Interleukin-10-1082G/A polymorphism and acute liver graft rejection: A meta-analysis

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Abstract

AIM: To investigate the association between interleukin (IL)-10-1082 (G/A) promoter polymorphism and acute rejection (AR) in liver transplant (LT) recipients.

METHODS: Two investigators independently searched the Medline, Embase, China National Knowledge Infrastructure, and Chinese Biomedicine Databases. Summary odds ratios (ORs) and 95% CIs for IL-10-1082 G/A polymorphism and AR were calculated in a fixed- and a random-effects model as appropriate.

RESULTS: This meta-analysis included seven case-control studies, which comprised 652 cases of LT recipients in which 241 cases developed AR and 411 cases did not develop AR. Overall, the variant A allele was not associated with AR risk when compared with the wild-type G allele (OR = 0.94, 95% CI: 0.64-1.39). Moreover, similar results were observed when the AA genotype was compared with the AG/GG genotype (OR = 1.05, 95% CI: 0.55-2.02). When stratifying for ethnicity, no significant association was observed among either Caucasians or Asians. Because only one study was performed in Asian patients, the result of subgroup analysis by ethnicity would not be reliable for Asians. Limiting the analysis to the studies with controls in the Hardy-Weinberg equilibrium, the results were persistent and robust. No publication bias was found in the present study.

CONCLUSION: This meta-analysis suggests that IL-10-1082 G/A polymorphism may not be associated with AR risk in LT recipients among Caucasians.

Key words: Liver transplantation; Acute rejection; Interleukin-10; Gene polymorphism; Meta-analysis

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INTRODUCTION

Liver transplantation is regarded as an effective therapeutic option for end-stage liver disease as survival after liver transplantation has dramatically improved during...
the last two decades. Despite this success, graft dysfunction occurs in up to 13% of the patients during the first year after transplantation and rises to 35% in 5 years[12,3]. Acute rejection (AR) and recurrence of disease are two major immunological complications, which may lead to graft dysfunction. The inflammatory microenvironment within the graft may play a role in the precipitation of rejection[13], although the underlying mechanisms involved in such events remain unclear. A network of short-acting cytokines and growth factors in turn determines this environment. Cytokines have a central role in the immunologic events that occur after transplantation and are intimately implicated in graft rejection.

Interleukin-10 (IL-10), whose encoding gene is located on chromosome 1 (1q31-1q32), is an immunoregulatory cytokine produced by Th2 cells, monocytes/macrophages, and regulatory T cells, and is capable of downregulating T-cell activation and major histocompatibility complex expression on antigen-presenting cells in vitro[14]. Previous studies have suggested that IL-10 mRNA levels are increased just before a rejection episode[15]. The production of cytokines (including IL-10) is under genetic control and varies among individuals as a function of polymorphisms within the regulatory regions of the various genes that determine the transcriptional activation[16-19]. The promoter of the IL-10 gene contains three biallelic polymorphisms at positions -1082 (base G to A, dbSNP no. rs1800896), -819 (base C to T, dbSNP no. rs1800871), and -592 (base C to A, dbSNP no. rs1800872) from the transcription start site, and these influence the capacity of cells to produce IL-10[18]. For example, the G-to-A polymorphism at position -1082 of the IL-10 promoter reduces IL-10 production[1]. Alloimmune responses and variations in susceptibility to rejection may be influenced by individual variations in cytokine genes. Associations between cytokine gene polymorphisms and rejection of kidney[11,12], heart[18], and lung[14] have been reported.

Over the last two decades, a number of studies have assessed the association between the IL-10-1082 (G/A) promoter polymorphism and AR in liver transplant (LT) recipients in different populations; however, the results are inconsistent and inconclusive[16-22]. In 2005, Warlé et al[2] published findings from a meta-analysis of the IL-10-1082 (G/A) polymorphism and AR risk in LT recipients (based on five studies). The pooled results by Warlé et al[2] suggested that the IL-10 polymorphism at position -1082 was a genetic risk factor for acute liver graft rejection, and that LT recipients carrying the IL-10-1082 A allele displayed a lower rejection rate. However, this manuscript had some limitations mainly due to the small sample size and data retrieval. In order to derive a more comprehensive estimation of the association between IL-10-1082 polymorphism and AR risk in LT recipients, we conducted a meta-analysis to re-evaluate the association.

