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META-ANALYSIS

Interferon-associated retinopathy risk in patients with diabetes and hypertensive hepatitis C

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Abstract

AIM: To investigate the association of hypertension and diabetes mellitus (DM) with interferon-associated retinopathy (IAR) risk in chronic hepatitis C (CHC).

METHODS: Two investigators independently searched PubMed and Embase for eligible articles published prior to December 2013; additional studies were identified by reviewing the bibliographies. Only case-control or cohort studies that evaluated the association between hypertension and/or DM and IAR incidence in CHC patients were included. IAR was characterized by the presence of cotton-wool spots and/or retinal hemorrhage, and was defined as the primary efficacy measure. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were estimated using data extracted from papers based on random-effects models.

RESULTS: Eight eligible studies were included in the present meta-analysis. The outcomes showed that patients with CHC and hypertension were at higher risk of IAR (48/189 *vs* 96/455, RR = 1.90; 95%CI: 1.15-3.15, $P < 0.05$). Patients with DM receiving interferon (IFN)-based therapy for CHC infection may be at higher risk for IAR (18/72 *vs* 60/256, RR = 1.56, 95%CI: 1.11-2.20, $P < 0.05$); however, the outcome was not stable. There was no significant difference in IAR risk between genotype-1-infected patients and non-genotype-1-infected patients (RR = 1.09, 95%CI: 0.64-1.87, $P > 0.05$). Comparable incidences of IAR were also found between patients treated with pegylated interferon (PIFN) α-2a and those treated with PIFN α-2b (RR = 0.84, 95%CI: 0.56-1.24, $P > 0.05$) and between patients treated with IFN α and those treated with PIFN α (RR = 1.04, 95%CI: 0.72-1.50, $P > 0.05$).

CONCLUSION: Patients with hypertension have a higher risk of retinopathy when receiving IFN-based therapy for CHC.

Key words: Hepatitis C infection; Interferon-associated retinopathy; Hypertension; Diabetes mellitus; Interferon

Core tip: This meta-analysis demonstrated that patients with hypertension were at higher risk for developing retinopathy when receiving interferon-based therapy for chronic hepatitis C infection. Further studies are needed to clarify the association between diabetes mellitus and interferon-associated retinopathy.

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INTRODUCTION

Chronic hepatitis C (CHC) infection, which affects > 170 million people worldwide[1], may eventually lead to cirrhosis and/or hepatocellular carcinoma (HCC)[2,3]. According to recent guidelines, the combination of pegylated interferon (PIFN) α and ribavirin is still regarded as the standard chemotherapy for CHC[4]. Two new direct-acting antiviral agents (DAAs), telaprevir and boceprevir, specifically inhibit the activity of the hepatitis C virus (HCV) NS3/4A protease and have been recently approved for HCV genotype 1 infection[5,6]. This new treatment regimen clearly led to a 20%-30% increase in the sustained viral response (SVR) rate of genotype-1-infected patients[7,8]. However, triple therapy that includes interferon (IFN) α and the two DAAs has some limitations. First, triple therapy is only used in genotype-1-infected patients. Second, the cost of treatment is increased, and 40% of the treated patients show additional side effects, such as cutaneous rash and anemia[7,8]. Moreover, triple therapy is associated with the rapid onset of drug resistance[9,10]. Although many other direct antiviral therapies and IFN-free regimens are in development, these therapies are unlikely to reach clinical application in the next few years. For the reasons given above, we may safely conclude that IFN α plus ribavirin will remain the central therapeutic option for several years[5,6]. Thus, the clinicians must continue to manage side effects related to treatment with IFN α.

Various adverse effects, including ophthalmological side effects[11-17] have been reported with the use of IFN. The most commonly documented ocular complication is retinopathy which is characterized by cotton-wool spots and/or retinal hemorrhage[11,13,16]. Several studies have investigated the possible risk factors for retinopathy in patients with CHC during antiviral therapy using IFN α and/or PIFN α. However, the results have been controversial. Some studies have suggested that diabetes mellitus (DM) and hypertension are possible risk factors for interferon-associated retinopathy (IAR)[11,18,19], and others have not identified these risk factors[20-22]. Therefore, the question of whether ophthalmologic screening should be recommended for CHC patients with hypertension or DM before, during, and after treatment is controversial. To address this issue, we performed a meta-analysis of studies that assessed the association of hypertension and/or DM and IAR risk among CHC patients.

