

Mycophenolate Mofetil Treatment for IgA Nephropathy: A Meta-Analysis

Gaosi Xu^{a,b} Weiping Tu^a Dongfeng Jiang^b Chengyun Xu^a

^aDepartment of Nephrology, Second Affiliated Hospital, Nanchang University, Nanchang, and

^bDepartment of Immunology, Shangrao Branch of Jiangxi Medical College, Shangrao, PR China

Key Words

Immunoglobulin A nephropathy · Mycophenolate mofetil · Meta-analysis

Abstract

Background: Worldwide, IgA nephropathy (IgAN) is the most common type of glomerulonephritis. Mycophenolate mofetil (MMF) is relatively selective for lymphocytes and inhibits antibody production by B cells more than other immunosuppressants. Several randomized controlled trials (RCTs) have analyzed the role of MMF in patients with IgAN. We conducted this meta-analysis of all available RCTs to ascertain the benefits and risks of MMF treatment in comparison with placebos or steroids in patients with IgAN. **Methods:** The studies were identified by extended computer-based searches of the PubMed database (April, 2008) and the Cochrane Library, without language restriction. References in Medline-cited studies were reviewed to identify additional reports not indexed by Medline. RCTs comparing treatment of IgAN with mycophenolate against placebo or steroids were included in the analysis. **Results:** We identified 32 potentially relevant articles, but only 4 RCTs, which had enrolled a total of 168 patients, were included. Our meta-analysis demonstrated that MMF treatment did not have statistically significant effects in reducing proteinuria or protecting renal function in patients with IgAN. **Conclusion:** The currently available evidence does not support the rou-

tine use of MMF in patients with IgAN. Larger international collaborations should be put in place to further address this issue.

Copyright © 2008 S. Karger AG, Basel

Introduction

IgA nephropathy (IgAN) is a disease that affects patients across the world. It is a cause of end-stage renal disease, which occurs in 15–20% of patients within 10 years and in 30–40% within 20 years from the apparent onset of IgAN. No specific treatment has yet been established, but many approaches have been investigated. Mycophenolate mofetil (MMF) is able to inhibit the proliferation of both B and T lymphocytes, and it also reduces antibody production. In addition, it has effects on adhesion molecules, and hence may influence interactions between leukocytes and the endothelium [1]. MMF has proved to be a potent immunosuppressant that is used for prophylaxis and the treatment of renal-transplant rejections, in which it has a favorable side effect profile [2]. MMF treatment also appeared to offer benefits to patients who were refractory to conventional therapies for glomerulopathies [3]. Bergner et al. [4] reported 3 pa-

G.X. and W.T. contributed equally to this work.

Table 1. Characteristics of individual studies of MMF treatment for IgAN

Study	Year	MMF patients, n	Control patients, n	MMF dosage g/day	Period of treatment, months	Placebo or steroids	Jadad score
Chen et al. [5]	2002	31	31	1.0–1.5	18	steroids	3
Maes et al. [7]	2004	21	13	2.0	36	placebo	3
Frisch et al. [8]	2005	17	15	2.0	24	placebo	5
Tang et al. [6]	2005	20	20	1.5–2.0	18	placebo	3

tients with IgAN who were treated with MMF for more than 1 year. Renal functions remained stable and proteinuria decreased significantly in all 3 patients. Furthermore, 2 recent randomized controlled trials (RCTs) from China [5, 6] found MMF to be significantly better than prednisone for the reduction of proteinuria in patients with IgAN. However, conflicting results have occurred [7, 8]. We conducted this meta-analysis of all available RCTs to ascertain the benefits and risks of MMF treatment in comparison with placebos or steroids in patients with IgA nephropathy.

Methods

Identification of Eligible Studies

Studies were identified by extended computer-based searches of the PubMed database (April, 2008) and the Cochrane Library, without language restriction. References in Medline-cited studies were reviewed to identify additional reports not indexed by Medline. The following key words and subject terms were used in the search: IgA nephropathy, immunoglobulin A (IgA) nephropathy, IgA nephritis, IgA glomerulonephritis, Berger's disease, mycophenolate mofetil (MMF), mycophenolic acid (MPA), and their derivative words.

