Systematic Review and Meta-Analysis

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Effect of *MDR1* C1236T polymorphism on cyclosporine pharmacokinetics

A systematic review and meta-analysis

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Abstract

Background: Cyclosporine (CsA) is one of the immunosuppressive drugs, whose pharmacokinetic characteristics vary greatly among individuals. The published data reveal conflicting effects of the polymorphism of *MDR1* exon 12 SNP C1236T on the pharmacokinetics of cyclosporine.

This study aims to conduct a meta-analysis to investigate the effect of SNP C1236T on the pharmacokinetics of cyclosporine.

Methods: A literature retrieval was conducted to find the relevant papers in databases including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wan Fang Database (Wan Fang), Chinese Biomedical Literature Database (CBM), VIP Database for Chinese Technical Periodicals (VIP) electronic source for published studies until January 2017. The pharmacokinetic parameters, including C_0 (trough blood concentration), C_2 (whole-blood levels at 2 hours after drug intake), C_{max} (the maximum concentration), and daily dose were extracted and a meta-analysis was performed by RevMan 5.3.

Results: A total of 11 papers concerning 1361 individuals were included in the meta-analysis. As for dose adjusted C_0, the results showed difference between subjects carrying CC genotypes and TT genotypes (MD: 6.76, 95% CI [2.38, 11.14], $P = .02$]. As for C_2, the results showed significant difference between subjects carrying CC genotypes and CT genotypes (MD: −18.50, 95% CI [−35.49, −1.52], $P = .03$), as well as CC genotypes and TT genotypes (MD: −19.01, 95% CI (−35.85, −2.16), $P = .03$). As for C_{max}, daily dose, and C_0, the overall results showed no major influence.

Conclusions: MDR1 C1236T polymorphism may have a minor effect on cyclosporine pharmacokinetics in transplantation patients.

Abbreviations: C_0 = trough blood concentration, C_2 = whole-blood levels at 2 hours after drug intake, C_{max} = the maximum concentration, CsA = cyclosporine, MDR1 = multidrug resistance gene, SNP = single nucleotide polymorphisms.

Keywords: cyclosporine, *MDR1*, pharmacokinetics, SNP C1236T

1. Introduction

Cyclosporine is a calcineurin inhibitor used to prevent allograft rejection after transplantation, including solid organ transplantation and stem cell transplantation. Since it is characterized by a narrow therapeutic index and drug interactions occur frequently, its pharmacokinetic characteristics vary greatly among individuals, and daily doses must be adjusted to the whole-blood cyclosporine concentration.[1] It is well clinically recognized that cyclosporine response shows significant interindividual variation among transplant patient.[2] Exposure to cyclosporine is known to be closely associated with the acute rejection rate. Clase et al suggested that early adequate exposure to immunosuppressive agents is critical and that failing to reach target concentrations as early as the third postoperative day may result in acute rejection.[3] Researching on the interindividual variability of cyclosporine pharmacokinetics is of critical importance for adjusting dosage to avoid rejection.

Cyclosporine is a substrate of P-glycoprotein (P-gp) and the product of the multidrug resistance gene (*MDR1*, also known as *ABCB1*).[4] P-gp is a transmembrane efflux pump involving energy-dependent export of xenobiotics from inside to outside the plasma membrane.[5] It may affect the absorption, distribution, and excretion of drugs in the body. *MDR1* encodes P-gp and its gene is highly polymorphic. So far, at least 32 single nucleotide polymorphisms (SNP) have been identified.[6] Two synonymous SNPs (C1236T in exon 12 and C3435T in exon 26) and a non-synonymous SNP (G2677T in exon 21) have been found.[2]

Since the initial observation by Anglicheau et al indicated the effect of *MDR1* SNP C1236T expression, many studies have been performed on the influence of SNP C1236T on drug metabolism. However, the results were controversial. Haufroid et al[4]

Editor: Giovanni Tarantino.

This research was funded by Natural Science Foundation of China, evidence-based establishment of evaluation index system for pediatric rational drug use in China (No. 81373381), and program for Yangtze River Scholars and Innovative Research Team in University (No. IRT0935).

The authors declare no conflicts of interest.