MATERIALS AND METHODS

Literature search strategy
We searched the PubMed, Embase, CNKI (China National Knowledge Infrastructure) and Chinese Biomedicine databases for all articles on the association between IL-10 polymorphisms and AR risk in LT recipients (last search update 20th March 2011). The following key words were used: “interleukin-10” or “IL-10”; “acute rejection” or “early graft rejection”; “liver transplantation”. The search was performed without restriction on language, but conducted on human subjects. The reference lists of reviews and retrieved articles were hand searched at the same time. We did not consider abstracts or unpublished reports. If more than one article was published by the same author using the same case series, we selected the study where the most individuals were investigated.

Inclusion and exclusion criteria
We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) evaluation of the association between IL-10-1082 G/A polymorphism and AR in LT recipients; (2) a case-control or cohort design; and (3) sufficient genotype data presented to calculate the odds ratio (OR) with 95% confidence interval (CI). Major reasons for exclusion of studies were: (1) duplicate data; (2) an abstract, comment, review or editorial; and (3) no sufficient data were reported.

Data extraction
Two investigators (Liu F and Li B) extracted information from all eligible publications independently according to the inclusion criteria listed above. Disagreements were resolved by discussion between the two investigators. The following information was collected from each study: first author, year of publication, transplant period, indication for transplantation, patient characteristics (age, gender, etc), definition of AR, immunosuppressive regimen, country of the first or corresponding author, ethnicity, number of AR cases and controls (non-AR), genotyping methods and evidence of Hardy-Weinberg equilibrium (HWE). Ethnicities were categorized as Asian or Caucasian.

Statistical analysis
We first assessed HWE in the controls for each study using the goodness-of-fit test (χ² or Fisher’s exact test) and a P < 0.05 was considered as significant disequilibrium. The strength of the association between AR and the IL-10-1082 G/A polymorphism was estimated using the OR and corresponding 95% CI. For the -1082G/A polymorphism, we estimated the risk of the variant A allele compared with the wild-type G allele, and then evaluated the risk of AA vs (AG + GG) which assumed a recessive effect of the variant A allele. We also carried out the stratified analyses by ethnicity (Caucasians/Asians) and HWE in controls (yes/no).

Both the Cochran Q statistic[24] to test for heterogeneity and the I² statistic to quantify the proportion of the total variation due to heterogeneity[25] were calculated. A P value of more than the nominal level of 0.10 for the Q
RESULTS

Characteristics of studies

There were 59 papers relevant to the search words. Via steps of screening the title and reading the abstract, 10 studies were identified\(^{(15-22,30,31)}\). Of these, three studies were excluded (two did not report the association between IL-10-1082 G/A polymorphism and AR in LT recipients\(^{(15,17)}\); two articles\(^{(22,31)}\) were published by a different first author using the same case series, and we selected the latest study\(^{(22)}\); thus, seven studies\(^{(15,17,22,29)}\) which included 241 AR cases and 411 non-AR cases were found to match our inclusion criteria. The flow chart of selection of studies and reasons for exclusion is presented in Figure 1. Characteristics of studies included in the meta-analysis are presented in Tables 1 and 2.

There were six studies of Caucasian descendents, one study of Asian descendents. Studies had been carried out in China, Turkey, the United States, Netherlands, Israel and the United Kingdom. All studies defined rejection as biopsy-proven episodes of AR during the early post-transplant period (AR within first 4-8 wk), treated with high-dose steroids, except for the study of Karasu et al\(^{(14)}\). Immunosuppressive regimen in all studies consisted of a calcineurin inhibitor (cyclosporin or tacrolimus) and prednisone with or without azathioprine. Mycophenolate mofetil was only used in a subgroup of patients studied by Xie et al\(^{(20)}\) and Mas et al\(^{(3)}\). Most studies extracted DNA from peripheral blood, and only two studies\(^{(25,31)}\) from surgically explant liver tissue from recipients. Several genotyping methods were used, including PCR-RFLP, PCR-SSP, direct sequencing, ARMS-PCR and AS-PCR. The genotype distributions among the controls of all studies were consistent with HWE except for Tambur’s study\(^{(20)}\).