Inclusion and Exclusion Criteria

We included only reports of RCTs that were conducted on adult humans and which used MMF as the intervention. Studies were excluded if they did not clearly report the numbers of patients who recovered, deteriorated or had renal-replacement treatment. All articles underwent a multilevel, systematic review by a team of 2 physicians.

Quality Assessment of Primary Studies

We assessed the quality of the studies included in the analysis with the Jadad scale, which is the established procedure by which study methodologies are evaluated [9]. The scale assigns 0 or 1 points to each of the following 5 items: (1) with or without randomization; (2) the appropriateness of the randomization methods, if used; (3) with or without double-blind elements; (4) the appropriateness of double blinding, if used, and (5) the incidence of withdrawals and dropouts. Thus, the Jadad score can range from 0 to 5.

Data Extraction

Two investigators independently extracted standard information from the selected studies. From each study, the following information was obtained: first author, journal, year of publication, demographics, study population, follow-up time, the number of cases, MMF dosage, placebo or steroids, the number of patients who experienced a 50% decline in proteinuria, the number of patients who experienced a 50% increase in serum creatinine (SCr), the number of patients who needed renal-replacement therapy.

Statistical Analysis

Statistical analyses were performed using Cochrane RevMan software, version 4.2 (Cochrane Library, UK). The results were expressed as relative risks (RR), for dichotomous outcomes, and weighted mean differences, for continuous outcomes, with 95% confidence intervals (95% CI). Heterogeneity among the included trials was analyzed using the heterogeneity Q statistic test. If the significant Q statistic ($p < 0.05$) indicated heterogeneity across studies, the DerSimonian and Laird method in the random effects model was used for meta-analysis. Otherwise, the Mantel-Haenszel method in the fixed-effect model was selected.

The potential for publication bias was examined by the funnel plot method, Begg's test for publication bias, which was performed by Stata statistical software, version 8.1 (Stata Corp., College Station, Tex., USA). $p < 0.05$ was considered to be statistically significant.

Results

Studies Included in the Meta-Analysis

We identified 32 potentially relevant articles. However, only 4 RCTs, which had enrolled a total of 168 patients, were included in the final analysis: 3 trials compared MMF with placebo, and 1 compared it with steroids. In 3 RCTs, patients received conventional treatment with blockers of angiotensin-converting enzyme inhibition. Four RCTs were of optimal quality (as judged by Jadad scores; table 1).

Characteristics of the Included Studies

The patient characteristics, MMF dosage, period of treatment, interventions and total Jadad score are sum-