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Medicine (2017) 96:47(e8700)

Received: 13 April 2017 / Received in final form: 11 October 2017 / Accepted: 15 October 2017

http://dx.doi.org/10.1097/MD.0000000000008700

reported no association was found between blood concentrations or dose and *MDR1* genotype. Qiu et al demonstrated it had a correlation between *MDR1* C1236T and cyclosporine pharmacokinetics in the early stage after transplantation.[7] Fredericks et al suggested *MDR1* C1236T did not appear to have a major influence on cyclosporin pharmacokinetics.[8]

Moreover, there is no evidence from systematically evaluating the effect of *MDR1* C1236T on cyclosporine pharmacokinetics. It remains unclear about the reason for these conflicting results. The limited sample size of each single study could be another reason. Hence, this study conducts a meta-analysis to investigate whether SNP C1236T influences the pharmacokinetics of cyclosporine in transplant patients.

2. Materials and methods

2.1. Literature search

We designed a search strategy via 3 English language databases including PubMed, Embase and Cochrane Library. Four Chinese electronic database including China National Knowledge Infrastructure (CNKI), Wan Fang Database (Wan Fang), Chinese Biomedical Literature Database (CBM), and VIP Database for Chinese Technical Periodicals (VIP) were also searched in Chinese.

The following principal search terms and MeSH headings were used: "cyclosporine" or "ciclosporin" or "CsA" and "polymorphism" or "genotype" or "genes" or "alleles" or "SNP" and "*MDR1*" or "MDR-1" or "ABCB1." We would look for additional studies in reference lists of included articles, contact with authors about details of published or unpublished articles. The results were crosschecked to eliminate duplicates. The deadline of all retrieval was December 2016.

2.2. Study selection

The following studies were included in analysis: patients treated with cyclosporine, regardless of race, sex; patients needed to accept *MDR1 Cl236T* gene polymorphism detection and detection methods are not limited; and studies published in either English or Chinese. Studies with incomplete information were excluded from the analysis.

2.3. Data extraction

Data extraction form designed according to Cochrane Systematic Review Handbook (version 5.3) was used to extract the relevant information independently. Two independent reviewers screened all the titles and abstracts to determine potential usefulness and eligibility of the articles. Then they independently and blindly applied the eligibility criteria to perform the final selection. When discrepancies occurred between both reviewers regarding the inclusion of the articles, they would discuss and identify the reasons of inclusion or exclusion to make an agreement and take a final decision. If they could not reach agreement, a final decision would be based on a third reviewer.

2.4. Statistical analysis

Meta-analysis was conducted with RevMan 5.3. The data was pooled and as analyzed for relative risks (RR) with 95% confidence interval (CI). Assessment of heterogeneity was done by *I*-squared (I^2) statistics. A fixed-effects model was initially conducted. If significant heterogeneity was found among trials ($I^2 > 50\%$), a random-effects model was used.

2.5. Ethical statement

As all analyses were grounded on previous publications, ethical approval was not necessary.

3. Results

3.1. Study selection and characteristics

A total of 608 records were identified for initial screening and 11 eligible articles were included in this meta-analysis (Fig. 1). These studies were published between 2004 and 2013. Of these 11 articles, patients from 7 articles were treated with renal transplantation, 3 were treated with bone marrow transplant, and 1 was treated with myasthenia gravis. The meta-analysis results were presented in Table 1.

3.2. Effect of C1236T on dose adjusted C_0

A total of 8 studies in Table 1 assessed the relationship between SNP C1236T and dose adjusted C_0. There was no significant difference between subjects carrying CC genotypes and CT genotypes (MD: 0.24, 95% CI [−4.39, 4.86], $P = .92$) with no heterogeneity. The Q-statistic indicated significant heterogeneity between subjects carrying CC genotypes and TT genotypes, as well as between subjects carrying CT genotypes and TT genotypes. After sensitivity analysis (excluding the study of Zhang 2008 and Wang 2009, respectively), there was significant difference between subjects carrying CC genotypes and TT genotypes (MD: 6.76, 95% CI [2.38, 11.14], $P = .02$]. However, there was no significant difference between subjects carrying CT genotypes and TT genotypes (MD: 3.12, 95% CI [−0.59, 6.82], $P = .1$) with no significant heterogeneity (Fig. 2).