MATERIALS AND METHODS

Search strategy

Two investigators independently searched PubMed and Embase (up to December 31, 2013) to collect all eligible papers. The search strategies for PubMed and Embase were as follows: ("retinal diseases" [MeSH Terms] OR "retinal diseases" [All Fields] OR "retinopathy" [All Fields]) AND ("interferons" [MeSH Terms] OR "interferons" [All Fields] OR "interferon" [All Fields]) AND ("hcv" [All Fields] OR "hepatitis c" [MeSH Terms] OR "hepatitis C" [All Fields]), and ("retinal diseases"/exp OR "retinal diseases" OR "retinopathy"/exp OR "retinopathy") AND ("interferons"/exp OR "interferons" OR "interferon"/exp OR "interferon") AND ("hepatitis C"/exp OR "hepatitis C"), respectively. In addition, we also reviewed the bibliographies of relevant articles that were not found by database searches. Disagreements were resolved by discussion and consensus between the two reviewers.

Inclusion and exclusion criteria

The following inclusion criteria were used when collecting published studies: (1) evaluation of the association between IAR incidence and hypertension and/or DM; (2) a case-control or cohort study; (3) sufficient information for estimating the relative risks (RRs) and their 95% confidence intervals (CIs); and (4) English or Chinese publications. The exclusion criteria were as follows: (1) a case report, review, conference abstract, comment or editorial letters; (2) a lack of control groups; (3) overlapping articles or articles with duplicate data; and (4) an inability to obtain the necessary data.

Data extraction and definition of end-points

Two investigators independently extracted the following information from each study: name of first author, year of publication, ethnicity, type of IFN, numbers of cases and controls, length of follow-up, and end-points and risk estimates (or the relevant data needed to calculate them). We calculated the duration of follow-up from the start of IFN therapy and discarded pre-existing retinopathy at baseline. Whenever possible, we contacted the authors to inquire about insufficient data. Any disagreement was resolved by consensus between the reviewers.

Retinopathy was used as the only end-point for this analysis, which was defined as the presence of any of the following lesions: cotton-wool spots, retinal hemorrhage, or microaneurysms.

Quality assessment

For observational cohort studies, the methodological quality was assessed independently by two authors using the Newcastle-Ottawa Scale (NOS)[23] based on the following criteria: (1) selection of cases and controls (or cohort); (2) comparability of cases and controls (or cohort); and (3) ascertainment of exposure/outcome. Studies with an overall score ≥ 6 were classified as high quality.

Statistical analysis

The RRs and corresponding 95%CIs were used as the effect measurements. All unadjusted RRs were calculated using available data. To combine crude risk estimates, a quantitative meta-analysis was performed using STATA version 12.0 (STATA Corporation, College Station, TX, United States). Both Cochran's Q test and I^2 measure-

