ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

ABSTRACT

BACKGROUND

The outcomes of immunosuppressive therapy, when added to supportive care, in patients with IgA nephropathy are uncertain.

METHODS

We conducted a multicenter, open-label, randomized, controlled trial with a two-group, parallel, group-sequential design. During a 6-month run-in phase, supportive care (in particular, blockade of the renin–angiotensin system) was adjusted on the basis of proteinuria. Patients who had persistent proteinuria with urinary protein excretion of at least 0.75 g per day were randomly assigned to receive supportive care alone (supportive-care group) or supportive care plus immunosuppressive therapy (immunosuppression group) for 3 years. The primary end points in hierarchical order were full clinical remission at the end of the trial (protein-to-creatinine ratio <0.2 [with both protein and creatinine measured in grams] and a decrease in the estimated glomerular filtration rate [eGFR] of <5 ml per minute per 1.73 m^2 of body-surface area from baseline) and a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2 at the end of the trial. The primary end points were analyzed with the use of logistic-regression models.

RESULTS

The run-in phase was completed by 309 of 337 patients. The proteinuria level decreased to less than 0.75 g of urinary protein excretion per day in 94 patients. Of the remaining 162 patients who consented to undergo randomization, 80 were assigned to the supportive-care group, and 82 to the immunosuppression group. After 3 years, 4 patients (5%) in the supportive-care group, as compared with 14 (17%) in the immunosuppression group, had a full clinical remission (P=0.01). A total of 22 patients (28%) in the supportive-care group and 21 (26%) in the immunosuppression group had a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2 (P=0.75). There was no significant difference in the annual decline in eGFR between the two groups. More patients in the immunosuppression group than in the supportive-care group had severe infections, impaired glucose tolerance, and weight gain of more than 5 kg in the first year of treatment. One patient in the immunosuppression group died of sepsis.

CONCLUSIONS

The addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgA nephropathy did not significantly improve the outcome, and during the 3-year study phase, more adverse effects were observed among the patients who received immunosuppressive therapy, with no change in the rate of decrease in the eGFR. (Funded by the German Federal Ministry of Education and Research; STOP-IgAN ClinicalTrials.gov number, NCT00554502.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Floege at the Division of Nephrology and Clinical Immunology, RWTH Aachen University, Pauwelsstr. 30, 52057 Aachen, Germany, or at juergen.floege@rwth-aachen.de.

*A complete list of participating centers and investigators in the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Rauen and Eitner contributed equally to this article.

N Engl J Med 2015;373:2225-36.
DOI: 10.1056/NEJMoa1415463

IgA nephropathy is the most common form of glomerulonephritis.[1] Several findings support the use of immunosuppressive therapy to target mesangial IgA deposits and circulating IgA autoantibodies.[2]

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines regarding IgA nephropathy recommend treatment with a blocker of the renin–angiotensin system (i.e., an angiotensin-converting–enzyme inhibitor or an angiotensin II–receptor blocker) in patients who have proteinuria with urinary protein excretion of more than 1 g per day.[3-5] The KDIGO guidelines also suggest the use of systemic glucocorticoids in patients who have a proteinuria level above 1 g of urinary protein excretion per day and a glomerular filtration rate (GFR) higher than 50 ml per minute despite supportive care.[3] However, the key randomized, controlled trials[6-9] on which this suggestion was based have been criticized[10] because the blockade of the renin–angiotensin system either was inconsistent[6,7] or was temporarily halted and then reinitiated at baseline.[8,9] Another randomized, controlled trial showed that immunosuppressive combination therapy stabilized GFR in patients with an aggressive course of IgA nephropathy[11]; however, in that trial the blockade of the renin–angiotensin system was also inconsistent.

We tested the hypothesis that immunosuppressive therapy plus comprehensive supportive care would be superior to supportive care alone in patients with IgA nephropathy, with the use of two primary end points: full clinical remission and a decrease in the estimated GFR (eGFR) of at least 15 ml per minute per 1.73 m^2 of body-surface area after 3 years of follow-up. We first enrolled all patients in a run-in phase during which they received intensive supportive care.[12] After this phase, only the patients who were still considered to be at high risk were randomly assigned to continue supportive care alone or to receive supportive care with the addition of immunosuppressive therapy.