3.3. Effect of C1236T on dose adjusted C_2

A total of 3 studies in Table 1 reported the relationship between SNP C1236T and dose adjusted C_2. There was difference between subjects with CC genotypes and CT genotypes (MD: −18.50, 95% CI [−35.49, −1.52], $P = .03$) with no significant heterogeneity, as well as between subjects with CC genotypes and TT genotypes (MD: −19.01, 95% CI [−35.85, −2.16], $P = .03$]. However, there was no difference between subjects carrying CT

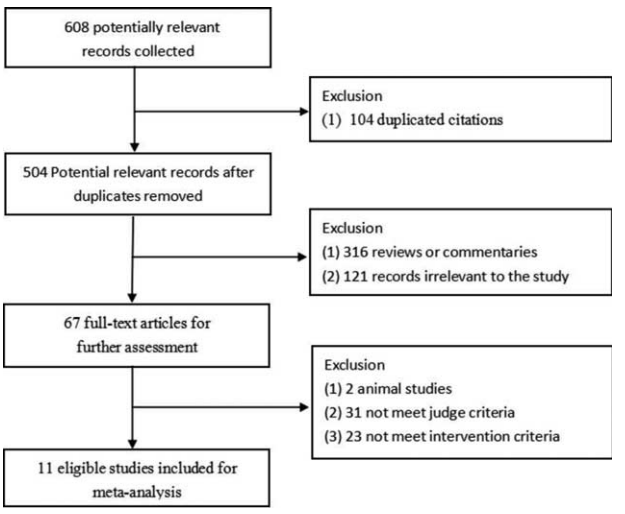

Figure 1. Flow diagram of selecting study.

Table 1

Characteristics of included studies.

Author	Year	Subjects	Age, y	Body weight, kg	Sex (male/female)	Administration	Genotype (no.)
Anglicheau et al[1]	2004	Renal transplant recipients	44.7±14.4	67.4±13.1	70/36	Multiple oral dose of CsA adjusted according to blood concentration	CC (36) CT (47) TT (17)
Haufroid et al[4]	2004	Renal transplant recipients	50.6±11.2	NR	29/21	Multiple oral dose of CsA adjusted according to blood concentration	CC (19) CT (21) TT (10)
Qiu et al[9]	2008	Renal transplant recipients	37±9 41±10 41±10	57±7 57±10 60±12	63/26	Multiple oral dose of CsA adjusted according to blood concentration	CC (15) CT (31) TT (43)
Ranjana et al[10]	2008	Renal transplant recipients	35.3±10.4	52.9±8.8	131/24	Multiple oral dose of CsA adjusted according to blood concentration (initial 8 mg/kg twice daily)	CC (17) CT (68) TT (70)
Fang et al[11]	2008	Renal transplant recipients	44.4±11.9	56.7±9.6	40/25	Multiple oral dose of CsA adjusted according to blood concentration	CC (25) CT (35) TT (5)
Wang et al[12]	2009	Renal transplant recipients	46.9±13.2	52.3±12.5	59/53	Multiple oral dose of CsA adjusted according to blood concentration	CC (18) CT (47) TT (47)
Xin et al[13]	2013	Renal transplant recipients	41.6±11.3	58.2±10.1	235/104	Multiple oral dose of CsA adjusted according to blood concentration	CC (40) CT (163) TT (136)
Wei[14]	2010	Bone marrow transplant recipients	21±18	47.5±23.7	54/54	Multiple oral dose of CsA adjusted according to blood concentration	CC (11) CT (47) TT (50)
Qiu et al[7]	2011	Bone marrow transplant recipients	21.7±17.2	49.4±23.3	47/44	Multiple oral dose of CsA adjusted according to blood concentration	CC (12) CT (41) TT (38)
Zhang[15]	2012	Bone marrow transplant recipients	35±9	63±10	24/16	Multiple oral dose of CsA adjusted according to blood concentration	C (22) TT (18)
Zhang[16]	2008	Myasthenia gravis recipients	40.6±10.6	64.0±15.2	66/63	Multiple oral dose of CsA adjusted according to blood (initial 50 mg twice daily)	CC (11) CT (52) TT (66)

genotypes and TT genotypes (MD: −7.02, 95% CI [−17.11, 3.07], $P=.17$] with no heterogeneity (Fig. 3).

3.4. Effect of C1236T on dose adjusted C_{max}

A total of 3 studies in Table 1 reported the relationship between SNP C1236T and dose adjusted C_{max}. There was no difference between subjects carrying CC genotypes and CT genotypes (MD: −0.05, 95% CI [−0.10, 0.01], $P=.12$), CC genotypes and TT genotypes (MD: −0.05, 95% CI [−0.11, 0.01], $P=.08$), as well as CT genotypes and TT genotypes (MD: 0.01, 95% CI [−0.04, 0.09], $P=.79$). At the same time, the 3 subgroups had no heterogeneity (Fig. 4).