Quantitative synthesis

Overall, the variant A allele was not associated with AR risk when compared with the wild-type G allele (OR\(_{random} = 0.94, 95\% CI: 0.64-1.39, \text{ Heterogeneity} = 0.07\) (Figure 2). When the AA genotype was compared with AG/GG genotype (recessive model), no significant association was observed (OR\(_{random} = 1.05, 95\% CI: 0.55-2.02, \text{ Heterogeneity} = 0.01\) (Figure 3). When stratified for ethnicity, no significant association was observed among either Caucasians or Asians (for Caucasians: A allele \(rs G \) allele, OR\(_{random} = 0.95, 95\% CI: 0.61-1.47, \text{ Heterogeneity} = 0.04; \text{ AA vs AG/GG, OR} = 1.07, 95\% CI: 0.49-2.32, \text{ Heterogeneity} = 0.01; for Asians: A allele \(rs G \) allele, OR\(_{random} = 0.96, 95\% CI: 0.34-2.68; \text{ AA vs AG/GG, OR} = 0.96, 95\% CI: 0.33-2.77). Because only one study was performed in Asian patients, the result of subgroup analysis by ethnicity could not be reliable for Asians.

In Tambur's study, the distribution of IL-10-1082 genotypes among controls was not in HWE. Limiting the analysis to the studies within HWE, the estimated association remained unchanged (A allele \(rs G \) allele, OR\(_{random} = 0.81, 95\% CI: 0.61-1.07, \text{ Heterogeneity} = 0.13; \text{ AA vs AG/GG, OR} = 0.98, 95\% CI: 0.46-2.11, \text{ Heterogeneity} = 0.009). Publication bias

Begg’s funnel plot and Egger’s test were performed to evaluate the publication bias of studies of AR in LT recipients. Figures 4 and 5 display funnel plots that examined the IL-10-1082 polymorphism and overall AR risk included in the meta-analysis. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry. The statistical results did not show publication bias (A allele \(rs G \) allele; Begg’s test \(P = 0.55\), Egger’s test \(P = 0.26\); AA vs AG/GG: Begg’s test \(P = 0.76\), Egger’s test \(P = 0.67\)).

DISCUSSION

In spite of major advances in the field of immunosuppressive therapy, acute hepatic allograft rejection remains an important problem after liver transplantation. Almost 30%-50% of patients experience at least one episode of rejection within the first year\(^{(32)}\). Cytokines, a group

Figure 1 Flow chart of selection of studies and specific reasons for exclusion from the meta-analysis.
of small, soluble, or cell membrane-bound protein or glycoprotein molecules, play an essential role in the regulation of inflammatory and immune responses. Despite the many variables that influence acute rejection, previous reports indicate that cytokine genotypes that result from polymorphisms can sometimes correlate with acute allograft rejection\[13,34\]. Alloimmune responses and variations in susceptibility to rejection may be influenced by individual variations in cytokine genes. An association between susceptibility to graft rejection and polymorphism in cytokine gene promoters in kidney, heart, lung, and bone marrow recipients has been reported by some centers\[14,30\], although others have not confirmed this\[36,38\].

IL-10 is an anti-inflammatory cytokine, which can inhibit the production of tumor necrosis factor-\(\alpha\), IL-1, IL-6, IL-8, and IL-12 in monocytes/macrophages and interferon-\(\gamma\) in T cells\[4\]. Therefore, in the context of allograft rejection, local IL-10 release may have inhibitory properties on macrophages, T cells, and cytokines. However, the role of IL-10 in LT patients remains controversial. For example, some studies have suggested that IL-10 mRNA levels are increased just before a rejection episode\[3\], while others have indicated that IL-10 levels are unchanged during rejection of the LT\[9\]. In animal models, overexpression of IL-10 by gene transfer prolonged graft survival of orthotopic LTs\[40\]. Since some studies\[33,34\] reported that cytokine genotypes that result from polymorphisms can sometimes correlate with acute

