pISSN 2508-1357, eISSN 2508-139X
J Biomed Transl Res 2016;17(3):052-057
http://dx.doi.org/10.12729/jbtr.2016.17.3.052
Received 29 Jul. 2016, Revised 29 Aug. 2016, Accepted 1 Sep. 2016

Original article

Interleukin-10 polymorphism (-1082, G/A) on acute rejection risk in solid organ transplant recipients in a Caucasian population: a meta-analysis

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Cytokines may play an important role in the acute rejection (AR) of solid organ transplantation. Many studies have investigated the association between interleukin-10 gene (*IL-10*) polymorphisms and risk of AR. The aim of this study was to determine the relationship between *IL-10* polymorphism (-1082, G/A) and AR risk after solid organ transplantation in Caucasian population. A comprehensive electronic search of PUBMED, Google Scholar, and Korean databases was performed. Meta-analysis was performed using comprehensive meta-analysis software (Biostat, NJ,USA). We assessed the pooled p-value, odds ratio (OR), and 95% confidence interval (CI) to measure the association between the risk of AR and *IL-10* polymorphism (-1082, G/A). The OR and 95% CI were used to evaluate the strength of the association. P-values less than 0.05 were considered statistically significant. Fourteen case-control studies were included in this meta-analysis. In overall analysis, we observed that *IL-10* polymorphism (-1082, G/A) was associated with the AR in liver transplantation (G allele vs. A allele, OR = 1.436, 95% CI = 1.006-2.050, p = 0.046 in fixed model). However, *IL-10* polymorphism (-1082, G/A) did not show any significant association with solid organ transplantation and renal transplantation (p>0.05 in each model, respectively). Our meta-analysis suggests that *IL-10* polymorphism (-1082, G/A) may be related to susceptibility of AR in liver transplantation recipients.

Key words: *IL-10*, polymorphism, acute rejection, meta-analysis, transplantation

Introduction

Despite improvements in surgical techniques and immunosuppressive therapies, acute rejection (AR) remains an important event after solid organ transplantation. Recently, there has been increasing interest in the role of cytokines in the occurrence of AR in solid organ allograft recipients. Cytokines may play an important role in the immunologic events that follow transplantation and therefore, may significantly influence the status of the graft.

Interleukin-10 (*IL-10*) is a cytokine that is produced by many cells, including monocytes, T-helper-2 cells, mastocytes, and a certain subset of activated T cells and B cells [1]. *IL-10* has a key role in suppressing the immune response. It has multiple- and pleiotropic-effects in immune regulation [2, 3]. Emerging evidence showed that the expression of *IL-10* is increased before a rejection episode [4]. It suggested that *IL-10* may be closely correlated with the AR of allograft. In previous studies, relationships between *IL-10* polymorphism (-1082, G/A) and rejection in organs including kidney, heart, and lung were reported. The *IL-10* gene is located on human chromosome 1, which consists of 5 exons. The *IL-10* polymorphism (-1082, G/A) in the promoter region has recently been identified. This polymorphism influences the capacity of cells to reduce *IL-10* production [5].

Up to now, a number of studies have been conducted to evaluate the association between *IL-10* polymorphism (-1082, G/A) and the risk of acute allograft rejection [6-19]. However, the results are conflicting rather than conclusive.

Meta-analysis is used as a statistical tool for combining results from different studies in the same topic and is becoming a popular method for resolving discrepancies in genetic association studies. Meta-analysis in polymorphisms studies is an effective tool in order to understand complex diseases and presentes new insight.

Therefore, we performed a meta-analysis of all eligible case-control studies to clarify the association between *IL-10* polymorphism (-1082, G/A) and risk of AR in solid

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organ allograft recipients in a Caucasian population.

Materials and Methods

Search strategy

In order to identify all eligible studies, a comprehensive electronic search of PUBMED, Google Scholar, and Korean databases was conducted. The following keywords were used to search: *IL-10*, interleukin 10, allograft, transplantation, rejection, polymorphism, polymorphisms, genotype and variant. Additionally, the articles of relevant original studies and review articles were also screened to identify additional studies. No language restrictions were applied.