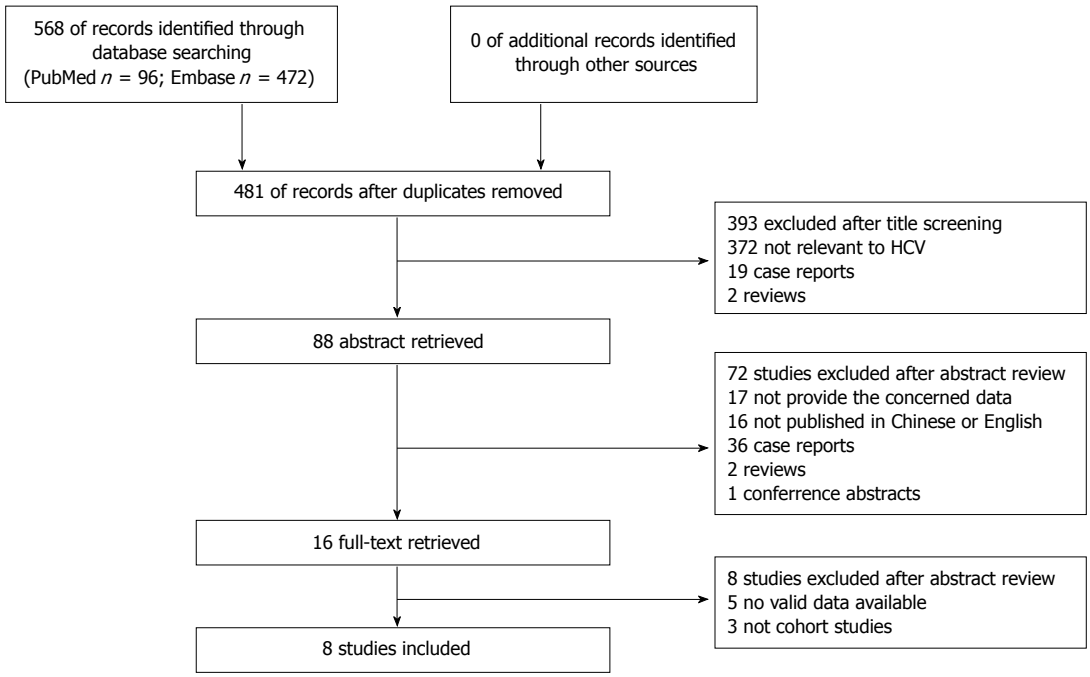

Figure 1 Flow chart illustrating the process of article selection.

ments were performed to evaluate intra-study heterogeneity. Substantial heterogeneity was indicated if the *P* value was $\leqslant 0.10$ or I^2 was $\geqslant 50\%$. However, irrespective of the presence of significant heterogeneity, a random-effect model was utilized to allow comparisons among different pooled risk estimates. Publication bias was evaluated by Egger's test[24]. $P \leqslant 0.10$ indicated the presence of publication bias. Sensitivity analysis was performed to evaluate the validity and reliability of the primary meta-analysis. Subgroup analysis was also conducted to evaluate the effects of study design, ethnicity, and treatment duration on the incidence of IAR among CHC patients with or without hypertension or DM. We also pooled the unadjusted risk estimates of IAR for age, type of IFN, and HCV genotypes to evaluate whether old age, PIFN treatment, or genotype 1 infection portends an increased risk of IAR.

RESULTS

Search results and characteristics of included studies

Of the 568 references identified, 87 duplicates were deleted. Screening of the title, abstract, and full text yielded eight studies involving 606 patients (Figure 1)[11,18-22,25,26]. Among these studies, two[20,21] were retrospective cohort studies, and the remainder[11,18,19,22,25,26] were prospective cohort studies. Two studies each were conducted in Japan[11,19] and the United States[20,21], and one report each was published in Egypt[22], Canada[26], France[25] and South Korea[18]. Conventional IFN, PIFN, and a combination of IFN and PIFN were used in two[11,19], three[20,22,26], and three[18,21,25] studies, respectively. The patients in one study[19] were followed for 24 wk, while the patients in the other studies[11,18,20-22,25,26] had a longer follow-up. The mean follow-up time was 46.50 ± 13.51 wk. Ophthalmic examinations were performed by ophthalmologists in all the studies except one[19], which did not provide the information on who performed the examination. Baseline ophthalmic examination in one[20] study was performed within 12 wk of initiating therapy, while in the remaining studies it was performed before the start of therapy[11,18,19,21,22,25,26]. Follow-up ophthalmic examinations varied among the studies. The two retrospective studies[20,21] might have underestimated the incidence of retinopathy, because only patients with reported symptoms underwent a follow-up eye examination. According to the scoring system, five studies[19,20,22,25,26] were of high methodological quality and three[11,18,21] were not. All the articles were published in English as full-text articles (Table 1).

Hypertension and IAR

The incidence of IAR was compared between CHC patients with and without hypertension in all studies. Although four studies[11,20-22] did not demonstrate a significantly increased risk of IAR in patients with CHC and concomitant hypertension, the remaining four[18,19,25,26] reported a significantly increased risk of IAR in patients with CHC and concomitant hypertension. The meta-analysis showed that the incidence of IAR was significantly higher in CHC patients with than in those without hypertension (48/189 *vs* 96/455, RR = 1.90, 95%CI: 1.15-3.15, $P = 0.013$) (Figure 2A). Significant intra-study heterogeneity was observed among the included studies ($I^2 = 70.6\%$, $P = 0.001$) (Figure 2A). No evidence of publication bias was found by Egger's test ($P = 0.28$).