3.5. Effect of C1236T on daily dose

A total of 6 studies in Table 1 reported the relationship between C1236T SNP and daily dose. Q-statistic indicated significant heterogeneity between subjects carrying CC genotypes and CT genotypes. After sensitivity analysis (excluding the study of Zhang 2008), there was no difference between subjects carrying CC genotypes and CT genotypes (MD: 0.08, 95% CI [−0.18, 0.33], $P=.57$). Moreover, there was no difference between subjects carrying CC genotypes and TT genotypes (MD: 0.10, 95% CI [−0.13, 0.33], $P=.40$), as well as CT genotypes and TT genotypes (MD: 0.17, 95% CI [−0.01, 0.35], $P=.07$) (Fig. 5).

3.6. Effect of C1236T on C_0

A total of 6 studies in Table 1 reported the relationship between C1236T SNP and C_0. There was no difference between subjects carrying CC genotypes and CT genotypes (MD: 4.75, 95% CI [−7.67, 17.18], $P=.45$), CC genotypes and TT genotypes (MD: 4.84, 95% CI [−7.98, 17.66], $P=.46$), as well as CT genotypes and TT genotypes (MD: −1.39, 95% CI [−9.76, 7.00], $P=.75$). At the same time, the 3 subgroups had no heterogeneity (Fig. 6).

4. Discussion

The characterization of *MDR1* gene and the utilization of pharmacogenetic testing for the identification of different *MDR1* alleles may provide a useful tool for optimizing therapy involved with drugs that are substrates of P-glycoprotein, which would improve efficacy of drugs and prevent adverse effects.[17] Since the studies on the correlation between genotype of *MDR1* C1236T and pharmacokinetics of cyclosporine revealed conflicting results, this meta-analysis mainly assessed the effect of SNP C1236T on pharmacokinetic parameters of cyclosporine.

Pharmacokinetic studies on transplant patients have demonstrated that the area under the concentration time curve (AUC) is a precise predictor of clinical outcomes.[18] However, the AUC methodology is difficult to apply in routine clinical practice, so other methods have been developed to replace the AUC, such as

