10.25). Similarly, in the meta-analysis by Chen et al. [12], the SVR rate was significantly higher in patients with the CC genotype of *IL28B* than in non-CC patients (OR = 4.76, 95 % CI 3.15–7.20).

Considering the relatively low rate of SVR following double therapy, especially in patients with HCV genotypes 1 and 4, new drugs have been developed. Several studies that used triple therapy (PegIFN + ribavirin + direct antiviral agents) in patients with HCV genotype 1 infection have been published in the last 2–3 years [13–17]. The most studied direct antiviral agents are boceprevir and telaprevir [15–17], which are currently the only direct antiviral agents used in clinical practice.

Since *IL28B* polymorphism has an important proven role in achieving SVR in chronic hepatitis C patients treated with PegIFN and ribavirin [11, 12], it would logically follow that it would influence the SVR rates with triple therapy, but little information is available.

The aim of this meta-analysis was to establish the role of the rs12979860 (CC vs. CT+TT genotype) allele of *IL28B* (the most researched allele of *IL28B*) as a predictor of SVR in patients with chronic C viral hepatitis treated with triple therapy.

2 Methods

2.1 Eligibility Criteria

This meta-analysis included all studies (abstracts or full-length articles) published in English until 15 July 2012 that evaluated the SVR rates in patients with HCV infection (genotype 1) treated with triple therapy: PegIFN (alpha-2a 180 μg/week or alpha-2b 1.5 μg/kg of bodyweight/week), ribavirin (dosage range: 600–1,200 mg/day) and direct antiviral agents (telaprevir 750 mg every 8 h or boceprevir 800 mg three times daily). The treatment duration ranged between 12 and 48 weeks. Telaprevir was administered for 8 or 12 weeks and boceprevir for 24 or 44 weeks. The genetic polymorphisms of *IL28B* (rs12979860 allele) was studied in all patients. Naïve patients as well as previously treated patients were considered. The category of previously treated patients included prior relapsers (undetectable HCV RNA in serum by real-time polymerase chain reaction [PCR] RNA-HCV at the end of PegIFN + ribavirin therapy, but detectable PCR RNA-HCV after the end of therapy), prior partial responders (reduction with $\geq 2\log^{10}$ viral load at week 12 in PegIFN + ribavirin therapy, but never achieving undetectable PCR RNA-HCV) and null responders (reduction with $<2\log^{10}$ of viral load at week 12 in PegIFN + ribavirin therapy, and the therapy was stopped at that moment).

2.2 Outcomes

The prespecified primary outcome was the SVR rate in chronic hepatitis C patients treated with triple therapy according to the *IL28B* genetic polymorphism. SVR was defined as undetectable PCR RNA-HCV at 6 months after discontinuation of therapy. The secondary outcomes were the possible relationships between the SVR rate according to the *IL28B* polymorphism and the following factors: patient status (naïve or formerly treated with standard PegIFN + ribavirin) and type of direct antiviral agents (telaprevir and boceprevir).

2.3 Data Sources and Searches

Relevant studies published until 15 July 2012 were searched in the MEDLINE, Lilacs, Scopus, Ovid, EMBASE, Cochrane and Medscape databases as well as among the abstracts presented at the following congresses: European Association for the Study of the Liver, American Association for the Study of Liver Diseases, Asian Pacific Association for the Study of the Liver, Digestive Disease Week and United European Gastroenterology Week.

The following keywords were used: *IL28B* polymorphism, chronic hepatitis C, sustained virologic response, SVR, triple therapy, telaprevir, boceprevir

2.4 Study Selection and Data Collection

Two authors independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. The following data were extracted: country of origin of studies, year of publication, number of patients, race, mean age and bodyweight of patients, patient status (naïve and previously treated), type of direct antiviral agent used, duration of treatment, *IL28B* polymorphism analysed, and number of patients with SVR according to the *IL28B* polymorphism.

2.5 Data Synthesis and Analysis

Statistical analyses were carried out with RevMan software, version 5.1.4 (http://ims.cochrane.org/revman; Copenhagen, 2011). The association strength between *IL28B* polymorphism (rs12979860) and SVR in chronic hepatitis C patients treated with triple therapy was determined by calculating the OR with 95 % confidence interval. The significance of the pooled ORs was determined by the Z-test, and a p-value <0.05 was considered significant. A fixed–effects model and random effects model (using DerSimonian and Laird's method) [18] were used in this meta-analysis. Because fixed effects can be invalid in cases in which significant heterogeneity exists between the

studies included in the meta-analysis, the results of the random–effects model were considered as the final results, since in the random–effects model both the random variation within the studies and the variation between different studies are incorporated. Publication bias was investigated by funnel plot, Egger's linear regression method and Begg's rank correlation method [19]. Statistical heterogeneity of data was quantified using the I^2 statistic. To ensure the reliability and accuracy of the results, two authors independently uploaded the data into the statistical software programs and verified that the results were identical. The results were represented on a Forest plot.