Significant intra-study heterogeneity was observed among the included studies, therefore, the data were subgrouped with the aim of removing the heterogeneity. In the subgroup analysis of the association between hypertension and IAR in CHC patients by study design,

Table 1 Main characteristics of the studies included in the meta-analysis

Ref.	Year	Country	Study design	Type of IFN	No. of HCV (+) IAR (+) cases/HCV (+) IAR (-) controls	Reported end-points	Follow-up	Study quality
Kawano *et al*[11]	1996	Japan	Prospective cohort	Natural IFN α, recombinant IFN α-2a/2b	17/49	Retinopathy	48 wk	5
Okuse *et al*[19]	2006	Japan	Prospective cohort	Recombinant IFN α-2b	18/56	Retinopathy	24 wk	6
d'Alteroche *et al*[25]	2006	France	Prospective cohort	IFN α, PIFN α	11/133	Retinopathy	72 wk	6
Panetta *et al*[21]	2009	United States	Retrospective cohort	Consensus IFN, PIFN α-2a/2b	114/48	Retinopathy	48 wk	5
Mehta *et al*[20]	2010	United States	Retrospective cohort	PIFN	26/39	Retinopathy	48 wk	4
Kim *et al*[18]	2010	South Korea	Prospective cohort	PIFN, conventional IFN	13/22	Retinopathy	36 wk	8
Vujosevic *et al*[26]	2012	Canada	Prospective cohort	PIFNα-2a/2b	22/66	Retinopathy	36/60 wk	8
Mousa *et al*[22]	2013	Egypt	Prospective cohort	PIFN α-2a/2b	40/42	Retinopathy	48 wk	6

IFN: Interferon; PIFN: Pegylated interferon.

the pooled RR was only significant in prospective studies (RR = 2.38, 95%CI: 1.46-3.87, P = 0.000) and not in retrospective studies (RR = 0.74, 95%CI: 0.16-3.33, P = 0.690) (Table 2). The subgroup analysis by ethnicity showed that the pooled RR was significant only in Asians (RR = 1.56, 95%CI: 1.07-2.27, P = 0.021) and not in Caucasians and Africans (for Caucasians: RR = 1.96, 95%CI: 0.78-4.92, P = 0.154; for Africans: RR = 2.21, 95%CI: 0.15-33.50, P = 0.567) (Table 2). Subgroup analysis by ethnicity was not reliable for Africans due to the fact that only one study was performed. In addition, the subgroup analysis by ethnicity indicated that studies conducted on Caucasians were the main source of heterogeneity (I^2=84%, P = 0.000) (Table 2). Finally, we stratified the studies by treatment duration and found that the pooled RR was significant only in patients treated for 24 wk (RR = 1.56, 95%CI: 1.07-2.27, P = 0.021) and not in patients treated for 48 wk (RR = 2.00, 95%CI: 0.85-4.68, P = 0.112) (Table 2).

DM and IAR

The incidence of IAR was compared between patients with CHC with and without DM in six studies[11,18-22]. The meta-analysis showed that there was an increased risk of IAR among CHC patients with DM (18/72 *vs* 60/256, RR = 1.78, 95%CI: 1.33-2.38, P = 0.000) (Figure 2B). This association remained significant after the removal of three small studies (RR = 1.55, 95%CI: 1.04-2.32, P = 0.033). No significant heterogeneity was observed among the included studies (I^2 = 0.0%, P = 0.518). The sensitivity analysis showed that the result changed significantly (RR = 1.50, 95%CI: 0.82-2.76, P = 0.192) after the study of Kawano *et al*[11], which clearly carried the most weight, was omitted from the analysis, suggesting that the outcome was not stable.

HCV genotypes and IAR

Three studies[18,19,25] provided sufficient data for evaluating the effect of HCV genotypes on the development of IAR. We found comparable incidences of IAR between genotype-1-infected and non-genotype-1-infected patients (RR = 1.09, 95%CI: 0.64-1.87, P = 0.746) (Figure 2C). Significant heterogeneity was found (I^2 = 84.7%, P = 0.001) in these studies. Egger's test did not detect the presence of publication bias (P = 0.335).

