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Research paper

Influence of *IL10* Gene polymorphisms on the sustained virologic response of patients with chronic hepatitis C to PEG-interferon/ribavirin therapy

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ABSTRACT

There are accurate but inconclusive data on the association of interleukin (IL) 10 polymorphisms with sustained virological response (SVR) in chronic hepatitis C (CHC). This meta-analysis aimed to derive a more precise estimation of the effects of *IL10* gene polymorphisms (-1082G/A, -819C/T, -592C/A) and their haplotypes on SVR in CHC patients receiving pegylated interferon alpha (PEG-IFN-a) plus ribavirin. Literature search was conducted up to Jan., 2016, in PubMed, EMBASE and ISI Web of Science electronic databases. Statistical analyses were performed by STATA11.0 software, with odds ratios (ORs) and their 95% confidence intervals (CIs). A total of 14 studies involving 1687 CHC cases met the inclusion criteria. Analyses were stratified either by ethnicity or genotype of hepatitis C virus (HCV). The results indicated that *IL10*-1082A/G was associated with a significantly decreased SVR rate based on the heterozygous model (OR: 0.662, 95% CI: 0.467–0.938) and dominant model (OR: 0.648, 95% CI: 0.440–0.955). Similar results were found in the Egyptian and HCV-4 genotype in all gene models except the recessive model. Moreover, we observed that *IL10*-819T allele carriers was associated with a significantly increased SVR in the Caucasian population (OR: 1.380, 95% CI: 1.018–1.871). However, we did not detect any significant association of the -592C/A polymorphism or haplotypes with SVR in the total or subgroup populations. In conclusion, *IL10*-1082GG genotype and -1082G allele were associated with decreased SVR rate in CHC patients, especially for the Egyptian and HCV-4 genotype. Moreover, *IL10*-819T allele was more likely to get SVR in the Caucasian population.

1. Introduction

Hepatitis C is a global health problem and there were 120–180 million hepatitis C virus (HCV) carriers worldwide, with worldwide prevalence estimated at 3% (Shepard et al., 2005). The combination of pegylated interferon (PEG-IFN) plus ribavirin is well accepted as the standard of care for chronic hepatitis C (CHC) (Mutimer et al., 2011; McHutchison et al., 2009). Nevertheless, only 50–60% of treated patients achieve a sustained virologic response (SVR). Moreover, this treatment is long and costly, and is associated with significant adverse effects (Manns et al., 2001; Fried et al., 2002). For these reasons, identification of the determinants of response to therapy is a high priority.

Several viral and host factors have been implicated in the course of HCV infection and the response to IFN-based therapy (Rehermann, 2000). Recently, polymorphisms in genes that potentially play a key role in regulating antiviral immune responses have also been identified to exert some efforts on the response to antiviral therapy in CHC patients (Shaker and Sadik, 2012; Edwards-Smith et al., 1999; Yee et al., 2001).

The cytokine interleukin 10 (IL10) is mainly produced by type-2 helper T (Th2) cells, activated T cells, monotypes/macrophages as well as regulatory T cells. It is a multifunctional cytokine with potent immunoregulatory and anti-inflammatory properties (Moore et al., 2001). Recent evidence suggests that IL10 has the ability to downregulate the release and function of a number of Th1 pro-inflammatory cytokines, such as tumour necrosis factor-a (TNF-α) and IFN-γ, which are key factors in host defence against HCV infection (Höhler et al., 1998; Zein et al., 2004). An imbalance in Th1 and Th2 cytokines may influence the clinical outcome and the progression of HCV infection (Bouzgarrou et al., 2009). Moreover, previous studies have also indicated that excessive IL10 production has been correlated with poor response to interferon therapy (Shaker and Sadik, 2012; Sadik et al., 2015; Gao et al., 2004).

Abbreviations: CHC, chronic hepatitis C; CI, confidence intervals; HCV, hepatitis C virus; HWE, Hardy–Weinberg equilibrium; IL10, interleukin 10; OR, odds ratio; PEG-IFN-a, pegylated interferon alpha; SNPs, single-nucleotide polymorphisms; SVR, sustained virological response; Th2, type-2 helper T cells.

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These findings indicated that IL10 may be an important mediator in the antiviral therapy of CHC patients.

The important anti-inflammatory and immunoregulatory action of IL10 is determined largely by the amount of IL10 produced in response to infection (Koziel MJ., 1999). Previous studies indicated that biallelic polymorphisms in the promoter region determine gene expression and were associated with differential IL10 production in human (Edwards-Smith et al., 1999; Turner et al., 1997). This means that these single nucleotide polymorphisms (SNPs) may influence IL10-mediated inflammatory response in the antiviral therapy of CHC patients.

A series of epidemiological studies have evaluated the implications of *IL10* gene promoter polymorphisms (-1082A/G, -819C/T, -592C/A) in the SVR in CHC patients. However, results have been inconsistent. For instance, some studies indicated that patients with the low IL10 production genotypes had a lower SVR rate in CHC patients (Shaker and Sadik, 2012; Edwards-Smith et al., 1999; Yee et al., 2001; Sadik et al., 2015; Shaker et al., 2015; Morgan et al., 2008), whereas other studies did not observe any associations of these SNPs with the outcome of antiviral therapy (Pasha et al., 2013; Dogra et al., 2011; Abbas et al., 2009; Chuang et al., 2009; Mao and Yue, 2006; Mangia et al., 2004; Constantini et al., 2002). Interestingly, Knapp et al. (2003) reported that individuals with the high IL10 production genotypes (-1082GG and GCC haplotype) were more likely to response to interferon therapy. The discrepancy may be due to the limitations of individual case-control studies in sample size, particularly with regard to discrepancies in the ethnicity, geographical region and the characteristics of the participants.