Methods

Study Population

From February 2008 through October 2011, we screened 379 patients with IgA nephropathy at 32 nephrology centers in Germany (all participating nephrology centers are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org). A total of 42 patients were excluded because of patient or physician decision, incomplete data, or other reasons, and 337 patients were enrolled in the run-in phase. The key inclusion criteria were primary IgA nephropathy confirmed on biopsy; an age of 18 to 70 years; and a proteinuria level above 0.75 g per day of urinary protein excretion plus arterial hypertension (defined by the use of antihypertensive medication or by an ambulatory blood pressure ≥140/90 mm Hg), impaired renal function (defined as an eGFR <90 ml per minute per 1.73 m^2), or both. Major exclusion criteria were an eGFR lower than 30 ml per minute per 1.73 m^2, secondary and rapidly progressive, crescentic IgA nephropathy, other chronic renal diseases, and any prior immunosuppressive therapy. Written informed consent was obtained from all participants. The study was approved by the ethics committee at each participating center.

Study Design

We conducted a prospective, open-label, randomized, controlled clinical trial with a two-group, parallel, group-sequential design.[13] The protocol is available at NEJM.org. All the authors collected the data and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol. The decision to submit the manuscript for publication was made by all the authors.

During a 6-month run-in phase, all the patients received comprehensive supportive care that included blockers of the renin–angiotensin system to lower blood pressure to a target below 125/75 mm Hg. If proteinuria remained above the target of 0.75 g per day of urinary protein excretion despite blood-pressure control, the dose of renin–angiotensin system blocker was increased to the maximum approved daily dose or to the highest dose at which the patient did not have unacceptable side effects. Patients received dietary counseling and were advised to quit smoking and to avoid nonsteroidal antiinflammatory drugs and other nephrotoxins. Total cholesterol levels were lowered to less than 200 mg per deciliter (5.2 mmol per liter) with the use of statins, if necessary.

High-risk patients who had persistent proteinuria with urinary protein excretion of at least 0.75 g per day, but lower than 3.5 g per day, at

the end of the run-in phase entered the 3-year study phase and were randomly assigned to continue supportive care alone (supportive-care group) or to receive supportive care with the addition of immunosuppressive therapy (immunosuppression group). Participants whose proteinuria dropped below 0.75 g of urinary protein excretion per day at the end of the run-in phase did not undergo randomization; if proteinuria exceeded the threshold of 0.75 g of urinary protein excretion per day in these patients despite supportive care during the randomization phase of the trial, the patients were eligible for randomization. At the end of the run-in phase, patients who had a urinary protein excretion rate above 3.5 g per day, an eGFR lower than 30 ml per minute per 1.73 m^2, or a decrease in the eGFR of more than 30% from the start of the run-in phase were not randomly assigned (dropout criteria).

Patients randomly assigned to the immunosuppression group who had an eGFR of at least 60 ml per minute per 1.73 m^2 received glucocorticoid monotherapy for 6 months (methylprednisolone, administered intravenously at a dose of 1 g per day for 3 days at the start of months 1, 3, and 5; and oral prednisolone at a dose of 0.5 mg per kilogram per 48 hours on the other days).[6,7] On the basis of the literature available in 2007, patients with an eGFR between 30 and 59 ml per minute per 1.73 m^2 received cyclophosphamide at a dose of 1.5 mg per kilogram per day for 3 months, followed by azathioprine at a dose of 1.5 mg per kilogram per day during months 4 through 36, plus oral prednisolone at a dose of 40 mg per day, tapered to 10 mg per day, over the first 3 months of the study, 10 mg per day during months 4 through 6, and 7.5 mg per day during months 7 through 36.[11] All drugs were administered as part of general medical care and were not donated specifically for the trial.