### Table 1  Baseline characteristics of studies included in the meta-analysis

| Ref. | Transplant period | Indications for transplantation | Patients characteristics (age, gender) | Definition of acute rejection | Immunosuppression regimens |
|------|-------------------|---------------------------------|----------------------------------------|-------------------------------|---------------------------|
| Bathgate et al\[31\] | 1992-1998 | ALD, PBC, PSC, chronic viral hepatitis, acute liver failure, autoimmune hepatitis, other | Not described | Liver biopsy and treatment with high-dose steroids | CsA/tacrolimus + prednisone + azathioprine |
| Tambur et al\[32\] | Not described | Hepatitis B and/or hepatitis C, PBC, PSC, cryptogenic, other | 20-69 yr, M/F: 32/36 | Liver biopsy (AR within first 6 wk) | CsA/tacrolimus + prednisone with or without azathioprine. |
| Warlé et al\[33\] | 1992-1999 | Hepatitis B, hepatitis C, PBC, PSC, ALD, other | AR group: 47 ± 11 yr, M/F: 22/19 | Liver biopsy and treatment with high-dose steroids (AR within first 4 wk) | CsA/tacrolimus + prednisone with or without azathioprine. |
| Fernandes et al\[34\] | Not described | Not described | 19-73 yr, M/F: 26/27 | Liver biopsy and treatment with high-dose steroids | Tacrolimus + prednisolone |
| Mas et al\[35\] | 1999-2000 | Hepatitis B, Hepatitis C, PSC, HCC, ALD, Cryptogenic, other | 24-60 yr, M/F: 44/33 | Liver biopsy (AR within first 8 wk) | CsA/tacrolimus + steroids + MMF |
| Karasu et al\[36\] | 2002-2003 | Viral, nonviral | AR group: 44.4 ± 12.7 yr, M/F: 17/9 | Treatment with high-dose steroids (AR within first 8 wk) | CsA/tacrolimus + steroids Maintain target therapeutic blood levels of 5-10 ng/mL for tacrolimus |
| Xie et al\[37\] | 2003-2005 | HBV-related cirrhosis, HBV-related HCC, fulminating hepatitis B | AR group: 43.6 ± 9.0 yr, M/F: 35/6 | Liver biopsy (AR within first 4 wk) | CsA/tacrolimus + prednisolone + MMF |

ALD: Alcoholic liver disease; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; HCC: Hepatocellular carcinoma; HBV: Hepatitis B viral; CsA: Cyclosporine A; MMF: Mycophenolate mofetil; AR: Acute rejection.

### Table 2  Characteristics of studies included in the meta-analysis

| Ref. | Country | Ethnicity | No. of case/control | Case | Control | Genotyping methods | HWE in controls |
|------|---------|-----------|---------------------|------|---------|-------------------|----------------|
| Bathgate et al\[31\] | United Kingdom | Caucasian | 68/76 | 16 | 22 | PCR-SSP | Yes |
| Tambur et al\[32\] | Israel | Caucasian | 33/30 | 19 | 14 | PCR-SSP | No |
| Warlé et al\[33\] | Netherlands | Caucasian | 41/48 | 6 | 17 | ARMS-PCR | Yes |
| Fernandes et al\[34\] | United States | Caucasian | 13/40 | 4 | 15 | ARMS-PCR | Yes |
| Mas et al\[35\] | United States | Caucasian | 19/55 | 12 | 43 | DNA-sequencing | Yes |
| Karasu et al\[36\] | Turkey | Caucasian | 26/17 | 12 | 8 | PCR-SSP | Yes |
| Xie et al\[37\] | China | Asian | 41/145 | 36 | 127 | PCR-RFLP | Yes |

PCR-SSP: Polymerase chain reaction and sequence-specific primer typing; ARMS-PCR: Amplification refractory mutation system-polymerase chain reaction; AS-PCR: Allele-specific polymerase chain reaction; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium.
allograft rejection, a number of studies have assessed the association between the IL-10-1082 promoter polymorphism and AR in LT recipients in different populations. However, some of the results were conflicting, even in the same population, and thus a systematic review and meta-analysis of the association between IL-10-1082 G/A polymorphism and AR risk was of great value.

A meta-analysis can overcome some problems caused by a single study, such as small sample size, low test power and selection bias; however, some concerns have to be addressed before aggregating data. First, the definition of AR, as the main outcome measure for this analysis, should be consistent among included studies. In six studies, AR was defined as “early” biopsy-proven AR within the first 4-8 wk after liver transplantation, treated with high-dose steroids. However, Karasu et al defined AR as an increase in liver enzymes in the absence of vascular or biliary problems, associated with an improvement in liver function. Other definitions included treatment with high-dose steroids for normalization of liver function tests, or a combination of both. This heterogeneity in definitions makes it difficult to compare the results from different studies.