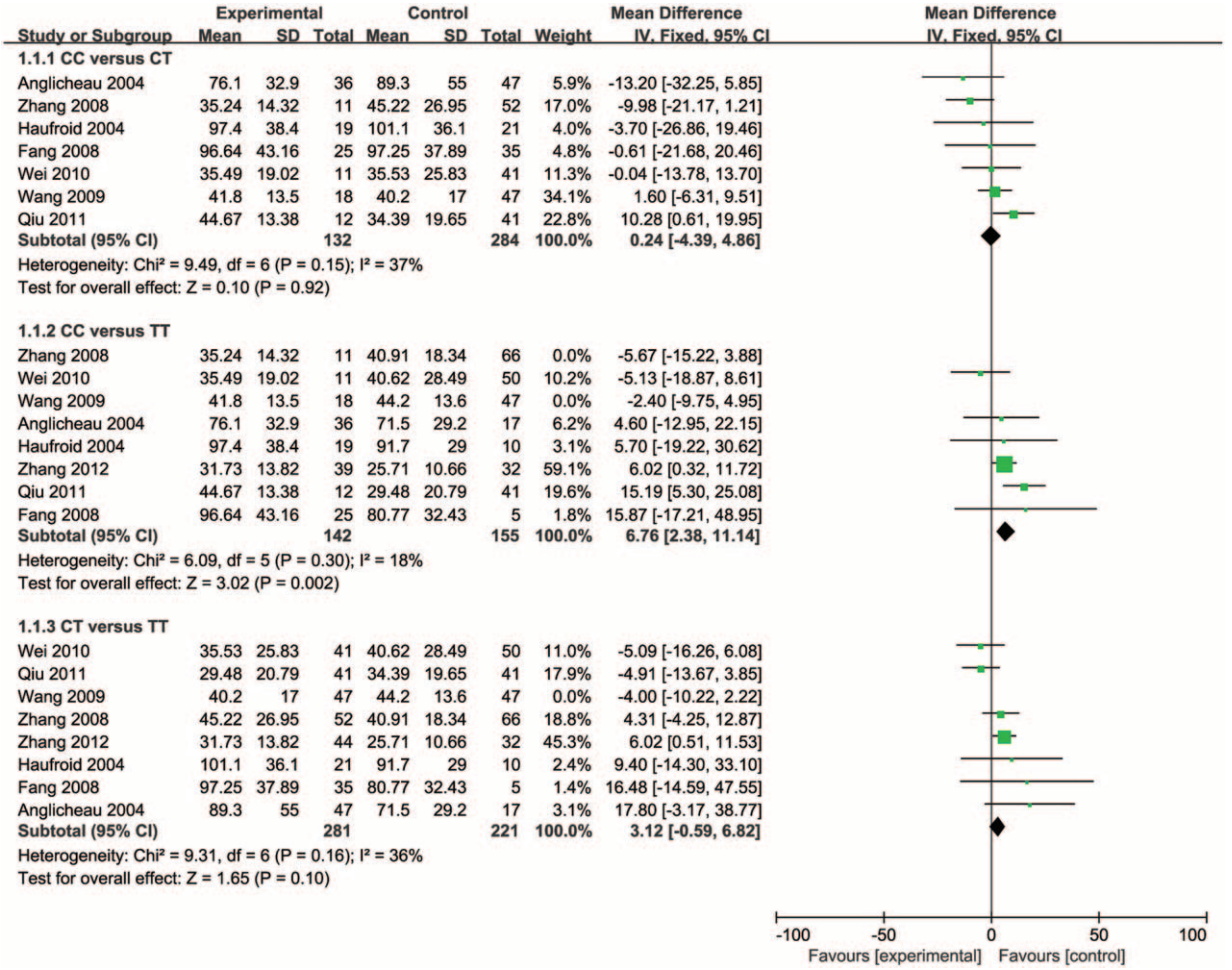

Figure 2. Forest plot of C1236T on adjusted C_0.

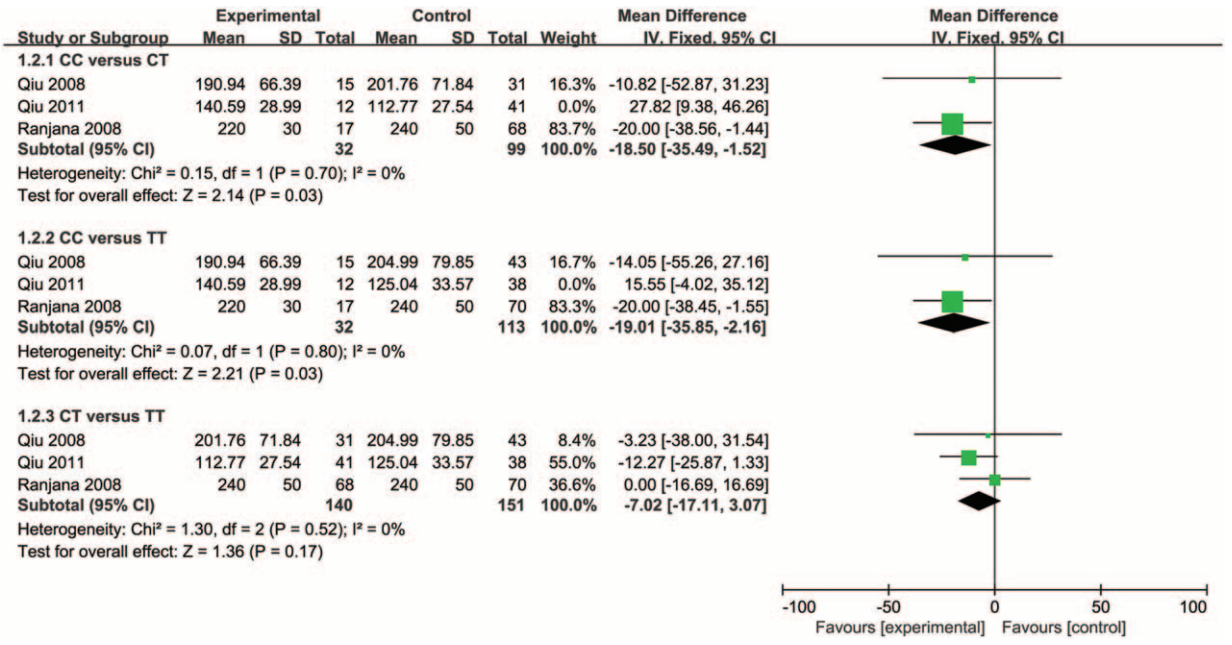

Figure 3. Forest plot of C1236T on adjusted C_2.