The run-in phase included visits at weeks 0, 4, 8, 16, 20, 23, and 24. At week 24 (defined as baseline), eligible patients underwent randomization, and study visits occurred at 2 weeks after randomization, once a month thereafter for 3 months, and then once every 3 months until month 36. GFR was estimated with the use of the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation (www.kidney.org/professionals/KDOQI/gfr_calculator). The level of proteinuria was quantified according to 24-hour urine collections and was expressed as grams per day of urinary protein excretion during the run-in phase, as in most randomized, controlled trials; however, during the randomized, controlled trial phase, we switched to using the protein-to-creatinine ratio (with both protein and creatinine measured in grams), given the greater accuracy of this approach.[14] Data that determined primary end points (i.e., eGFR and proteinuria) were confirmed by repeated measurements after a 2-week interval, and the mean value of all the measurements was used in the analysis. Patients provided three home measurements of blood pressure before each visit. The mean of these measurements was recorded. If home measurements were not provided (which was the case for <20% of the patients at each single visit), office measurements were recorded.

STUDY END POINTS

The two primary end points in hierarchical order were full clinical remission (defined as proteinuria with a protein-to-creatinine ratio of <0.2 and stable renal function with a decrease in the eGFR of <5 ml per minute per 1.73 m^2 from the baseline eGFR at the end of the 3-year trial phase) and a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2 from the baseline eGFR. Secondary end points were the absolute decrease in the eGFR, a decrease in the eGFR of at least 30 ml per minute per 1.73 m^2 from the baseline eGFR, the need for dialysis (onset of end-stage renal disease), the mean annual change in the slope of the reciprocal of serum creatinine concentration, proteinuria at 12 and 36 months, and disappearance of microhematuria as determined by means of a dipstick or urinary sediment test.

STATISTICAL ANALYSIS

We calculated that a sample of 74 patients per group (including a 10% dropout adaptation) would give the study 80% power, at a two-sided significance level of 5%, to detect rates of full clinical remission (the first primary end point) of 5% in the supportive-care group and 25% in the immunosuppression group (with these rates assumed on the basis of prior randomized, controlled trials[6,11]). We used a chi-square test with continuity correction and adjustment for two interim analyses (after one third and two thirds of the cohort had completed the trial).[15]

Randomization codes that were used to assign patients in a 1:1 ratio were generated by means

of covariate adaptive randomization with respect to factors that had the potential to modify the treatment effect (i.e., eGFR and proteinuria).[13,16] Data are presented as means and standard deviations for continuous variables and as counts, percentages, and odds ratios with 95% confidence intervals for categorical variables. The full-analysis set was used for the primary analyses, with patients with missing data considered to have treatment failure.[17] A logistic-regression model that included two stratification factors (baseline eGFR and baseline proteinuria) was fitted to the data of the two primary end points. The individual significance level of the two end points was set to 5% according to the hierarchical order; the significance level was corrected for the group sequential design to 0.0005 at the first interim analysis, 0.0141 at the second interim analysis, and 0.0451 at the final analysis.[15,18] Various sensitivity analyses were performed with the use of an available-case analysis set, multiple-imputation techniques to account for missing observations, and a permutation test.

Secondary end points were analyzed on the basis of available cases with the use of multivariate models that included two stratification factors (baseline eGFR and baseline proteinuria). Additional details regarding the analyses of the secondary end points are provided in the trial statistical analysis plan (available with the protocol at NEJM.org). Adverse events were analyzed by means of Fisher's exact test, except for the total number of events of infection and serious adverse events of infection, for which the Wilcoxon signed-rank test was used to determine significance levels.

RESULTS

RUN-IN PHASE AND RANDOMIZATION

A total of 337 patients entered the run-in phase and received supportive care for 6 months (Fig. 1); 28 patients did not complete the run-in phase. Among the 309 patients who completed the run-in phase, 106 had a response to supportive care (proteinuria level, <0.75 g of urinary protein excretion per day after the end of the run-in phase) and were not eligible for randomization. A total of 38 patients did not meet inclusion criteria or met exclusion criteria at the time of randomization. A total of 165 patients had no response at the end of the run-in phase, and of the 106 patients who had a response to supportive care during the run-in phase, 12 were found to have a proteinuria level above 0.75 g per day of urinary protein excretion at a later stage of follow-up; thus 177 patients were eligible. Of the 177 eligible participants, 15 declined to undergo randomization, 80 were randomly assigned to the supportive-care group, and 82 were assigned to the immunosuppression group. Patient characteristics are listed in Table 1. In the immunosuppression group, 55 patients had an eGFR of at least 60 ml per minute per 1.73 m^2 and received glucocorticoid monotherapy, whereas 27 had an eGFR between 30 and 59 ml per minute per 1.73 m^2 and were treated with the immunosuppressive combination regimen of cyclophosphamide (followed by azathioprine) plus prednisolone (see Table S1 in the Supplementary Appendix).