Type of IFN and IAR

The incidence of IAR was compared between the PIFN α-2a and PIFN α-2b treatment groups in three studies[11,20,21], and four studies[11,18,21,25] had results on the incidence of IAR in patients who received IFN α and PIFN α therapies. Comparable incidences of IAR were observed between patients treated with PIFN α-2a and those treated with PIFN α-2b (RR = 0.84, 95%CI: 0.56-1.24, P = 0.374) and between patients treated with IFN α and those treated with PIFN α (RR = 1.04, 95%CI: 0.72-1.50, P = 0.845) (Figure 2D). No substantial heterogeneity was found (PIFN α-2a *vs* PIFN α-2b: I^2 = 8.6%, P = 0.335; IFN α *vs* PIFN α: I^2 = 0%, P = 0.792) in these groups. No evidence of publication bias was found by Egger's test (PIFN α-2a *vs* PIFN α-2b: P = 0.694; IFN α *vs* PIFN α: P = 0.458).

Age and IAR

One study[27] identified age as an independent predictor of IAR by multiple logistic regression analysis. However, only three[18,19,26] of the included studies reported that the adjusted odds ratios (ORs) or hazard risks (HRs), which could not be combined in our meta-analysis because there were only two ORs (one study did not provide the 95%CI) and one HR. Although the three studies reported a positive association between hypertension and IAR risk, no association was found between DM or age and IAR risk when adjusted by factors such as sex, levels of viremia, levels of alanine aminotransferase (ALT), and response to therapy. Moreover, none of the studies included in this meta-analysis were age-matched studies. Therefore, we could not evaluate the association of age with IAR in CHC patients with hypertension or DM.

DISCUSSION

Ocular side effects are well-recognized complications of the current standard chemotherapy for hepatitis C; the most common of which is ischemic retinopathy. Most patients developed retinopathy within 2 mo after IFN

