

## ◆ MANUSCRITO ORIGINAL

# A meta-analysis of patients with chronic hepatitis C treated with interferon-alpha to determine the risk of autoimmune thyroiditis

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## Summary

**Objective.** In order to analyze the effect on autoimmune thyroiditis (AT) of current anti-hepatitis C virus (HCV) treatment in HCV-infected patients, we performed a systematic review with meta-analysis of the available literature. The present meta-analysis was conducted to evaluate the strength and the consistency of the association between treatments with interferon-alpha (IFN- $\alpha$ ) for HCV infection and AT. **Material and methods.** A search in Medline, PubMed, and EMBASE was conducted with a systematic review of clinical studies in English and other languages. Only studies in HCV subjects compared to a control group with hepatitis B (positive HBsAg) were considered. The relative risk (RR) of AT was regarded as the most reliable outcome end-point. The pooled odds ratio (OR) and 95% confidence intervals (95% CI) were calculated from the raw study data using the Mantel-Haenszel methods. We used a statistical evaluation of heterogeneity by the  $\chi^2$ -test to assess whether the variation in treatment effect within trials of the same group was greater than it might be expected. **Results.** We identified 35 clinical trials with a total of 6,403 patients. Five trials were selected for analysis involving a total of 625 patients with hepatitis C treatment with IFN- $\alpha$  and 456 HBsAg-positive controls. These studies yielded a combined adjusted OR of 4.98 (95% IC 1.56-15.91). The test for heterogeneity was significant ( $P = 0.0008$ ), and the test for overall effect was Z statistic 2.71 ( $P = 0.007$ ). **Conclusion.** Our meta-analysis

indicates that treatment with IFN- $\alpha$  for HCV infection has an increased risk of AT.

**Key words.** Hepatitis C virus, hepatitis B virus, thyroid, autoimmunity, interferon-alpha, meta-analysis.

## Un meta-análisis de pacientes con hepatitis C crónica tratados con interferón-alfa para determinar el riesgo de tiroiditis autoinmune

### Resumen

**Objetivo.** Con el fin de analizar el efecto del tratamiento actual del virus de la hepatitis C (HCV) sobre la tiroiditis autoinmune (TA), se realizó una revisión sistemática de la literatura disponible con un meta-análisis. El presente meta-análisis se realizó para evaluar la fuerza y la coherencia de la asociación entre el tratamiento con interferón-alfa (IFN- $\alpha$ ) para la infección por HCV y de la TA. **Material y métodos.** Se realizó una búsqueda en Medline, PubMed, EMBASE, y se llevó a cabo una revisión sistemática de los estudios clínicos publicados en inglés y otros idiomas. Solo fueron considerados los estudios en sujetos con HCV comparados con un grupo control con hepatitis B (HBsAg positivo). El riesgo relativo (RR) de la TA se consideró como el resultado final más fiable. La odds-ratio (OR) y los intervalos de confianza del 95% (IC 95%) se calcularon a partir de los datos del estudio primario utilizando el método de Mantel-Haenszel. Se utilizó una evaluación estadística de la heterogeneidad con una prueba de  $\chi^2$  para evaluar si la variación del efecto del tratamiento en los ensayos de un mismo grupo fue mayor de lo que cabría esperar. **Resultados.** Se

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*identificaron 35 ensayos clínicos con un total de 6.403 pacientes. Cinco ensayos fueron seleccionados para el análisis con un total de 625 pacientes con tratamiento de la hepatitis C con IFN- $\alpha$  y 456 controles HbsAg positivos. Estos estudios arrojaron una OR ajustada combinada de 4,98 (IC 95% 1,56-15,91). La prueba de heterogeneidad fue significativa ( $P = 0,0008$ ) y la prueba para el efecto global tuvo estadística Z 2,71 ( $P = 0,007$ ). **Conclusión.** Nuestro meta-análisis indica que el tratamiento con IFN- $\alpha$  para la infección por HCV tiene un riesgo mayor de desarrollar TA.*

**Palabras claves.** Virus de la hepatitis C, virus de la hepatitis B, tiroides, autoinmunidad, interferón-alfa, meta-análisis.