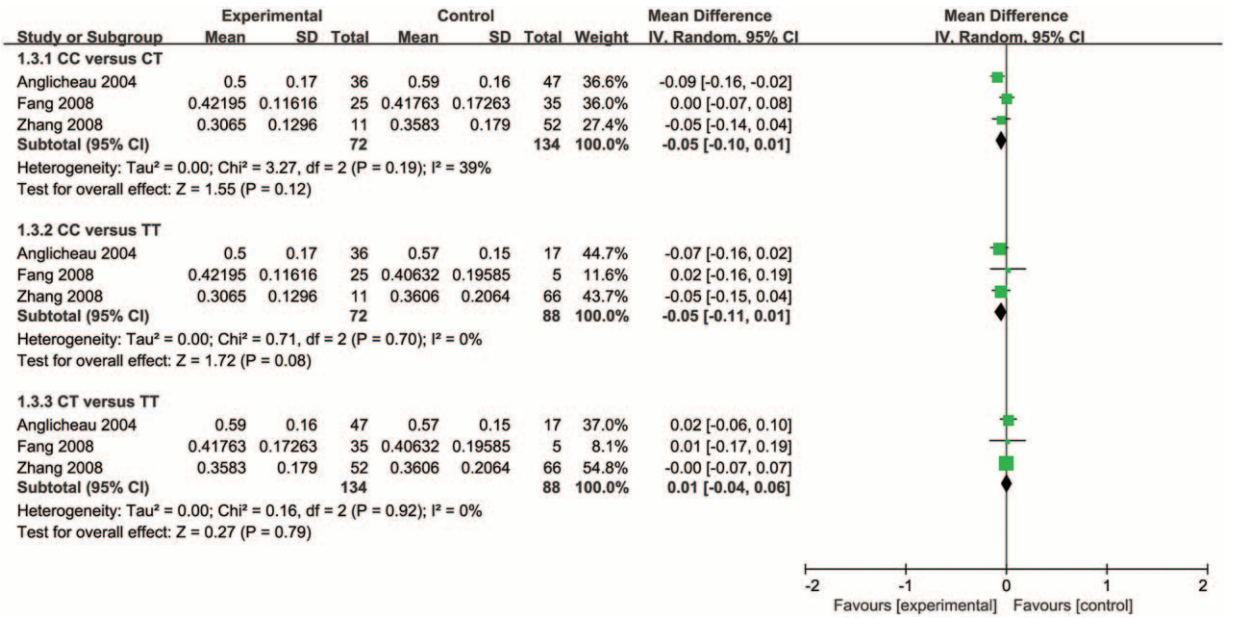

Figure 4. Forest plot of C1236T on adjusted C_{max}.