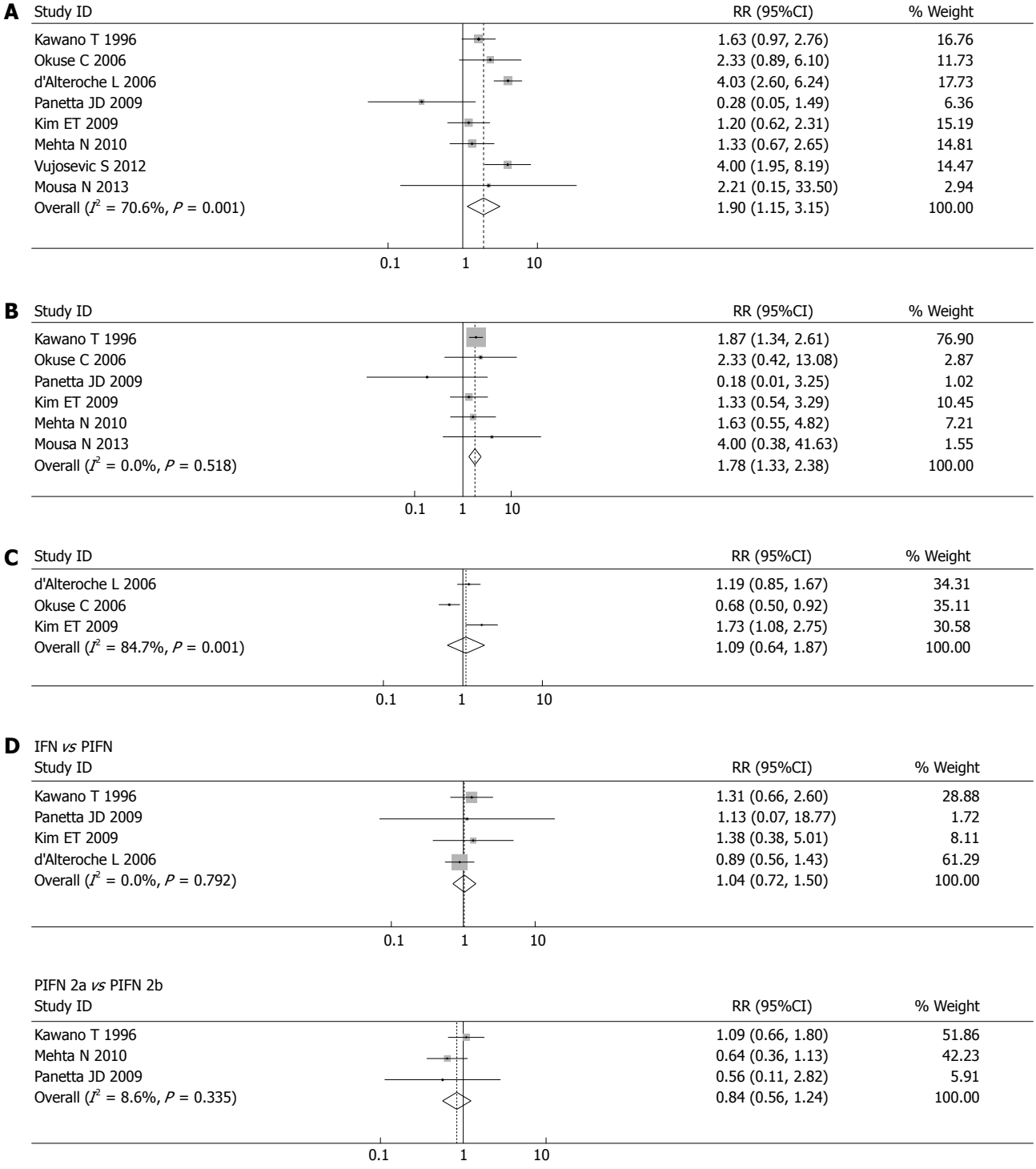

Figure 2 Forest plot. A: RRs for the association of IAR and hypertension. Squares represent the study-specific RR. Diamonds represent the summary relative risks (SRRs). Horizontal lines represent 95%CIs. A random-effect model was used. An overall tendency toward the right side of the reference line (RR = 1) indicated that hypertension could increase the incidence of IAR; B: RRs for the association of IAR and DM. Squares represent the study-specific RR. Diamonds represent the SRRs. Horizontal lines represent 95%CIs. A random-effect model was used. An overall tendency towards the right side of the reference line (RR = 1) indicated that DM could increase the incidence of IAR; C: RRs for the association of IAR and HCV genotypes. Squares represent the study-specific RR. Diamonds represent the SRRs. Horizontal lines represent 95%CIs. A random-effect model was used. The contact of overall diamond with the reference line (RR = 1) indicated that there was no difference in IAR incidence between genotype-1-infected and genotype-2-infected patients; D: Effect of different types of IFN on IAR risk. Squares represent the study-specific RR. Diamonds represent the SRRs. Horizontal lines represent 95%CIs. A random-effect model was used. The contact of overall diamond with the reference line (RR = 1) indicated that there was no difference in IAR incidence between the PIFN α-2a group and the PIFN α-2b group or between the IFN α group and the PIFN α group.

treatment[11-14,28,29]. Several studies[13,16,30] showed that no retinal lesions were detected in any sample from patients with CHC who were not undergoing IFN therapy. These results further support the hypothesis that IFN treatment induces retinopathy in patients with CHC. Cotton-wool spots and retinal hemorrhage were the most common

Table 2 Summary relative risks for the association of hypertension and interferon-associated retinopathy risk by study design, ethnicity

	Subgroup	Ref.	RR (95%CI)	Z (*P* value)	Heterogeneity of study design		
					χ^2	Df (*P* value)	I^2
HTN	Study design						
	Prospective	[11,18-20,25,26]	2.38 (1.46-3.87)	3.49 (0.000)	13.62	5 (0.018)	63.30%
	Retrospective	[20,21]	0.74 (0.16-3.33)	0.40 (0.690)	2.99	1 (0.084)	66.50%
	Ethnicity						
	Asian	[11,18,19]	1.56 (1.07-2.27)	2.31 (0.021)	1.33	2 (0.514)	0.00%
	Caucasian	[20,21,25,26]	1.96 (0.78-4.92)	1.43 (0.154)	18.69	3 (0.000)	84.00%
	African	[22]	2.21 (0.15-33.50)	0.57 (0.567)	-	-	-
	Treatment duration						
	24 wk	[11,18,19]	1.56 (1.07-2.27)	2.31 (0.021)	1.33	2 (0.514)	0.00%
	48 wk	[20-22,25,26]	2.00 (0.85-4.68)	1.59 (0.112)	18.67	4 (0.001)	78.60%
	Overall	[11,18-22,25,26]	1.90 (1.15-3.15)	2.50 (0.013)	23.82	7 (0.001)	70.60%

HTN: Hypertension; -: Could not be calculated.

manifestations of IAR[11,18-22,25,26], whereas decreased visual acuity and subjective symptoms were rare. In most patients who have retinopathy, the treatment can safely be continued in close collaboration with an ophthalmologist. However, serious complications, such as a severe decrease in visual acuity due to retinal vein occlusion and vitreous hemorrhage, have been reported in some cases[31-33], especially in individuals with risk factors for retinopathy. Patients with retinopathy were reported to drop out of IFN treatment in all the included studies. The present study examined the association between hypertension, DM, HCV genotype, type of IFN, and risk of IAR in CHC patients receiving IFN therapy.