Inclusion criteria

Studies were included in our meta-analysis if they were designed as case-control studies that evaluated the association between the *IL-10* polymorphism (-1082, G/A) and AR in a Caucasian population. The included studies must also contain a sufficient distribution of the *IL-10* polymorphism (-1082, G/A) in both the AR group and non-AR group in order to calculate an odds ratio (OR), 95% confidence interval (CI), and p-value. The genotypes distribution in the control group was confirmed Hardy–Weinberg equilibrium using the goodness-of-fit test.

Data extraction

We extracted the following data from the included studies. The data included the name of the first author, year of publication, subject population, number of subjects, and genotype frequency of *IL-10* polymorphism (-1082, G/A).

Statistical analysis

Meta-analysis was performed using comprehensive meta-analysis software (Biostat, NJ, USA). The pooled p-value, OR, and corresponding 95% CI were used to assess the strength of association between the risk of AR and *IL-10* polymorphism (-1082, G/A). The significance of the pooled ORs was determined by the Z-test, and P-values <0.05 were considered statistically significant. Considering the possible sources of heterogeneity, the studies were stratified by genotype and the analysis was repeated separately for each group. First, to calculated the heterogeneity, the chi-square-based Q test and I^2 test were applied. The random-effects Mantel–Haenszel method was used when the result of the Q test was $p<0.05$ or the I^2 statistic was >50%. Otherwise, the fixed-effects Mantel–Haenszel method was adopted. To assess potential publication bias, the Egger's weighted regression method was performed.

Results

In order to evaluate the association between *IL-10* polymorphism (-1082, G/A) and susceptibility of AR, we selected a total of eligible 14 articles (Table 1) [6-19].

Table 1. Information of eligible studies included in the meta-analysis

First author	Year	Ethnicity	Transplant organ	AR/non-AR	AR		Non-AR		AR		Non-AR	
					G/G	A/A+A/G	G/G	A/A+A/G	G	A	G	A
Kocierz et al	2011	Caucasian	Renal	143/56	41	102	2	54	135	151	53	69
Grinyo´ et al	2008	Caucasian	Renal	112/108	13	99	33	75	51	71	146	172
Dmitrienko et al	2005	Caucasian	Renal	50/50	14	36	19	31	48	52	58	42
Chen et al	2014	Caucasian	Renal	50/275	14	36	63	212	28	72	126	424
Plothow et al	2003	Caucasian	Renal	39/26	4	35	3	23	26	52	17	35
Hutchings et al	2002	Caucasian	Renal	24/26	2	22	4	22	19	29	21	31
Hahn et al	2000	Caucasian	Renal	32/81	6	26	24	57	26	38	86	86
Pelletier et al	2000	Caucasian	Renal	32/67	9	23	12	55	32	32	53	81
Bathgate et al	2000	Caucasian	Liver	68/76	22	46	16	60	44	92	32	120
Tambur et al	2001	Caucasian	Liver	33/30	4	29	7	23	8	58	14	46
Warle´ et al	2002	Caucasian	Liver	41/48	14	27	9	39	28	54	18	78
Fernandes et al	2002	Caucasian	Liver	13/40	2	11	5	35	4	22	10	70
Mas et al	2004	Caucasian	Liver	19/55	0	19	0	55	0	38	0	110
Karasu et al	2004	Caucasian	Liver	26/17	2	24	2	15	4	48	4	30

AR: acute rejection; non-AR: non acute rejection.

Among 14 articles, the transplant organ types of AR were including renal (8 articles) and liver (6 articles). Table 2 and Fig.1 show the results of the overall meta-analysis of association between *IL-10* polymorphism (-1082, G/A) and susceptibility of AR in allele model (A allele vs. G allele) and dominant model (G/G genotype vs. A/A+A/G genotypes).

In allele model, heterogeneity among studies did not exist (heterogeneity $p>0.05$). Fixed model was applied in meta-analysis. When the G allele of *IL-10* polymorphism (-1082, G/A) was compared with A allele, the overall meta-analysis revealed that G allele did not show any significant association with AR (OR = 1.078, 95% CI = 0.912-1.275, p = 0.378 in fixed model). And G allele of *IL-10* polymorphism (-1082 G/A) were not also associated with AR in renal transplant recipients (OR = 0.994, 95% CI = 0.822-1.202, p = 0.413). However, G allele showed significant association with AR in liver transplant recipients (OR = 1.436, 95% CI = 1.006-2.050, p = 0.046 in fixed model).