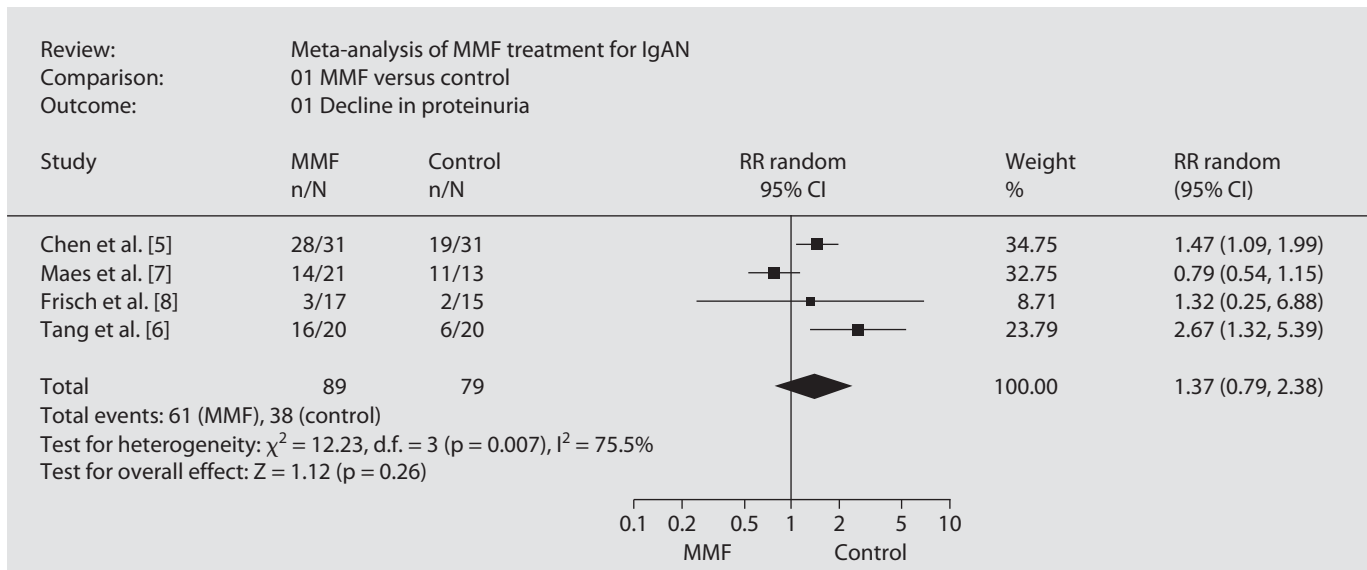


Fig. 1. Effect of MMF treatment on proteinuria in IgAN patients.

Table 2. Meta-analysis items of MMF treatment for IgAN

Study	Decline in proteinuria		Increase in SCr		Need for renal-replacement treatment	
	MMF	control	MMF	control	MMF	control
Chen et al. [5]	28	19	–	–	3	5
Maes et al. [7]	14	11	3	0	2	1
Frisch et al. [8]	3	2	10	7	5	2
Tang et al. [6]	16	6	1	3	–	–

Data are numbers of patients.

marized in table 1. The numbers of patients who exhibited a decline in proteinuria, an increase in SCr or the need for renal replacement in the MMF treatment groups and control groups are shown in table 2.

Effect on Proteinuria

Four studies assessed proteinuria in a total of 168 patients, of whom 89 were assigned to the treatment groups and 79 to the control groups. A 50% decline in proteinuria was seen in 61 of the 89 patients in the MMF treatment groups, and in 38 of the 79 patients in the control groups. Because heterogeneity was significant ($p = 0.007$), the randomized effects model was used to ascertain the

risk ratio for proteinuria, and a statistical analysis showed that this estimate was not statistically significant ($p = 0.26$, 95% CI 0.79–2.38; fig. 1).

Effect on SCr

Three studies assessed SCr in a total of 106 patients, 58 of whom were assigned to the treatment groups and 48 to the control groups. A 50% increase in the SCr was seen in 14 of the 58 patients in the MMF treatment groups, and in 10 of the 48 patients in the control groups. Because heterogeneity was not significant ($p = 0.34$), the fixed-effects model was used to ascertain the risk ratio for proteinuria, and a statistical analysis showed that this estimate was not statistically significant ($p = 0.60$, 95% CI 0.62–2.25; fig. 2).

Effect on the Need for Renal-Replacement Therapy

Three studies assessed the need for renal-replacement therapy in a total of 128 patients, 69 of whom were assigned to the treatment groups and 59 to the control groups. Ten of the 69 patients in the MMF treatment groups and 8 of the 59 patients in the control groups showed a need for renal-replacement therapy. Because heterogeneity was not significant ($p = 0.44$), the fixed-effects model was used to ascertain the risk ratio for the cases in need of renal-replacement therapy. A statistical analysis showed that this estimate was not statistically significant ($p = 0.83$, 95% CI 0.46–2.64; fig. 3).