PRIMARY END POINTS

The 3-year trial phase was completed by 76 patients (95%) in the supportive-care group and by 78 patients (95%) in the immunosuppression group. In the full-analysis set, 4 of the 80 patients (5%) in the supportive-care group, as compared with 14 of the 82 patients (17%) in the immunosuppression group, had a full clinical remission at the final visit (Fig. 2A). An analysis of all available cases yielded similar results — 4 of 72 patients (6%) in the supportive-care group had a full clinical remission at the final visit, as compared with 14 of 71 (20%) in the immunosuppression group. Additional analyses that included a permutation test, multiple imputation of missing information, and per-protocol analyses confirmed significant differences between the groups. Patients who had a remission had a lower mean (±SD) baseline level of proteinuria than did those who did not have a remission (protein-to-creatinine ratio of 0.7±0.3 vs. 1.1±0.6; $P<0.001$ by Welch's t-test). Renal function and blood pressure at baseline were similar in these groups. The higher rate of full clinical remission in the immunosuppression group than in the supportive-care group was related exclusively to the remission of proteinuria (9 patients in supportive-care group vs. 20 patients in the immunosuppression group); there was no significant difference between the two study groups in the number of patients with a decrease in the eGFR of less than 5 ml per minute per 1.73 m^2 during the trial (38 patients in each group).

With respect to the second primary end point (a decrease in the eGFR of at least 15 ml per