Our meta-analysis revealed that the risk of IAR in CHC patients with hypertension was elevated 1.90-fold, as compared with that in CHC patients without hypertension, even when any individual study was removed. However, significant heterogeneity was found among the included studies. The subgroup analysis by study design suggested that the two retrospective studies[20,21] underestimated the incidence of IAR, because these studies did not include appropriate eye examinations. One of the two studies[20] described the performance of the ophthalmic examinations within 12 and 24 wk of initiation of therapy. Another limitation of the study was that patients who did not undergo follow-up evaluations after their eye examinations were not actively pursued. The other study[21] conducted ophthalmic examinations only when the patients complained of symptoms. However, retinopathy occurred in most patients, which was often asymptomatic.

As stated previously, the prevalence of chronic hepatitis is higher in Asia, including South Korea and Japan, than in Europe or the United States[18]. Additionally, it appears that there may be geographic differences in the incidence of IAR[34]. Therefore, we stratified the included studies by ethnicity to evaluate the effect of ethnicity on the incidence of IAR among CHC patients with or without hypertension. The results showed that the association between hypertension and IAR was significant in Asians but not in Caucasians or Africans. This result may be attributed to the limited number of studies. Only a single study was performed on Africans, thus, the subgroup analysis on ethnicity might not have been reliable for the African population. Additional studies based on African patients should therefore be performed to re-evaluate the association between hypertension and risk of IAR in this population. According to the results of the subgroup analysis by treatment duration, the association between hypertension and IAR was significant in patients who were treated for 24 wk, but not in those treated for 48 wk. However, the only studies including patients who were treated for 24 wk were conducted on Asian patients. Therefore, the effect of treatment duration on IAR incidence could not be determined. The subgroup analyses revealed that the substantial heterogeneity might be due to the studies performed in non-Asian populations. Taken together, our results suggest that hypertension was associated with a significantly increased risk of IAR in CHC patients.

Six studies compared the incidence of IAR among CHC patients with or without DM. However, the number of patients with DM in three[18-20] of the six studies was too small. The pooled results revealed that CHC patients with DM have a significantly high risk of IAR. When several small studies were removed, the high risk of IAR in CHC patients with DM remained very significant. However, the overall trend was altered when the study of Kawano *et al*[11] was excluded. These results suggest that the outcome is not credible, therefore, the analyses should be reinvestigated in the future.

Additionally, our meta-analysis revealed that PIFN did not increase the incidence of IAR compared to IFN, which was different from the results of d'Alteroche *et al*[25]. Further studies are needed to identify the underlying cause of this inconsistency. This result may help us to exclude the influence of the different types of IFN used in each study on the incidence of IAR in patients with hypertension or DM. We also found that HCV genotype had no effect on the development of IAR. However, we cannot exclude the effect of patient age on IAR incidence among patients with hypertension or DM, due to a lack

of data.

IAR likely occurs due to disturbances in retinal microcirculation[35]. Guyer *et al*[36] speculated that IFN therapy may cause deposition of immune complexes in the retinal vasculature; this leads to leukocyte infiltration with subsequent retinal ischemia, which then leads to capillary non-perfusion, retinal hemorrhage, and cotton-wool spot formation. An ischemic insult, similar to that observed in patients with hypertension and diabetes, could be regarded as a potential mechanism. Therefore, previous retinal arteriole and venule anomalies may constitute susceptibility to retinopathy. Endothelial cells are known to play an important role in microcirculation[11]. There is evidence that IFN inhibits the proliferation and migration of vascular endothelial cells *in vitro* and inhibits experimental intraocular neovascularization[37,38]. Additionally, studies[30,39] have demonstrated high circulating levels of plasma-activated complement component 5 (C5a), which is a potent intravascular aggregator of granulocytes in patients receiving IFN therapy for hepatitis C. Complement activity associated with high C5a levels may cause retinal capillary infarction, manifesting as capillary non-perfusion, cotton-wool spots, and retinal hemorrhage. Compared with each individual factor, a combination of these factors may lead to greater effects during IFN α therapy.