Hepatitis C virus (HCV) is an RNA virus belonging to the family of *flavivirus*. HCV is a hepatotropic virus and causes hepatitis, liver cirrhosis, and hepatocellular carcinoma.<sup>1</sup> Approximately between 170 and 240 million people are infected with HCV worldwide, making this virus a major public health problem.<sup>2,3</sup>

HCV is one of the viruses that have been gaining interest as a potential trigger of autoimmune thyroiditis (AT) in individuals having genetic predisposing factors.<sup>4</sup>

Interferon-alpha (IFN- $\alpha$ ) based treatments are widely used for the treatment of chronic viral infections. Data support the pathogenic potential of IFN- $\alpha$  in autoimmunity, although it is clear that genetic and environmental factors are also important to the development of autoimmune conditions.<sup>5</sup>

Current practice guidelines recommend that individuals chronically infected with HCV be treated with pegylated IFN- $\alpha$  plus ribavirin (RBV).<sup>6</sup> IFN- $\alpha$  treatment for HCV is associated with the etiology of thyroid disorders, especially thyroid autoimmune disorders, and has been asserted on the grounds of epidemiology.<sup>7</sup>

The present meta-analysis was conducted to evaluate the strength and consistency of the association between the treatment with IFN- $\alpha$  for chronic HCV infection and AT.

## Material and methods

### Data collection

We performed a systematic review with meta-analysis of the available literature to identify the re-

levant articles with data on the association between AT and HCV treatment with IFN- $\alpha$ .

Searches in MEDLINE (National Library of Medicine, Bethesda, MD, USA) and EMBASE (Elsevier, New York, NY, USA) were performed to find articles reporting HCV and AT association between January 1<sup>st</sup>, 1990 and January 31<sup>th</sup>, 2010. The search strategy was based on MeSH terms used as keys and searching words included "chronic hepatitis C", "hepatitis C virus", "hepatitis B", "interferon-alpha", "thyroid", "thyroid autoimmunity", "thyroid disease" and "thyroiditis". We also checked the reference lists of all available review articles and original studies to identify other studies not found in the primary search.

Studies were included in the meta-analysis if they reported clinical data on the association between HCV treatment with IFN- $\alpha$  as the exposure variable and AT mentioned as the outcome variable.

### Criteria for selection

To assess quality, all collected studies were then evaluated against predetermined criteria. The following selection criteria were applied: both English and other languages clinical studies and only studies comparing HCV subjects to control groups with hepatitis B (positive HBsAg) were considered.

### Data extraction

Data were independently extracted from each study using predefined forms. The following information was extracted: areas where studies were performed, number of cases and controls, mean age of case- and control-groups, type of controls, number of cases and controls for each category of HCV and hepatitis B virus (HBV) infections, odds ratio (OR) and 95% confidence interval (CI) for each category of HCV and HBV infections.

### End-point for analysis

The selected end-point was the development of AT.

### Statistical evaluation

We extracted relative risks (RR) or hazard ratios (HR) from the selected publications and calculated their standard errors from the respective confidence intervals. The pooled OR and 95% CI

were calculated from the raw study data using the Mantel-Haenszel method. We used a statistical evaluation of heterogeneity by  $\chi^2$  test to assess whether the variation in the treatment effect within trials of the same group was greater than it might be expected.<sup>8</sup>

A statistically significant result was assumed when the 95% CI did not include one. Statistical heterogeneity of the trials was evaluated. We performed a sensitivity analysis to assess the stability of conclusions related to assumptions about the probabilities used in the analysis.

Review Manager 5.0 software (The Cochrane Collaboration, Oxford, UK) was used for meta-analysis.

## Results

### Literature search

We identified 346 potentially relevant articles from our search of the published literature (Figure 1). We excluded 311 articles and included 35 clinical trials with a total of 6,403 patients.<sup>9-44</sup> A total of 5 case-control studies satisfied the inclusion crite-

ria, involving a total of 625 patients with HCV infection treated with pegylated IFN- $\alpha$  and 456 HBsAg-postive controls.<sup>11,19,27,28,30</sup>

### Characteristics of Included Trials

Sample size was variable among studies with the smallest having a total sample size of 127 patients<sup>19</sup> and the largest 387 patients.<sup>27</sup> In total, the included trials enrolled 1,084 patients and 160 AT cases were detected, 128 in the 628 treated HCV patients (20.4%) and 32 in the 456 control patients (7%). The results of each study are summarized in Table 1.