3 Results

Of the 592 studies identified by the initial search, 198 were excluded for duplicated studies, 386 because the abstracts were subsequently published in full or because no information regarding the *IL28B* polymorphism was provided for patients with triple therapy, one was excluded because only the rs8099917 polymorphism of *IL28B* [20] was studied, and two articles were excluded for "overlap data" [21, 22] (Fig. 1). Finally, five papers including 1,641 patients were included in the analysis (three abstracts and two full-length articles) [23–27] (Table 1).

Five studies [23–27] showed the role of the rs12979860 allele of *IL28B* on the SVR rate (Table 2). In patients with the CC genotype, the SVR rate was significantly higher than in those with non-CC genotypes (CT and TT): OR = 3.92 (95 % CI 2.11–7.28), $p < 0.0001$ (Fig. 2). A significant heterogeneity was present between these five studies: $I^2 = 69$ %, $p = 0.01$.

The following factors were considered when analysing the influence of the rs12979860 genotype on the SVR rate:

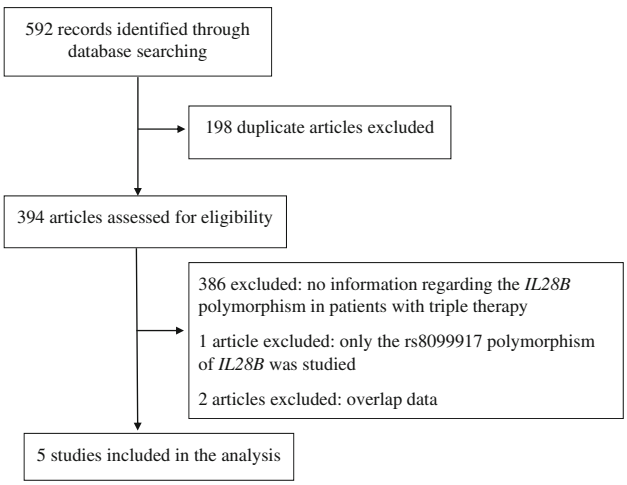

Fig. 1 Flowchart of the selection of studies. *IL28B* interleukin 28B, *rs* reference single nucleotide

type of article (abstracts or full-length articles), study design (randomized controlled trial), patient status (naïve or previously treated with standard PegIFN and ribavirin) and type of direct antiviral agents (telaprevir and boceprevir).

The SVR rate was significantly higher for CC genotype patients and the heterogeneity was significant between studies, even if only abstracts [24, 25, 27] or full-length articles [23, 26] were considered: OR = 4.12 (95 % CI 1.77–9.58, $p < 0.0001$) [$I^2 = 63$ %, $p = 0.05$] and OR = 4.36 (95 % CI 0.88–21.4, $p < 0.0001$) [$I^2 = 85$ %, $p = 0.008$], respectively.

Genotype *IL28B* CC patients had significantly higher SVR rates than non-CC patients when only triple therapy patients who were included in the randomized controlled trials [23–25, 27] were considered: OR = 3.09 (95 % CI 0.88–21.4, $p < 0.0001$) [significant heterogeneity between the studies: $I^2 = 61$ %, $p = 0.05$].

Three studies [23, 25, 27] reported data on naïve patients. The SVR rate was significantly higher in patients with CC genotype vs. those with non-CC genotypes (CT and TT): OR = 3.99 (95 % CI 1.67–9.51), $p < 0.0001$ (Fig. 3a). The heterogeneity between the studies was significant: $I^2 = 64$ %, $p = 0.03$.

Two studies [23, 24] reported data regarding patients who were previously treated with PegIFN and ribavirin. The SVR rate was again significantly higher in patients with the CC genotype vs. those with non-CC genotypes: OR = 2.15 (95 % CI 1.35–3.43), $p = 0.001$ (Fig. 3b). The heterogeneity between these two studies was not significant: $I^2 = 0$ %, $p = 0.48$.