### Table: Odds ratios and 95% CI of individual studies and pooled data for the association of the interleukin-10-1082 G/A polymorphism and acute rejection comparing A allele with G allele.

| Study         | OR (95% CI)    | % Weight |
|---------------|----------------|----------|
| Xie et al     | 0.96 (0.34, 2.68) | 9.75     |
| Karasu et al  | 1.08 (0.42, 2.72) | 11.15    |
| Tambur et al  | 1.66 (0.78, 3.51) | 14.32    |
| Bathgate et al| 0.72 (0.45, 1.14) | 21.41    |
| Warlé et al   | 0.48 (0.26, 0.88) | 17.78    |
| Fernandes et al| 0.82 (0.33, 2.01) | 11.61    |
| Mas et al     | 1.92 (0.89, 4.14) | 13.99    |
| Overall       | 0.94 (0.64, 1.39) | 100      |

### Table: Odds ratios and 95% CI of individual studies and pooled data for the association of the interleukin-10-1082 G/A polymorphism and acute rejection comparing AA genotype with AG/GG Genotype.

| Study         | OR (95% CI)    | % Weight |
|---------------|----------------|----------|
| Xie et al     | 0.96 (0.33, 2.77) | 14.37    |
| Tambur et al  | 1.55 (0.57, 4.20) | 15.09    |
| Bathgate et al| 0.76 (0.36, 1.60) | 17.8     |
| Warlé et al   | 0.31 (0.11, 0.89) | 14.53    |
| Fernandes et al| 0.74 (0.19, 2.83) | 11.74    |
| Mas et al     | 6.14 (1.98, 19.03) | 13.69    |
| Karasu et al  | 0.96 (0.28, 3.28) | 12.78    |
| Overall       | 1.05 (0.55, 2.02) | 100      |

### Figure 2: Begg's funnel plot of interleukin-10-1082 G/A polymorphism and acute rejection risk in liver transplant recipients (AA vs AG/GG). OR: Odds ratios.

### Figure 3: Egger's publication bias plot of interleukin-10-1082 G/A polymorphism and acute rejection risk in liver transplant recipients (AA vs AG/GG). OR: Odds ratios.
after treatment by increasing the dose of immunosuppressive drugs or pulse steroid therapy within the first 8 wk. In the overall meta-analysis performed in this study, the number of patients from the Karasu et al study is small, suggesting that this factor probably had little effect on the overall estimates. Moreover, the immunosuppressive regimen among different studies included is also an important factor which should be addressed. All LT patients included in this meta-analysis received more or less the same type of immunosuppression: a calcineurin inhibitor and prednisone, with or without azathioprine. However, there were some differences in the type of induction therapy, dosages and maintenance of target levels in blood, which can provide a possible explanation for significant heterogeneity in a recessive model.

This meta-analysis was based on seven case-control studies and showed that IL-10-1082 G/A polymorphism was not associated with the risk of AR in LT recipients. Our result is not consistent with a previous systemic review. This is probably because the previous meta-analysis had a relatively small sample size (the Warlé et al meta-analysis included only five studies for IL-10-1082 G/A polymorphism and AR risk in LT recipients) and may have generated a very rough risk estimate. The G-to-A polymorphism at position -1082 of the IL-10 promoter reduces IL-10 production, and individuals with the IL-10-1082-GG genotype showed the greatest IL-10 production after in vitro stimulation, whereas IL-10-1082-GA and -AA showed intermediate and low production, respectively. Moreover, previous studies showed that Th2 cytokines, such as IL-10, are associated with graft tolerance. Therefore, it can be deduced that patients with an IL-10 genotype corresponding to low IL-10 production are more susceptible to rejection, whereas the IL-10 genotype corresponding to high production is found mainly among nonrejectors. However, our result is inconsistent with the above hypotheses. This is probably because the notion, derived mainly from animal studies, that IL-10 has a role in human allograft tolerance needs re-evaluation. In addition, since the effect of the IL-10-1082 promoter polymorphism on in vitro and thus in vivo cytokine production is still inconclusive, its biological effect on acute liver graft rejection remains speculative.

As previously described, ethnicity can strongly influence the distribution of cytokine gene polymorphisms. In Caucasian patients, the IL-10 AA genotype at position -1082 occurred in 32.5%, while among Asian patients, it occurred in 88.2%.

In conclusion, this meta-analysis suggests that IL-10 -1082 G/A polymorphism may be not associated with AR risk in LT recipients among Caucasians. Since only one study was from an Asian population, it is critical that larger and well-designed multicenter studies based on Asian patients should be performed to re-evaluate the association.

**COMMENTS**

**Background**

Interleukin (IL)-10 is an anti-inflammatory cytokine, which can inhibit the production of tumor necrosis factor-alpha, IL-1, IL-6, IL-8 and IL-12 in monocytes/
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