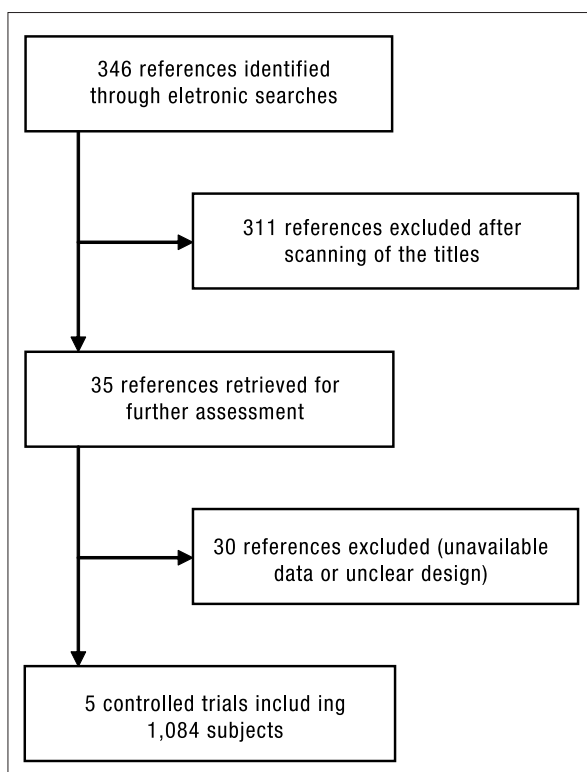
Mean age was 46.6 $\pm$ 8.1 years old for patients with HCV and 42.6 $\pm$ 8.1 years old for control group. There was a male preponderance in the 5 studies. No thyroid abnormality was detected at baseline. Treatment duration was 24 weeks and the end points were assessed at the end of treatment,<sup>11,19,27,28,30</sup> and 6<sup>27,28</sup> to 12 months<sup>11,19</sup> after stopping IFN- $\alpha$  treatment.

**Table 1.** Summary characteristics of studies.

Reference	Hepatitis C		Hepatitis B (control)	
	Total	AT	Total	AT
Deutsch et al 27	211	31	176	22
Fernandez-Soto et al 28	134	27	41	2
Huang et al 30	130	29	130	2
Preziati et al 19	78	33	49	5
Tran et al 11	72	8	60	1

AT: autoimmune thyroiditis

**Figure 1.** Study flow diagram of the search process and inclusion of studies into the review.



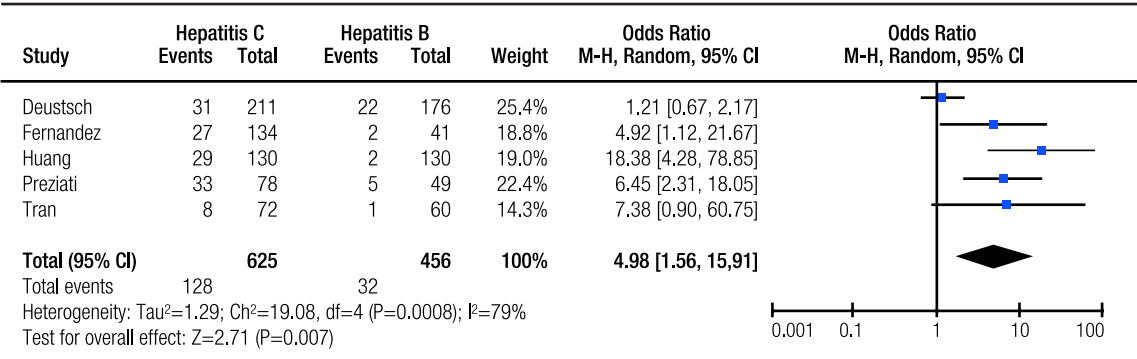
### Summary estimates

#### Risk of thyroid autoimmunity for HCV versus AgHBs+ patients

We tested the heterogeneity of the 5 case-control studies that provided information about prevalence, and the heterogeneity  $\chi^2$  statistics was 19.08 ( $P = 0.0008$ ). Therefore, the pooled estimates were evaluated under a random effects model instead of a fixed effects model. The pooled OR was 4.98 and the 95% CI was 1.56-15.91 ( $P = 0.007$ ) suggesting that AT is associated with the treatment with IFN- $\alpha$  (Figure 2).