In the present study, our meta-analysis from all eligible studies was aimed to derive a more precise estimation of the effects of *IL10* SNPs locus (-1082G/A, -819C/T, -592C/A) and their haplotypes on SVR in CHC patients receiving pegylated interferon alpha (PEG-IFN-a) plus ribavirin.

2. Materials and methods

2.1. Search strategy

An electronic search was conducted on Medline, PubMed, EMBASE, and ISI Web of Science electronic databases (last search update: January 31, 2016). The search terms"(IL-10, IL10, interleukin 10) and (gene or polymorphism or variants or alleles or mutation) and (hepatitis C or HCV)" were used to retrieve articles. The references reporting the genetic variation of *IL10* and SVR of PEG-IFN-a plus ribavirin treatment in patients with HCV mono-infection were identified. Additionally, the reference lists of relevant original studies and review articles were also screened to identify additional studies. No language restrictions were applied. Conference abstracts were also included if sufficient data were reported. Where there were repeated publications with the same subjects, the most complete and recent results were included.

2.2. Selection criteria

Studies were included in our analysis if they evaluated the association of SVR after PEG-IFN-a plus ribavirin therapy with the *IL10*-1082A/G, -819C/T, -592C/A polymorphisms and *IL10* (-1082, -819, -592) haplotype in treated patients with chronic HCV mono-infection. Sufficient available data could be extracted to assess the odds ratios (ORs) with 95% confidence intervals (CIs). Exclusion criteria were enrollment of patients co-infected with human immunodeficiency virus, HCV-infected liver transplant recipients, other antiviral therapies involved (including Telaprevir). The study that genotypes distribution in the control group did not conform to Hardy–Weinberg equilibrium (HWE) ($P > 0.05$) was excluded.

2.3. Definitions

SVR was absence of detectable HCV-RNA levels 24 weeks after cessation of treatment. Non-responders were patients whose HCV-RNA levels remained detectable at the end of treatment. Those who had undetectable levels of HCV-RNA at the end of treatment, but detectable HCV-RNA levels at 24 weeks after cessation of treatment were called "relapsers". Both the non-responders and relapsers were categorized as non-viral response (NVR).

2.4. Data extraction

Data was extracted independently by two investigators according to the standard protocol. Discrepancies were resolved by discussion with our research team or consulting with a third reviewer. From each study, the following information was abstracted: first author's name; year of publication; geographical location; HCV genotypes; DNA extraction and genotyping method; the numbers of SVR and non-SVR; and the frequency of available genotypes or haplotypes. Different ethnicity descents were categorized as Caucasian, Egyptian and Asian. Authors were contacted to provide Supplemental data, if data were not available in the relevant articles. When studies included subjects of more than one ethnicity, genotype data were extracted separately.

2.5. Statistical analysis

The pooled ORs with corresponding 95% CI were calculated to assess the strength of association of SVR with *IL10* SNPs in patients with chronic HCV mono-infection. Considering the possible sources of heterogeneity, the studies were stratified by ethnicity and HCV genotype, and the analysis was repeated separately for each group.

The heterogeneity of between-studies was estimated with Q-test, and a p value of <0.1was considered to be representative of statistically significant heterogeneity. The I^2 statistic describes the proportion of total variation contributed by heterogeneity (Higgins et al., 2003). If the I^2 was <50%, or the p value was >0.1, a fixed-effect model was used for meta-analysis. Otherwise, a random-effect model was used. The significance of the pooled ORs was determined by the Z-test, and $P < 0.05$ was considered as statistically significant. Furthermore, sensitivity analyses were performed to assess the stability of the results (Tobias, 1999). A forest plot and funnel plot were used to examine the overall effect and to assess the publication bias, respectively. Egger's linear regression test was used to further assess the funnel plot asymmetry, and $P < 0.05$ was defined as statistically significant (Egger et al., 1997).

All P-values were two-sided. The statistical analysis was performed using the statistical software Intercooled Stata version 11.0 for Windows (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Studies selection process and characteristics

Based on the literature search strategy, we obtained a total of 241 results. 205 studies were excluded after the review of title and abstract: of which 194 studies did not focus on the association of cytokine genes polymorphisms with the outcome of PEG-IFN-a plus ribavirin therapy in CHC patients, 6 studies were review articles, and the rest 5 studies were not performed on the *IL10* gene polymorphisms. Following a careful full text review, 22 additional studies were excluded: 5 studies were not performed on *IL10* gene polymorphisms, 11 focused on the association of *IL10* gene polymorphisms with the susceptibility to HCV infection and HCV spontaneous clearance, one was performed on other *IL10* gene polymorphisms, and the remaining 5 studies did not provide sufficient genotypes or haplotype data. Checking the references of the retrieved publications and the review articles did not reveal any additional papers. Therefore, a total of 14 studies involving a total number of 1687 CHC patients were included in the current meta-analysis (Shaker and Sadik, 2012; Edwards-Smith et al., 1999; Yee et al., 2001; Sadik et al., 2015; Shaker et al., 2015; Morgan et al., 2008; Pasha et al.,