In dominant model, heterogeneity among studies exists (heterogeneity $p<0.05$), not AR of liver group (heterogeneity $p>0.05$). Over analysis and analysis of AR in renal transplant recipients were applied with random model, and analysis of liver transplant recipients was applied with fixed model. G/G genotype applied random model did not show any significant association with overall AR (OR = 1.026, 95% CI = 0.629-1.706, p = 0.890). According to organ transplantation, G/G genotype of *IL-10* polymorphism (-1082, G/A) was not associated with AR in renal and liver transplant recipients ($p>0.05$). To identify publication bias in meta-analysis, we evaluated publication bias using Egger's regression. There was no publication bias ($p>0.05$).

Discussion

Acute allograft rejection is thought to be the result from multiple immunological interactions between various cytokines. Genetic polymorphisms may affect individual differences in cytokine activity. Many studies have investigated the role of cytokine gene polymorphisms in solid organ allograft survival. *IL-10* encodes a multifunctional anti-inflammatory cytokine that is involved in immunological activity after organ transplantation [1, 11]. A polymorphism of *IL-10* has been identified at the −1082 on promoter region, which appears to be closely associated with the expression of *IL-10* [5, 20].

Several studies have previously addressed the association between the *IL-10* polymorphism (-1082, G/A) and the risk of acute allograft rejection. However, because of the difference in sample sizes, patient populations, and genetic background, the evidence provided by these studies is insufficient to confirm an association. One meta-analysis that investigated renal allograft outcomes reported that recipient *IL-10* polymorphism (-1082, G/A) was associated with AR. The polymorphism was also associated with increased risk of recurrent AR. However, another meta-analysis investigating renal allograft outcomes demonstrated that this polymorphism was not associated with AR. Therefore, we conducted a meta-analysis including 14 case-control studies to evaluate the association between the *IL-10* polymorphism (-1082, G/A) and the development of acute allograft rejection.

In our study, we examined the association of *IL-10* polymorphism (-1082, G/A) with the risk for AR by meta-analysis. We found that this polymorphism was related to an increased risk of AR in liver transplantation recipients. The G allele of *IL-10* polymorphism (-1082 G/A) showed risk of AR in liver transplantation recipients.

It is important to mention that we identified heterogeneity in some comparisons in our meta-analysis. To get a full and accurate detail of the data, we used a random-effects model or a fixed model. The results were stable after the sensitivity analysis, which did not change the results of the meta-analysis.

This meta-analysis still has some limitations that should be considered when evaluating the results. First, this meta-analysis was a secondary and retrospective study that is limited by the quality of the primary studies. Second,

Table 2. Overall analysis between *IL-10* polymorphism (-1082, G/A) and susceptibility of AR

Organ	Comparison	Heterogeneity		Association test			Egger's regression p
		p	I^2	Model	OR (95% CI)	p	
All	G vs. A	0.062	40.881	Fixed	1.078 (0.912-1.275)	0.378	0.704
Renal	G vs. A	0.345	10.943	Fixed	0.994 (0.822-1.202)	0.949	0.413
Liver	G vs. A	0.055	56.730	Fixed	1.436 (1.006-2.050)	0.046	0.227
All	A/A+A/G vs. G/G	0.001	63.744	Random	1.036 (0.629-1.706)	0.890	0.644
Renal	A/A+A/G vs. G/G	0.001	72.404	Random	0.960 (0.483-1.906)	0.907	0.87
Liver	A/A+A/G vs. G/G	0.328	13.459	Fixed	1.436 (0.868-2.375)	0.159	0.227

AR: acute rejection; OR, odds ratio; CI, confidence interval.