Given the largest heterogeneity ( $I^2 = 79\%$ ), we employed a random effects analysis. It indicated an approximately 4.98-fold excess risk of AT among HCV patients treated with IFN- $\alpha$  compared to HBsAg-positive controls.

Figure 2. Study flow diagram of the search process and inclusion of studies into the review.



Discussion

This meta-analysis examined the association of IFN-α with AT in 5 case-control studies compared to HBsAg-positive control group and shows that IFN-α therapy for HCV is associated with an increased risk for AT.

Our study provides evidence supporting that AT is a consequence of IFN-α, with a pooled risk estimate that reveals a fivefold increase in the odds of developing AT after treatment with IFN-α. The current established and accepted treatment for HCV is the combination of pegylated IFN-α plus RBV, and this treatment regimen yields a cure rate of approximately 50% of cases.<sup>45</sup> Several studies of IFN-α-naïve HCV patients did not find a significant correlation between HCV and the presence of thyroid antibodies,<sup>46-48</sup> whereas others found elevated levels of thyroid antibodies in up to 42% of patients.<sup>11,19,28,49</sup> The immune activation triggered by IFN-α does not involve just the virus-specific immune response but a generalized breakout of the immune system, leading to unexpected untoward events in addition to therapeutic effects. Hypothetically, the immune system is sufficiently stimulated in an attempt to eradicate the virus and this process may also be enough to trigger AT. Moreover, potential mechanisms include viral-induced changes in self-antigen expression, molecular mimicry, alterations in the idiotypic network, formation of heat shock proteins and induction of major histocompatibility complex antigens on non-immune cells.<sup>50</sup>

Autoimmune thyroid diseases are the most prevalent autoimmune disorders,<sup>51</sup> affecting up to 5% of the general population.<sup>52</sup> In this study, there was a trend toward greater risk for new-onset AT compared with control group, implying that the risk is

in part related to the medication itself. In our study, the prevalence of AT was significantly higher in patients with HCV than in HBsAg-positive controls-.

Tran et al observed clustering of thyroid autoantibodies in female patients with HCV.<sup>11</sup> Moreover, Deutsch et al showed that the male/female ratio in the prevalence of thyroid autoantibodies was significantly lower in HCV patients than in HBsAg-positive patients (1.3 vs. 3.5), and the mean age was higher in females than in males (52 years old vs. 42 years old).<sup>27</sup> These findings, taken together, suggest that elderly female patients with HCV are at a particularly higher risk of developing thyroid abnormalities and raise the possibility that HCV triggers the appearance of autoimmune thyroid disease in a population already susceptible for autoimmune disorders.

Different immune manifestations might occur at different times of observation. The follow-up duration of studies reached the end-of-treatment or 6 to 12 months after the end-of-treatment. This last duration might account for the increase of thyroid dysfunction.<sup>11,27</sup> The duration of follow-up seems to influence the prevalence of AT on IFN-α treated patients. Regarding our results, the AT seems to have more severe consequences and longer evolution, pointing out the importance of the early detection in order to adapt the follow-up of thyroid function and the therapy without discontinuing the antiviral treatment.

It has been argued that virus-related factors, especially HCV itself, may predispose to the development of thyroid autoimmune disease.<sup>53</sup> The prevalence of AT in patients with HCV differs from that in HBsAg-positive patients before treatment, at the end-of-treatment, and 6 to 12 months after stop-



ping treatment.<sup>28</sup> In our study AT was found in 20% of patients with HCV and in 5% of HBsAg-positive patients, showing that IFN- $\alpha$  treatment may be associated with the virologic features of HCV in the development of this disease.

We conclude that HCV patients treated with IFN- $\alpha$  are more susceptible to develop AT than HBsAg-positive patients. Systematic screening of thyroid gland function and autoimmune thyroid disease in all HCV patients, before, during and after IFN- $\alpha$  therapy, appears to be necessary. This precaution is not necessary for HBsAg-positive patients.

**Conflict of interest.** *The authors declare that there is no conflict of interest that could be detrimental to the impartiality of this scientific work.*

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