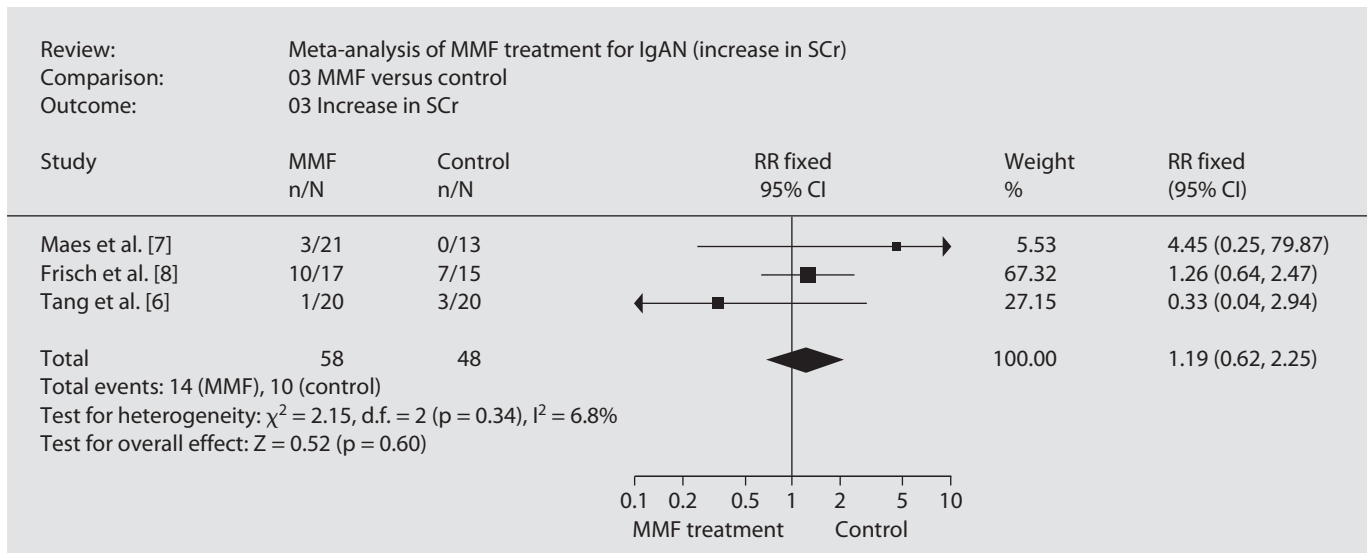


Fig. 2. Effect of MMF treatment on SCr of IgAN patients.

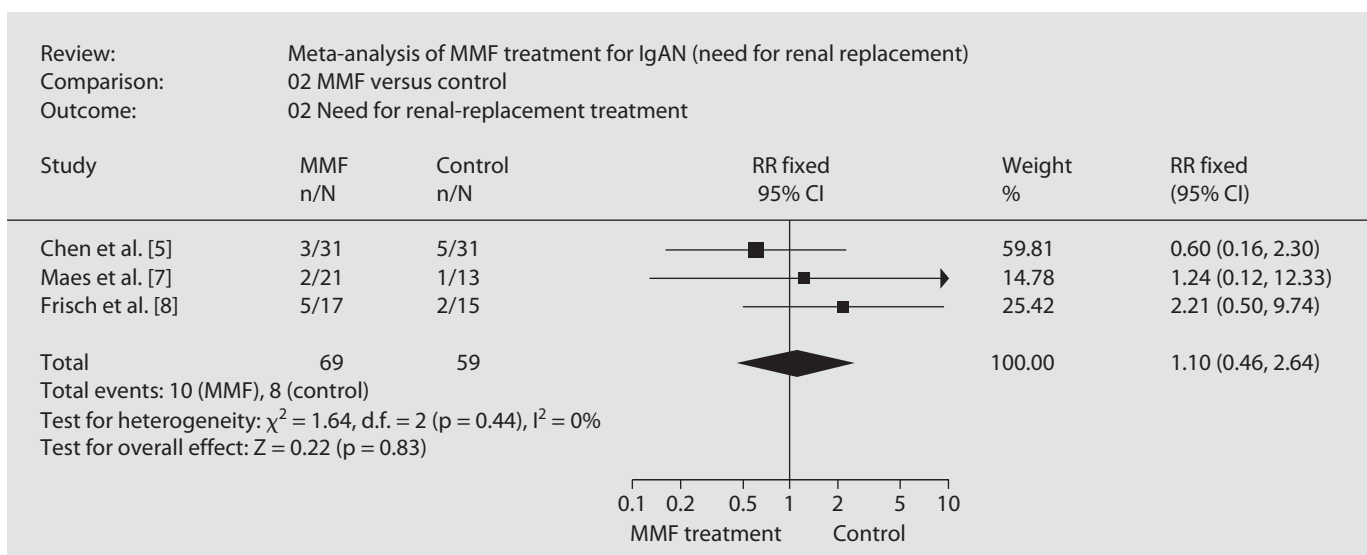


Fig. 3. Effect of MMF treatment on the need for renal-replacement therapy in IgAN patients.

Side Effects

The incidence of infections and gastrointestinal side effects (diarrhea and gastritis) was analyzed in the MMF treatment and control groups. No serious side effects were observed in any RCT.

Publication Bias

The funnel plots exhibited symmetric patterns for both proteinuria and renal function, as shown in figure 4. Because the sample sizes of the 4 RCTs included in this meta-analysis were all small, we conducted Begg's test to evaluate the publication bias using Stata software, which revealed no significant heterogeneity in the studies included.