Only one study [23] used boceprevir and the SVR rate was significantly higher in patients with the CC genotype than in those with non-CC genotypes: OR = 2.14 (95 % CI 1.41–3.22), $p = 0.0003$.

Four studies [24–27] used telaprevir as a direct antiviral agent in the triple therapy. The SVR rate was significantly higher in patients with the CC genotype vs. those with non-CC genotypes: OR = 5.25 (95 % CI 2.34–11.7), $p < 0.0001$ (Fig. 4). A significant heterogeneity was present between these four studies: $I^2 = 66$ %, $p = 0.03$.

The Begg's test and Egger's test were performed to assess the publication bias in this meta-analysis. Funnel plots did not show major asymmetry, which indicates the absence of relevant reporting bias (funnel plots not presented).

4 Discussion

It is well know that several factors influence the SVR rate in patients with chronic hepatitis C treated by with PegIFN + ribavirin: HCV genotype, age, gender, body mass

Table 1 Characteristics of the studies included in the meta-analysis

Study (year)	Type of study	No. of patients with triple therapy	Patients' status	Race	Treatment
Poordad et al. [23] (2012)	Randomized placebo-controlled	643 patients from the SPRINT-2 and RESPOND-2 trials [16, 28]	Naïve and previously treated (prior relapsers and partial responders)	All	PegIFN-alpha-2b (1.5 μg/kg of bodyweight/week) + ribavirin (600–1,400 mg/day) + boceprevir (800 mg three times daily); boceprevir: 24 or 44 weeks; PegIFN + ribavirin: 28 or 48 weeks
Pol et al. [24] (2011)	Randomized placebo-controlled	422 patients from the REALIZE trial [29]	Previously treated (prior relapsers, prior partial responders, null responders)	All	PegIFN-alpha-2a (180 μg/week) + ribavirin (1,000–1,200 mg/day) + telaprevir (750 mg every 8 h); telaprevir: 12 weeks; PegIFN + ribavirin: 48 weeks
Jacobson et al. [25] (2011)	Randomized placebo-controlled	414 patients from the ADVANCE trial [30]	Naïve	All	PegIFN-alpha-2a (180 μg/week) + ribavirin (1,000–1,200 mg/day) + telaprevir (750 mg every 8 h); telaprevir: 8 or 12 weeks; PegIFN + ribavirin: 24–48 weeks
Akuta et al. [26] (2010)	Cohort	81 patients	Naïve and previously treated (prior relapsers and null responders)	Asiatic	PegIFN-alpha-2b (1.5 μg/kg of bodyweight/week) + ribavirin (600–1,000 mg/day) + telaprevir (750 mg every 8 h); telaprevir: 12 weeks; PegIFN + ribavirin: 12 or 24 weeks
Bronowicki et al. [27] (2012)	Randomized placebo-controlled	81 patients from the PROVE 2 trial [31]	Naïve	All	PegIFN-alpha-2a (180 μg/week) + ribavirin (1,000–1,200 mg/day) + telaprevir (750 mg every 8 h); telaprevir: 12 weeks; PegIFN + ribavirin: 12 or 24 weeks

PegIFN pegylated interferon, *PROVE 2* Protease inhibitor for viral evaluation 2 trial, *RESPOND-2* Retreatment with HCV Serine Protease inhibitor Boceprevir and PegIntron/Rebetol 2 trial, *SPRINT-2* Serine Protease Inhibitor Therapy 2 trial

Table 2 Studies that analysed the sustained virological response rate in patients with rs12979860 polymorphism of interleukin-28B

Study (year)	Total no. of patients	CC genotype		Non-CC genotype	
		No. of patients	SVR (%)	No. of patients	SVR (%)
Poordad et al. [23] (2012)	643	182	80.2	461	65.7
Pol et al. [24] (2011)	422	76	78.9	346	60.4
Jacobson et al. [25] (2011)	414	95	88.4	319	65.8
Akuta et al. [26] (2010)	68	37	83.8	31	32.2
Bronowicki et al. [27] (2012)	81	28	96.4	53	49.1

rs reference single nucleotide, *SVR* sustained virological response

index, fibrosis stage, baseline HCV-RNA, rapid virological response (RVR), liver steatosis, aminotransferases level, iron level in the liver, etc. [4, 32–35]. In recent years many studies have shown the major importance of the genetic polymorphism of *IL28B* for achieving SVR, especially in HCV genotype 1 patients [9–12, 36–38].