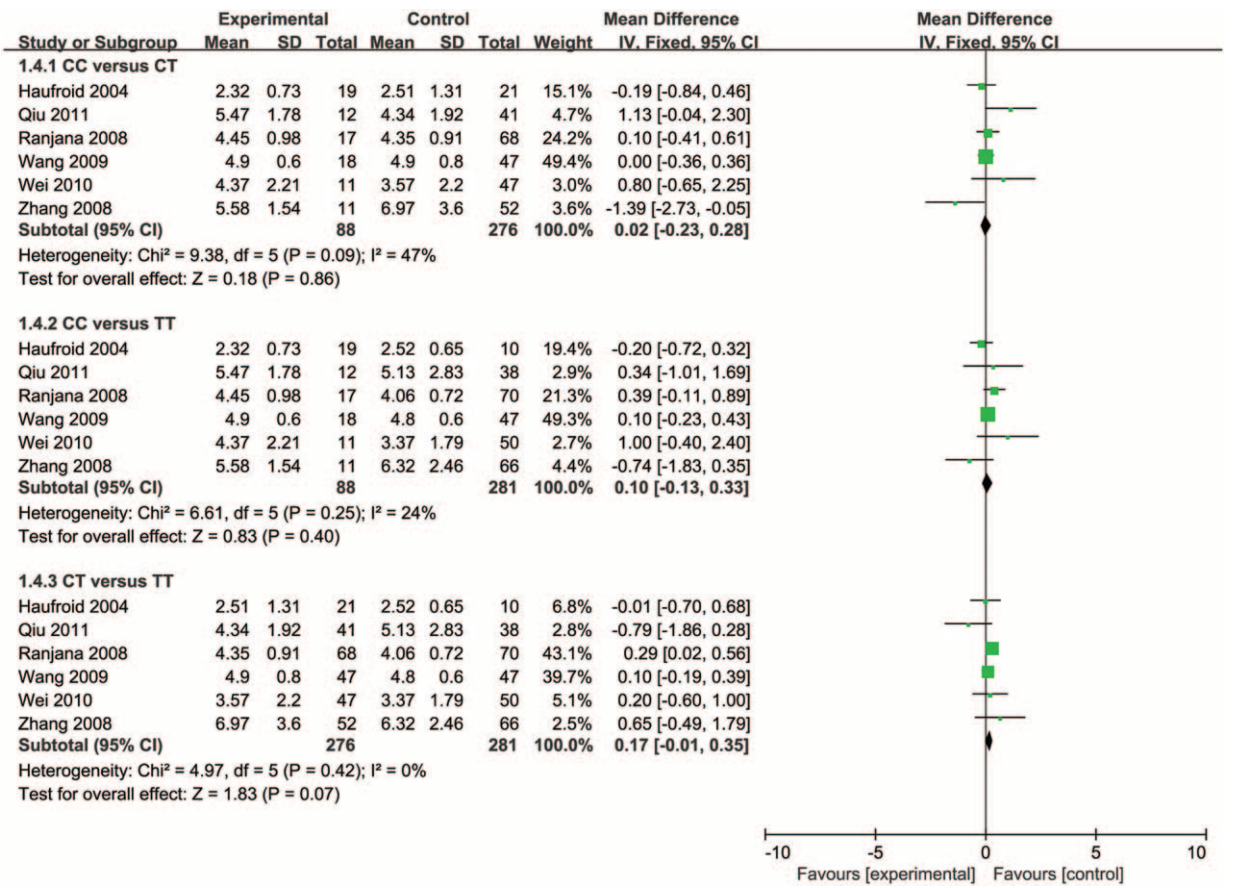

Figure 5. Forest plot of C1236T on daily dose.