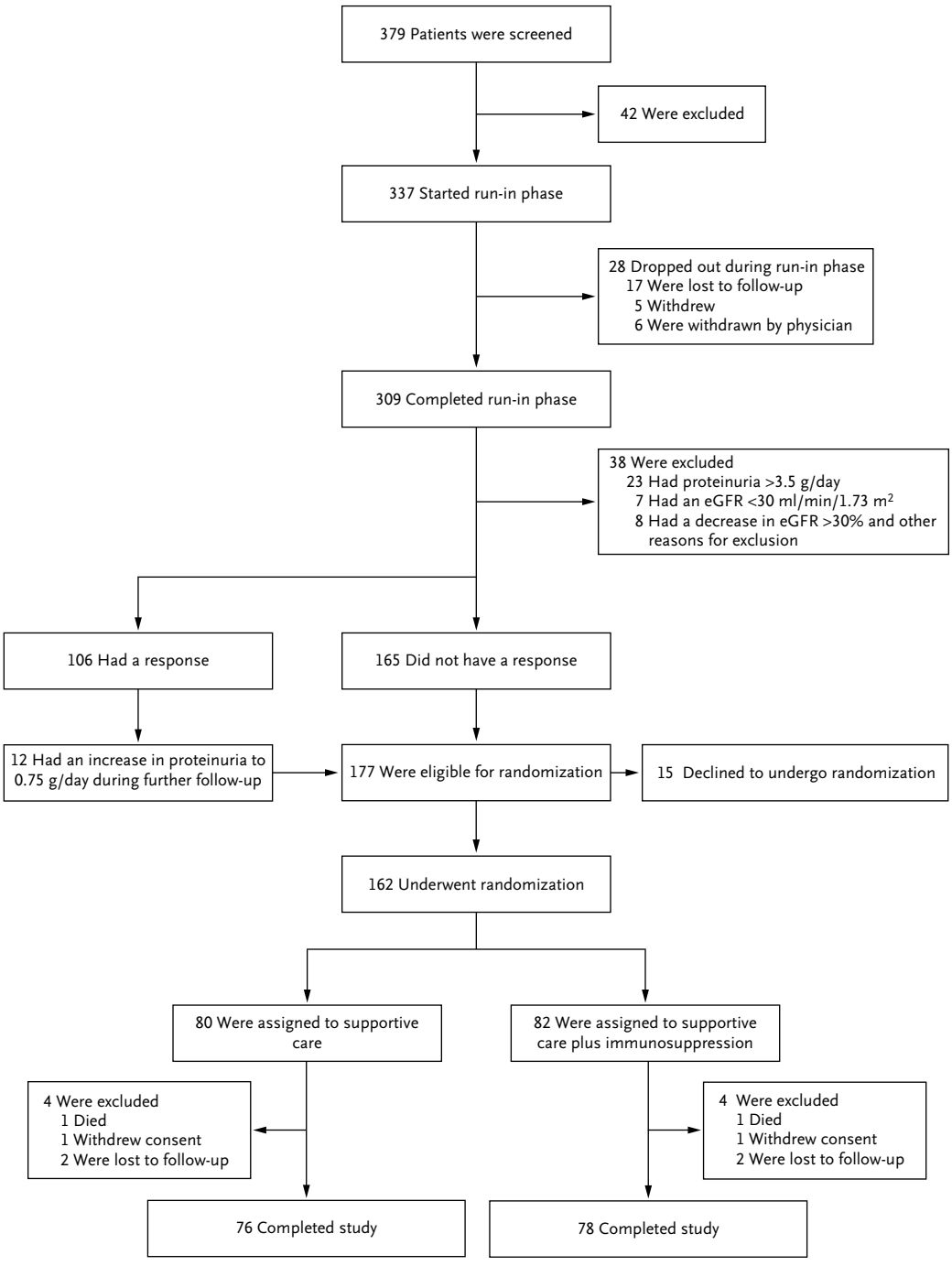

Figure 1. Eligibility, Enrollment, and Randomization.

A total of 379 patients with IgA nephropathy were screened for eligibility, of whom 337 entered the 6-month run-in phase, during which all patients received supportive care. Among the 309 patients who completed this phase, 165 still had proteinuria with urinary protein excretion rates of 0.75 to less than 3.5 g per day, and 106 had proteinuria with urinary protein excretion rates below 0.75 g per day. Among the latter 106 patients, 12 had an increase in urinary protein excretion rates to at least 0.75 g per day during further follow-up. Thus, 177 patients were eligible for the subsequent 3-year randomized trial phase, of whom 162 consented to participate in this phase and were randomly assigned to either continue supportive care or receive supportive care plus immunosuppressive therapy.

Table 1. Patient Characteristics at the Start of the Run-in Phase and at the Start of the Trial Phase.*

Characteristic	Run-in Phase (N=337)	Trial Phase (N=162)	
		Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)
Female sex — %	24	19	24
Smoker — %	18	16	17
Age — yr	43.7±12.8	45.8±12.5	42.8±13.1
Body-mass index†	27.9±5.3	28.6±5.3	27.0±5.0
Blood pressure — mm Hg			
Systolic	131±14.0	127±8.5	124±9.7
Diastolic	81±9.9	78±7.0	77±7.0
Serum creatinine — mg/dl	1.5±0.6	1.6±0.6	1.6±0.7
eGFR — ml/min/1.73 m^2‡	61.5±27.3	57.4±24.9	61.1±29.0
Creatinine clearance — ml/min	76.0±34.7	76.2±31.0	76.3±36.4
Urinary protein excretion rate — g/day	2.2±1.8	1.6±0.7	1.8±0.8
Protein-to-creatinine ratio§	1.4±1.4	1.0±0.5	1.1±0.6
Cholesterol — mg/dl	210.1±48.3	191.6±40.7	193.6±45.7
Antihypertensive drugs — no./patient	2.3±1.4	3.0±1.6	2.8±1.3
Therapy with RAS-blocking agents — % of patients	95	96	100
ACE inhibitor without ARB	51	34	49
ARB without ACE inhibitor	19	30	15
ACE inhibitor plus ARB	25	32	36
Maximum daily ACE inhibitor dose¶	32	37	48
Maximum daily ARB dose¶	18	33	17
Maximum ACE inhibitor and ARB dose¶	14	6	6
Aldosterone antagonist therapy — % of patients	1	0	4
Statin therapy — % of patients	57	73	81

* Plus–minus values are means ±SD. The only significant differences between the supportive-care group and immunosuppression group at the start of the trial phase were angiotensin II–receptor (ARB) without angiotensin-converting–enzyme (ACE) inhibitor (30% vs. 15%; P=0.034 by Fisher's exact test) and maximum daily ARB dose (33% vs. 17%; P=0.025 by Fisher's exact test). All other variables were not significantly different. Information on tonsillectomies performed before the study and fish oil used during the study was not available; however, both are being used infrequently in the treatment of IgA nephropathy in Germany. ARB denotes angiotensin II–receptor blocker, and RAS renin–angiotensin system.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The estimated glomerular filtration rate (eGFR) was estimated with the use of the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation.