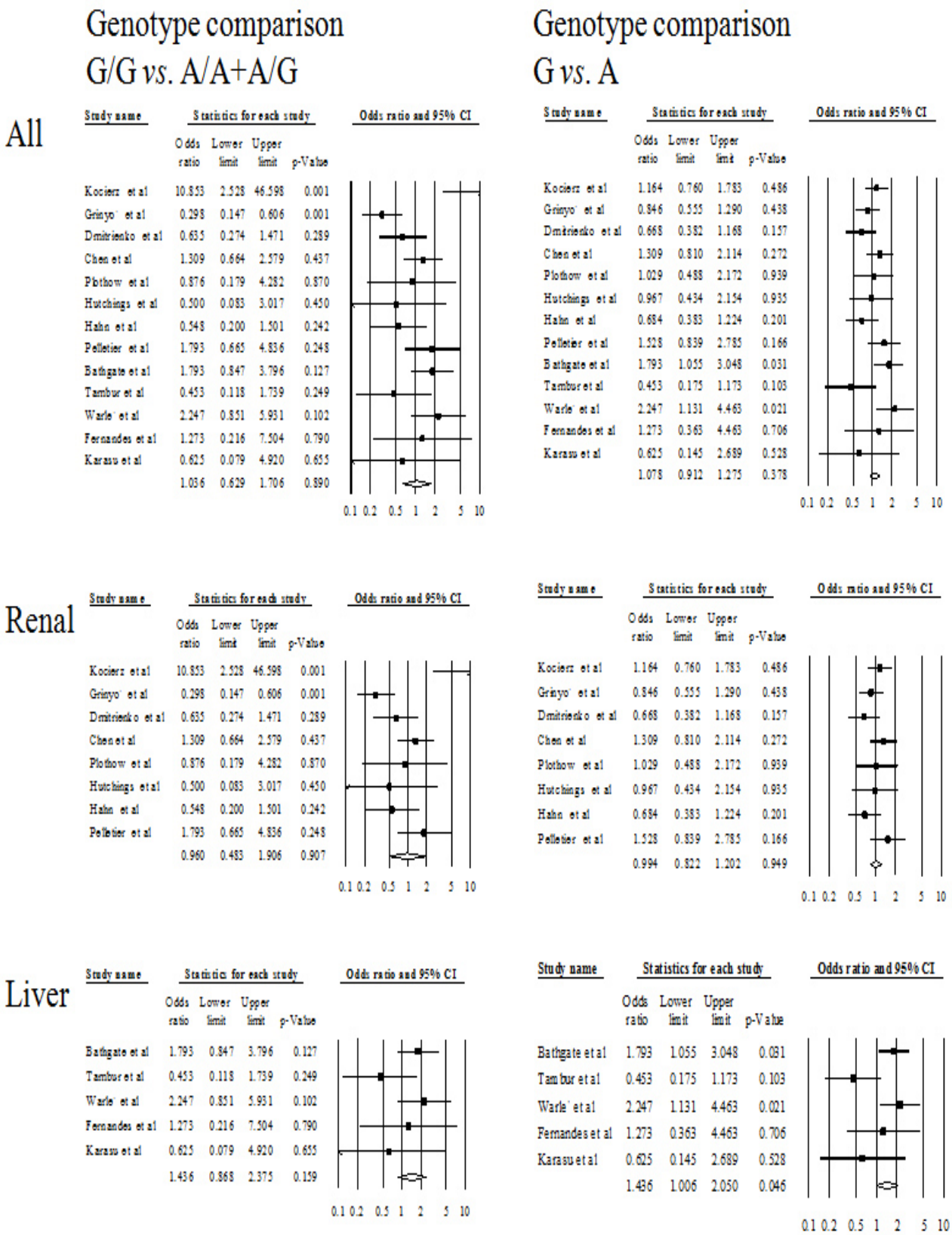

Fig. 1. The results of the overall meta-analysis of association between -*10* polymorphism (-1082 G/A) and susceptibility of AR in allele (G vs. A) model (right figure) and dominant (G/G genotype vs. A/A+A/G genotypes) model (left figure).

we were not able to analyze the gene-gene and gene-environment interactions.

In conclusion, the finding of our meta-analysis suggested that *IL-10* polymorphism (-1082, G/A) may be related to susceptibility of AR in liver transplantation recipients. In the future, larger-scale studies are required to clarify and confirm this association.

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