There are also several factors that contribute to the SVR rate in patients undergoing triple therapy: patient status in regard to previous PegIFN + ribavirin therapy (naïve or pretreated), baseline viral load, race, fibrosis stage and *IL28B* polymorphism [14, 16, 21, 23, 30].

This meta-analysis assessed the influence of the genetic polymorphism of *IL28B* (rs12979860 allele) on the SVR in patients with chronic hepatitis C treated with triple therapy.

The mechanism through which rs12979860 polymorphism, located 3 kb upstream of the *IL28* gene, is related to PegIFN + ribavirin response is not very well known. It is likely that the activity or levels of the nearby interferon-λ genes are influenced, because responders to treatment are characterized by a lower baseline immune response to HCV [39, 40]. This could also explain the paradoxical association of response genotype with higher viral load in some studies [36].

The SVR rate was significantly higher in patients with the rs12979860 CC genotype than with the CT+TT genotypes (OR = 3.92, $p < 0.0001$), but an important heterogeneity between the studies was present ($I^2 = 69$ %). We found an important difference between the SVR rates in CC vs. non-CC patients: from 14.5 % in favour of CC genotype in the study of Poordad et al. [23] to 51.6 % in the study of Akuta et al. [26]. This difference may be explained by treatment duration with PegIFN and ribavirin

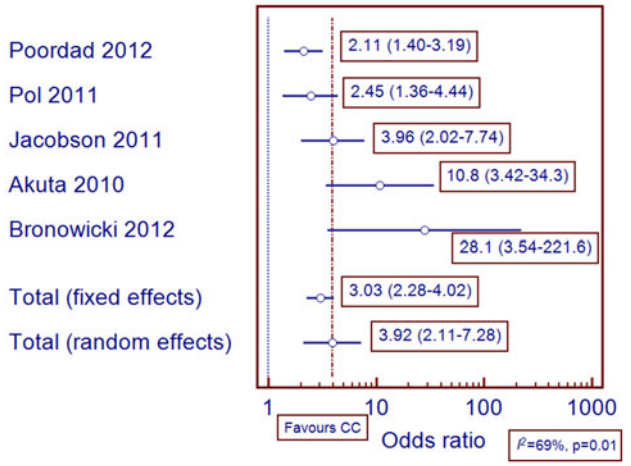

Fig. 2 Association of the interleukin-28B rs12979860 genotype CC and sustained virological response in all patients, compared with the non-CC genotype. Odds ratios (ORs) and 95 % confidence intervals are shown. The *broken line* represents the OR between sustained virological response rates obtained in all CC vs. non-CC patients. I^2 heterogeneity between the studies, *rs* reference single nucleotide

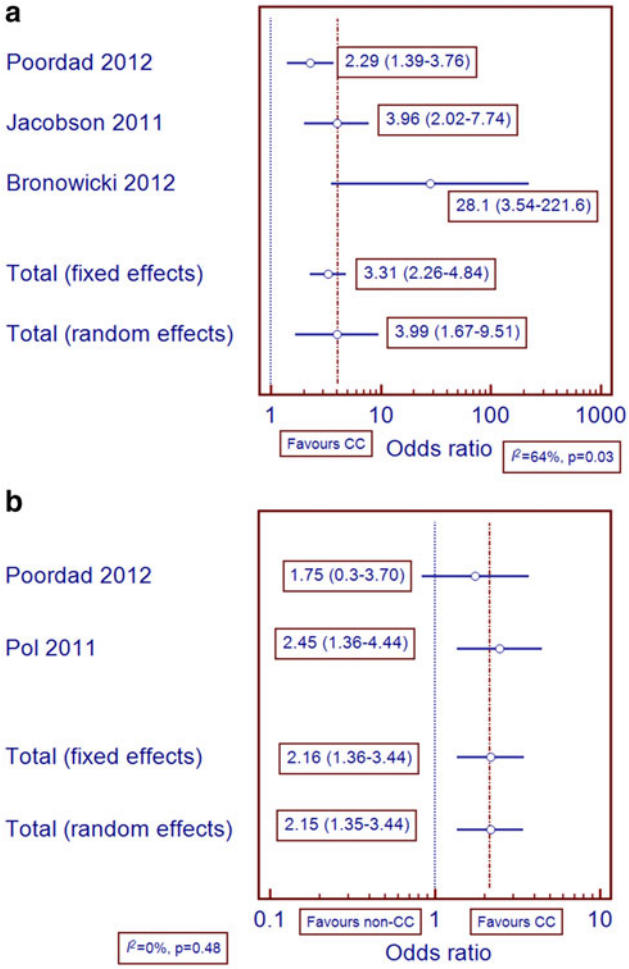

Fig. 3 Association of the interleukin-28B rs12979860 genotype CC and sustained virological response according to treatment status, compared with the non-CC genotype. Odds ratios (ORs) and 95 % confidence intervals are shown. The *broken line* represents the OR between sustained virological response rates obtained in CC vs. non-CC treatment-naïve patients (**a**) and previously treated patients (**b**). I^2 heterogeneity between the studies, *rs* reference single nucleotide