Our study showed that patients with hypertension were at particular risk for developing retinopathy during IFN therapy, and this is most likely related to the pre-existing disturbances in their retinal microcirculation. Chronic hypertension is associated with thickening of the arterial and small arteriolar walls[40]. Therefore, systemic hypertension predisposes patients to IAR. The fact that hypertensive retinopathy induces the formation of flame-shaped hemorrhage and white cotton-wool spots, which are also observed in IAR, indicates that systemic hypertension and IAR may be related to each other. Consequently, in these high-risk patients, severe retinal damage carries a risk of visual loss; thus, ophthalmic evaluations should be recommended prior to and during IFN therapy.

There were several limitations to this study. First, heterogeneity and confounding factors, such as patient age and response to chemotherapy, might have affected our meta-analysis. However, we are unable to account for these differences because of a lack of data. Second, we primarily studied the risk of IAR in CHC patients with DM in this meta-analysis. However, the association between DM and IAR in CHC patients remains unclear, owing to the limited data available in published studies. Therefore, further studies should be conducted to assess the association between DM and IAR in CHC patients. Finally, the effect of different antihypertensive drugs and the compliance of patients on IAR could not be evaluated in the current study due to the lack of data. In our meta-analysis, although some of the included studies indicated that hypertension and DM were well controlled, others did not provide the related information.

In conclusion, our meta-analysis suggests that patients with hypertension are more susceptible to the development of retinopathy. The influence of ethnicity and treatment duration on the incidence of IAR among CHC patients with or without hypertension should be re-evaluated. Moreover, further studies are needed to clarify the association between DM and IAR in patients with CHC.

COMMENTS

Background

Retinopathy is an adverse effect of interferon (IFN)-based therapy for chronic hepatitis C (CHC) infection; cotton wool spots and retinal hemorrhage are the most common manifestations of interferon-associated retinopathy (IAR). Some studies have suggested that hypertension and diabetes mellitus (DM) are possible risk factors for IAR, and others have not identified these risk factors. Therefore, the question of whether ophthalmic screening should be recommended for CHC patients with hypertension or DM before, during, and after treatment is controversial.

Research frontiers

Over the past two decades, many studies have been performed to identify the possible risk factors for retinopathy in patients with CHC undergoing antiviral therapy with IFN α and/or pegylated IFN (PIFN) α. These studies aimed to determine whether ophthalmic screening should be recommended for CHC patients with hypertension or DM before, during, and after treatment.

Innovations and breakthroughs

Discordant results have been reported regarding the influence of hypertension and DM on the development of IAR. To address this issue, authors performed a meta-analysis of studies that assessed the association of hypertension and/or DM with IAR risk among CHC patients. Authors showed that patients with hypertension are at higher risk for developing retinopathy when receiving IFN-based therapy for CHC infection. However, further studies are needed to clarify the association between DM and IAR.

Applications

This study provides a theoretical basis for determining whether ophthalmic screening should be recommended for CHC patients with hypertension or DM before, during, and after treatment.

Terminology

IAR is an adverse effect caused by the use of IFN, which manifests as cotton-wool spots and petechiae of the retina, perfusion abnormalities in the capillary system, microaneurysms, and retinal vein occlusion. Clinically, decreased visual acuity and subjective symptoms are rare. By contrast, in some case reports, cotton-wool spots (indicating a precapillary arteriolar occlusion) were symptomatic or were associated with other symptomatic ischemic signs of retinopathy, such as papilledema, retinal artery occlusion, and retinal vein thrombosis, and were sometimes responsible for a definitive decrease in visual acuity.

Peer review

This meta-analysis aimed to assess the association of hypertension and/or DM with IAR risk among CHC patients. The results are interesting and the issue is important. The authors found that patients with hypertension, but not those with DM, are at higher risk for developing retinopathy when receiving IFN-based therapy for CHC infection. This study was the first meta-analysis of relevant studies to examine retinopathy in patients with hypertension, and the results will be helpful for determining whether an ophthalmic screening should be recommended for CHC patients with hypertension or DM before, during, and after treatment.

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