§ For the protein-to-creatinine ratio, both protein and creatinine were measured in grams.

¶ Patients received the maximum daily dose according to prescribing information.

minute per 1.73 m^2), there was no significant difference between the groups (full-analysis set: 22 of 80 patients [28%] in the supportive-care group and 21 of 82 [26%] in the immunosuppression group; Fig. 2B). Similarly, in the analysis of all available cases, 18 of 76 patients (24%) in the supportive-care group and 17 of 78 (22%) in the immunosuppression group had a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2. When measured creatinine clearance instead of eGFR was used to assess this end point, there was also no significant difference between the study groups (odds ratio for a decrease in creatinine clearance of ≥15 ml per minute per 1.73 m^2

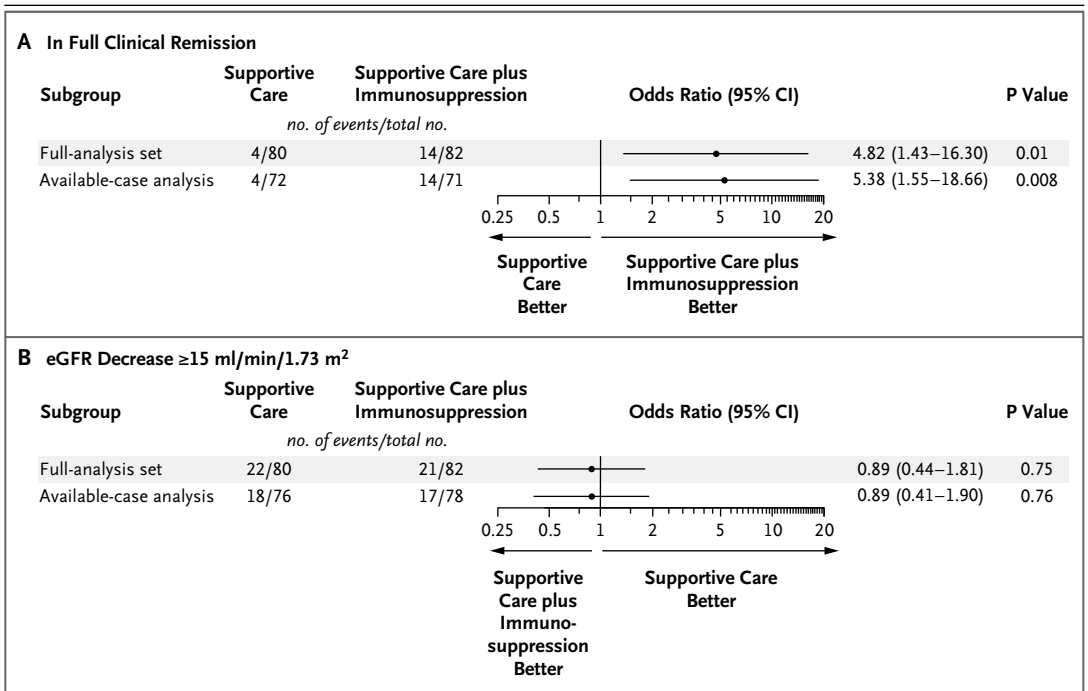

Figure 2. Primary End Points.

Panel A shows the first primary end point: full clinical remission at the end of the 3-year trial phase (protein-to-creatinine ratio <0.2 [with both protein and creatinine measured in grams] and a decrease in the estimated glomerular filtration rate [eGFR] of <5 ml per minute per 1.73 m^2 of body-surface area from baseline). Panel B shows the second primary end point: a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2 during the trial phase. A subgroup analysis was performed for both end points with the use of a full-analysis set and an available-case analysis set. In the full-analysis set, missing values in all events in all patients who underwent randomization were substituted by the worst clinical case (i.e., no clinical remission and decrease in the eGFR of at least 15 ml per minute per 1.73 m^2); in the available-case analysis set, only documented events among patients with available data were included in the analysis.

in the immunosuppression group, 1.15; 95% confidence interval, 0.62 to 2.14; P=0.66).