(in addition to telaprevir): the Japanese study [26] (which included naïve and previously treated patients) and the study of Bronowicki et al. [27] used PegIFN and ribavirin for 12 or 24 weeks; in the Pol et al. [24] study (including only previously treated patients), the treatment duration was 48 weeks; while in the study of Jacobson et al. [25] (only on naïve patients), the treatment duration with PegIFN and ribavirin ranged from 12 to 48 weeks according to RVR status.

Bronowicki et al. [27] presented their data separately for patients treated with PegIFN and ribavirin for 12 and 24 weeks, respectively, in addition to 12 weeks of telaprevir treatment. The SVR rates were similar in patients with the CC genotype treated with PegIFN and ribavirin for 12 or 24 weeks: 100 vs. 94 %, while in non-CC patients the SVR rate was higher in patients treated for 24 weeks with PegIFN and ribavirin: 61.9 vs. 40.6 %. It would probably be better to treat the patients with the non-CC genotype with PegIFN and ribavirin for a longer period, in addition to direct antiviral agents; however, future large, prospective studies are needed to study this problem.

Another explanation of the higher SVR rates in CC vs. non-CC patients could be the patients' race: the study of Akuta et al. [26] included only Asian (Japanese) patients, while the other studies [23–25, 27] included patients from all races.

In this present meta-analysis, even if both abstracts and full-length articles were included, the results were similar for these two types of papers, making our results more reliable.

In addition, in our meta-analysis, higher SVR rates were observed in chronic hepatitis C patients with the *IL28B* CC genotype, regardless of their therapeutic status (naïve or previously treated).

The strong points of the present meta-analysis are the large number of patients (1,641) treated with triple therapy in whom the role of *IL28B* polymorphism as a predictor of SVR was studied, and the fact that these patients come from the largest, most important and well-designed trials that compared triple therapy with PegIFN + ribavirin therapy [16, 28–31].

However, even if meta-analyses generally provide the most powerful data, our meta-analysis has some limitations: the small number of studies included in the analysis (five studies, three of which are abstracts); the small number of studies that analysed the SVR rate according to *IL28B* polymorphisms in naïve and previously treated patients (three and two studies, respectively); and the

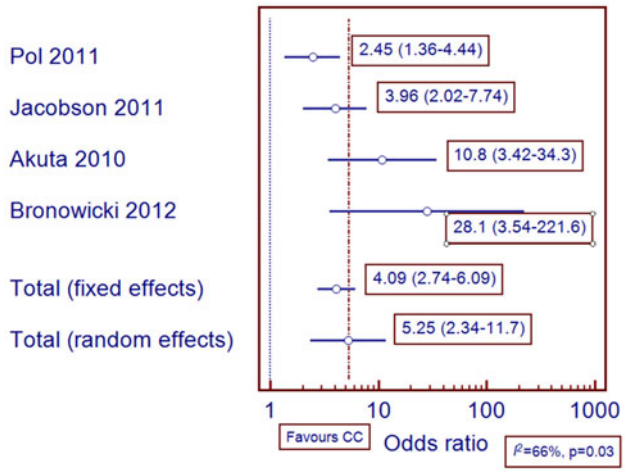

Fig. 4 Association of the interleukin-28B rs12979860 genotype CC and sustained virological response in patients treated with Peg-interferon, ribavirin and telaprevir, compared with the non-CC genotype. Odds ratios (ORs) and 95 % confidence intervals are shown. The *broken line* represents the OR between sustained virological response rates obtained in CC vs. non-CC patients treated with triple therapy including telaprevir. I^2 heterogeneity between the studies, *rs* reference single nucleotide

impossibility of analysing the role of race and baseline viral load on the SVR rate.

5 Conclusions

IL28B polymorphism seems to influence the SVR rate in patients with chronic HCV hepatitis treated with triple therapy (there is a high SVR rate in patients with the rs12979860 CC genotype), but further studies are required in order to clarify the underlying mechanisms as well as the role of other factors on the SVR rate.

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