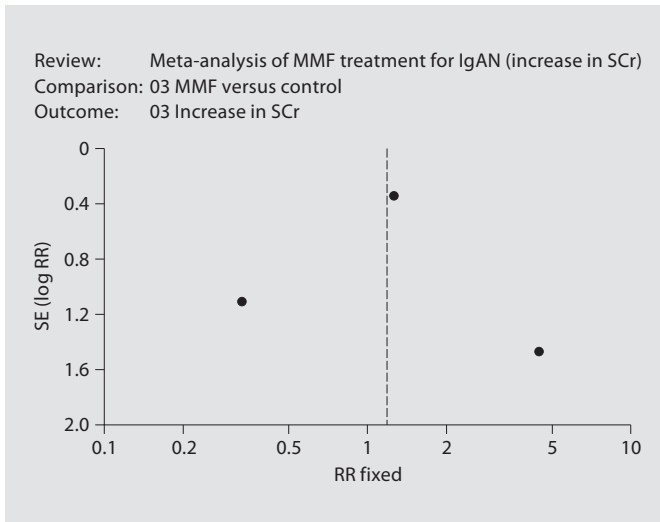


Fig. 4. Funnel plot of three RCTs for increase in SCr.

Discussion

Worldwide, IgAN is the most common type of glomerulonephritis [10]. Between 15 and 40% of adults and children diagnosed with IgAN will eventually progress to end-stage renal disease [11, 12]. MMF is relatively selective for lymphocytes and inhibits antibody production by B cells more than other immunosuppressants [13]. MMF also has a variety of nonimmune effects, such as those on glomerular cells, which may contribute to its clinical efficacy. Several studies have looked at the actions of MMF or MPA on mesangial cells, which may come down to inflammatory proliferative glomerulopathies. MMF inhibited mitogen-induced rat mesangial cell proliferation, and it also inhibited human mesangial cell proliferation. These effects can be inhibited by the addition of guanosine [14, 15]. MMF also has a variety of other effects; for example, it affects inducible nitric oxide synthase (iNOS), and may reduce renal iNOS mRNA expression and decrease glomerulosclerosis in the MRL/lpr lupus mouse model [16].

Case series suggest that MMF may be effective in reducing proteinuria in a variety of glomerular diseases, including IgAN [17, 18]. So far, few RCTs have analyzed the role of MMF in patients with IgAN.

A meta-analysis can summarize the results from different studies by producing a single estimate of the major effect that has enhanced precision [19]. One of the major advantages of meta-analyses is that they increase sample size, which may decrease the probability that random er-

rors will produce false-positive or false-negative associations [20].

In comparison with placebo, the use of MMF did not result in a significant reduction in proteinuria (4 RCTs, 168 patients: RR 1.37, 95% CI 0.79–2.38) or SCr (3 RCTs, 106 patients: RR 1.19, 95% CI 0.62–2.25) at the end of treatment period. The need for renal-replacement therapy (3 RCTs, 128 patients: RR 1.10, 95% CI 0.46–2.64) did not differ between the groups. No serious side effects were observed in any RCT.

As we restricted our study only to RCTs, the sample size in our meta-analysis was not enough to reach a definitive conclusion, so further properly designed studies are needed. Additional information may be provided by the ongoing North American IgA Nephropathy Study [21], but this is the only trial currently looking at the efficacy of MMF in IgAN.

Our meta-analysis had several limitations. First, the number of subjects included in this analysis was not particularly great. Second, the periods of treatment were not long enough to evaluate effects on this slowly progressing, chronic disease. Long-term follow-up studies that evaluate the true treatment outcome might yield different results. Finally, most of the patients in the studies, in both the intervention and control groups, received conventional treatment with blockers of angiotensin-converting enzyme inhibition. Studies are needed that assess the effects of MMF alone (or with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers) in patients who are not receiving other therapies.

In brief, the currently available evidence does not support the routine use of MMF in patients with IgAN. Studies that have larger sample sizes, longer treatment durations and which include patients with both mild and severe histopathological changes are needed before any meaningful conclusions can be drawn on the use of MMF in IgAN. In addition, larger international collaborations should be put in place to further address this issue.