SECONDARY END POINTS

No significant differences were observed between the supportive-care group and the immunosuppression group at the end of the trial phase with respect to the mean absolute change in eGFR, the mean annual change in the slope of the reciprocal of serum creatinine concentration, the number of patients with a decrease in the eGFR of at least 30 ml per minute per 1.73 m^2, and the number of patients with the onset of end-stage renal disease (Table 2).

Twelve months after randomization, patients in the immunosuppression group had a significantly lower mean proteinuria level than did those in the supportive-care group (Table 2). At month 36, the difference was no longer significant. Microhematuria, as assessed by means of a urine dipstick or sediment test, was noted in 87% of the patients at baseline (67 in the supportive-care group and 74 in the immunosuppression group). Among these patients, microhematuria was no longer present in 9 in the supportive-care group and in 24 in the immunosuppression group at the end of the study (P=0.004). In the immunosuppression group, more patients receiving glucocorticoid monotherapy than those receiving combination immunosuppressive therapy had remission of proteinuria, hematuria, or both (see Table S2 in the Supplementary Appendix).

The time courses of blood pressure levels, eGFR, and proteinuria are shown in Figure S1 in the Supplementary Appendix. Values were similar in the two study groups over the 3-year trial phase.

Table 2. Secondary End Points on the Basis of the Analysis of Available Cases at the End of the Trial Phase.*

Secondary End Point	Supportive Care (N=80)		Supportive Care plus Immunosuppression (N=82)		Odds Ratio (95% CI)	P Value
	Patients with Available Data	End-Point Value	Patients with Available Data	End-Point Value		
	no.	*mean ±SD or no. (%)*	*no.*	*mean ±SD or no. (%)*		
Absolute eGFR change at 36 mo — ml/min/1.73 m^2	71	−4.7±12.3	72	−4.2±14.1	Not determined	0.32
Mean annual change in the slope of the reciprocal of serum creatinine concentration — mg/dl	77	−0.02±0.06	74	−0.01±0.06	Not determined	0.60
At 12 mo	67	0.80±0.67	59	0.57±0.53	Not determined	0.01
At 36 mo	64	0.85±0.66	59	0.76±0.90	Not determined	0.66
eGFR decrease ≥30 ml/min/1.73 m^2	76	7 (9)	78	10 (13)	1.45 (0.51–4.10)	0.49
Onset of end-stage renal disease	76	6 (8)	78	6 (8)	0.97 (0.29–3.22)	0.96
Disappearance of microhematuria	55†	9 (16)	57†	24 (42)	3.73 (1.52–9.14)	0.004

* To convert the values for serum creatinine to micromoles per liter, multiply by 88.4.
† A total of 67 patients in the supportive-care group and 74 patients in the immunosuppression group had microhematuria at baseline.

ADVERSE EVENTS

The overall numbers of serious adverse events were similar in the two study groups (Table 3, and Tables S3 and S4 in the Supplementary Appendix). However, we observed more nonsevere and severe events of infection, predominantly of the gastrointestinal and respiratory tracts, in the immunosuppression group, of which 25% were considered by the investigators to be related to the study treatment. One patient in the supportive-care group died in a motor vehicle accident, and one patient who received cyclophosphamide plus glucocorticoid therapy in the immunosuppression group died of sepsis. We did not observe more hepatotoxic events or leukopenia in the immunosuppression group than in the supportive-care group, but there was a numerically higher number of malignant neoplasms, impaired glucose metabolism, and body-weight gain in the immunosuppression group. In the immunosuppression group, events of infection were almost equally distributed between the two immunosuppression subgroups (115 events among 55 patients receiving glucocorticoid monotherapy vs. 59 events among 27 patients receiving the combined immunosuppressive regimen), although impaired glucose tolerance was more common among the patients receiving glucocorticoid monotherapy than among those receiving the combined therapy (8 patients vs. 1 patient). The two cases of malignant neoplasm in the immunosuppression group were observed among the patients receiving the combined immunosuppressive regimen.