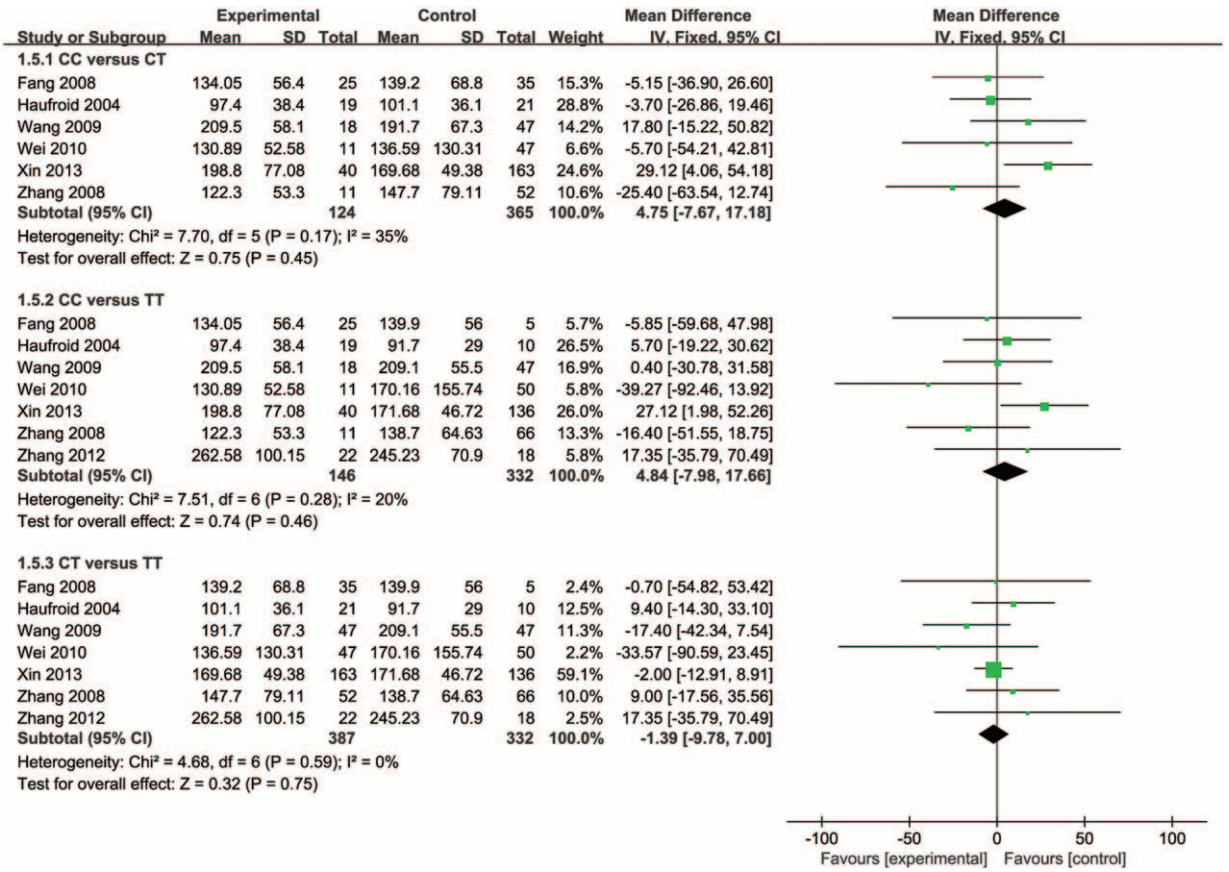

Figure 6. Forest plot of C1236T on C_0.

C_0, C_2.[19] This explains the reason why AUC is rarely reported in the included studies.

Trough concentration (C_0) and dose adjusted C_0 are the most common parameters in included studies. It is interesting to find there was no significant difference in C_0. But a significant difference was showed in dose adjusted C_0 in included studies. This suggested that we could choose dose adjusted C_0 of pharmacokinetic parameters as a detection indicator, to further guide the rational use of cyclosporine dose in different genotype of *MDR1* C1236T patients. Through subgroup analysis of dose adjusted C_0, the results suggested there was difference between subjects carrying CC genotypes and TT genotypes.

Whole-blood levels at 2 hours after drug intake (C_2) seem to provide a good surrogate of AUC for dose adjustment, which may better reflect intestinal absorption because it decreases the role of hepatic metabolism and renal excretion.[20] Through subgroup analysis of adjusted C_2, the results suggested there was significant difference between subjects carrying CC genotypes and CT genotypes, as well as CC genotypes and TT genotypes. However, this meta-analysis shows SNP C1236T has no significant difference in C_{max} and daily dose, which might demonstrate that the effect of different C1236T genotypes on the availability of cyclosporine was limited.

Although this meta-analysis analyzed the correlation between pharmacokinetic parameters and genotypes of *MDR1* C1236T, we recognized that our study still has limitations. First, since these studies are different in design, subjects, dosage, parameters, measurement method, and so on, selection bias exists in this meta-analysis. Second, C1236T is one of the *MDR1* SNPs, meaning that it is not the only polymorphism that could influence the *MDR1* expression. Third, this meta-analysis did not find a definitive correlation between pharmacokinetic parameters and genotype of *MDR1* C1236T. Balram et al indicated race maybe one important factor affecting the pharmacokinetic parameters of cyclosporine.[21] Chowbay et al suggested that *MDR1* haplotype, rather than single SNP polymorphism, might be responsible for influencing P-glycoprotein expression, thus influencing the pharmacokinetic parameters of cyclosporine.[22] Cyclosporine is also the substrate of CYP3A4 and CYP3A5 and polymorphism of CYP3A has the potential to affect cyclosporine metabolism.[23] Therefore, many facts would affect the correlation between pharmacokinetic parameters and genotypes of *MDR1* C1236T. It is hard to find a definitive correlation and we should be cautious with our results.

In summary, this meta-analysis demonstrated that MDR1 C1236T polymorphism may have a minor effect on cyclosporine pharmacokinetics in transplantation patients.

Acknowledgment

We thank Group of People with Highest Risk of Drug Exposure of International Network for the Rational Use of Drugs, China for providing support to coordinate the circulation of the manuscript to all the coauthors and collect comments from all the coauthors.

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