References

- 1 Adu D, Cross J, Jayne DR: Treatment of systemic lupus erythematosus with mycophenolate mofetil. *Lupus* 2001;10:203–208.
- 2 European Mycophenolate Mofetil Cooperative Study Group: Placebo controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995;345:1321–1325.
- 3 Sahin GM, Sahin S, Kantarci G, Ergin H: Mycophenolate mofetil treatment for therapy-resistant glomerulopathies. *Nephrology (Carlton)* 2007;12:285–288.

- 4 Bergner R, Hoffmann M, Brass H, Uppenkamp M: Therapy of IgA nephropathy with mycophenolate mofetil: report of 3 cases. *Clin Nephrol* 2004;61:207–212.
- 5 Chen X, Chen P, Cai G, Wu J, Cui Y, Zhang Y, Liu S, Tang L: A randomized control trial of mycophenolate mofetil treatment in severe IgA nephropathy (in Chinese). *Zhonghua Yi Xue Za Zhi* 2002;82:796–801.
- 6 Tang S, Leung JCK, Chan LYY, Lui YH, Tang CSO, Kan CH, Ho YW, Lai KN: Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy. *Kidney Int* 2005;68:802–812.
- 7 Maes BD, Oyen R, Claes K, Evenepoel P, Kuypers D, Vanwalleghem J, Van Damme B, Vanrenterghem YFC: Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. *Kidney Int* 2004;65:1842–1849.
- 8 Frisch G, Lin J, Rosenstock J, Markowitz G, D'Agati V, Radhakrishnan J, Preddie D, Grew J, Valeri A, Appel G: Mycophenolate mofetil (MMF) vs. placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. *Nephrol Dial Transplant* 2005;20:2139–2145.
- 9 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
- 10 Levy M, Berger J: Worldwide perspective of IgA nephropathy. *Am J Kidney Dis* 1988;12:340–347.
- 11 Velo M, Lozano L, Egido J, Gutierrez-Milet V, Hernando L: Natural history of IgA nephropathy followed up for more than 10 years in Spain. *Semin Nephrol* 1987;7:346–350.
- 12 Radford MG, Donadio JV Jr, Bergstralh EJ, Grande JP: Predicting renal outcome in IgA nephropathy. *J Am Soc Nephrol* 1997;8:199–207.
- 13 Van der Woude FJ: Mycophenolate mofetil (RS 61443): nothing new under the sun or an important break-through in the field of transplantation? *Nephrol Dial Transplant* 1995;10:1112–1115.
- 14 Dubus I, Vendrely B, Christophe I, Labouyrie JP, Delmas Y, Bonnet J, Combe C: Mycophenolic acid antagonizes the activation of cultured human mesangial cells. *Kidney Int* 2002;62:857–867.
- 15 Hauser IA, Renders L, Radeke HH, Sterzel RB, Goppelt-Struebe M: Mycophenolate mofetil inhibits rat and human mesangial cell proliferation by guanosine depletion. *Nephrol Dial Transplant* 1999;14:58–63.
- 16 Yu CC, Yang CW, Wu MS, Ko YC, Huang CT, Hong JJ, Huang CC: Mycophenolate mofetil reduces renal cortical inducible nitric oxide synthase mRNA expression and diminishes glomerulosclerosis in MRL/lpr mice. *J Lab Clin Med* 2001;138:69–77.
- 17 Nowack R, Birck R, van der Woude FJ: Mycophenolate mofetil for systemic vasculitis and IgA nephropathy. *Lancet* 1997;349:774.
- 18 Briggs WA, Choi MJ, Scheel PJ Jr: Successful mycophenolate mofetil treatment of glomerular disease. *Am J Kidney Dis* 1998;31:213–217.
- 19 Ioannidis JP: Genetic associations: false or true? *Trends Mol Med* 2003;9:135–138.
- 20 Lee YH, Harley JB, Nath SK: CTLA-4 polymorphisms and systemic lupus erythematosus (SLE): A meta-analysis. *Hum Genet* 2005;116:361–367.
- 21 Hogg RJ, Wyatt RJ: Scientific Planning Committee of the North American IgA Nephropathy Study: a randomized controlled trial of mycophenolate mofetil in patients with IgA nephropathy [ISRCTN62574616]. *BMC Nephrol* 2004;5:3.