DISCUSSION

We could not confirm our hypothesis that additional immunosuppressive therapy would provide substantial kidney-related benefits in patients with high-risk IgA nephropathy. Although the addition of immunosuppressive therapy to supportive care was superior to supportive care alone in inducing remission of proteinuria in a proportion of patients, there was no significant difference between the two study groups with respect to the second primary end point of decreasing the rate of fast decreases in the eGFR. These results were achieved with the use of a practical trial design that was in accordance with the KDIGO guidelines[3] and daily practice — namely, withholding immunosuppressive therapy until supportive care had been provided, with increasing doses, for 6 months. In the current trial, supportive care was handled in a standardized fashion by the trial investigators.

Table 3. Adverse Events during the Trial.

Variable	Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)	P Value
Patients with ≥1 serious adverse event — no.	21	29	0.24
Total no. of serious adverse events	29	33	0.18
Total no. of events of infection	111	174	0.07
Total no. of serious adverse events of infection	3	8	0.21
Diverticulitis or appendicitis	1	3	0.62
Pneumonia or respiratory tract infection	1	3	0.62
Viral exanthema	1	1	1.00
Knee empyema	0	1	1.00
Death — no.*	1	1	1.00
Additional adverse events of interest — no. of patients			
≥1 incidence of increase in liver-enzyme level (i.e., alanine aminotransferase >50 IU/ml)	12	13	1.00
≥1 incidence of observed leukopenia (i.e., leukocyte count <4000/μl)	3	2	1.00
Malignant neoplasm	0	2	0.50
Impaired glucose tolerance or diabetes mellitus	1	9	0.02
Gastrointestinal bleeding	0	0	Not determined
Fracture	0	1	1.00
Osteonecrosis — no. of patients	0	0	Not determined
Weight gain (≥5 kg within the first year)	5	14	0.049

* One patient who received supportive care alone died in a motor vehicle accident, and one patient who received additional immunosuppression died of pneumogenic sepsis, which corresponds to a "suspected unexpected serious adverse reaction" in clinical trials.

With this rigorous approach, 34% of patients had a response to supportive care, a finding that is consistent with published data[19]; additional immunosuppressive therapy was not considered in these patients. However, a majority of our cohort still had features associated with a high risk of progression of renal disease, particularly proteinuria levels above 0.75 g of urinary protein excretion per day.

Only 17% of patients in the immunosuppression group had a full clinical remission, despite receiving intense immunosuppressive therapy, which induced a considerable number of adverse effects. Remission of proteinuria after immunosuppressive therapy for IgA nephropathy has been used as an end point in trials involving children.[20,21] Proteinuria may remit spontaneously in children,[22] whereas remission is unusual in adult patients with IgA nephropathy. Remission of proteinuria was induced in children with the use of immunosuppressive therapy.[20] Many of the children in whom remission of proteinuria was induced had low-grade proteinuria and a normal eGFR, a finding that is consistent with the results of our study. This observation suggests that patients with early-stage IgA nephropathy, mild disease, or both are probably more likely to have remission of proteinuria.

Despite the significant, though moderate, effects on proteinuria, we did not observe a significant effect of immunosuppressive therapy on a decrease in the eGFR over the 3-year study period either on the basis of the primary end point of an eGFR decrease of 15 ml per minute per 1.73 m^2 or more from the baseline eGFR or on the basis of various secondary eGFR end points. This result appears to provide particularly strong evidence because approximately 25% of participants reached the primary end point of an eGFR decrease of 15 ml per minute per 1.73 m^2 or more, and rates in the two study groups virtually overlapped. Given a mean baseline eGFR of

approximately 60 ml per minute per 1.73 m^2, our primary end point corresponds to a loss of renal function of approximately 25%. To date, regulatory bodies have used a 50% loss of renal function as an end point. However, a recent workshop concluded that a decline in GFR of 30% could be a valid surrogate end point in randomized, controlled trials of treatments for chronic kidney disease[23] because it is associated with at least a quintuple increase in the risk of end-stage renal disease.[24]

We included in the randomized phase of the trial patients who had persistent proteinuria with a urinary protein excretion rate above 0.75 g per day to enrich our analyses with patients with high-risk IgA nephropathy. Proteinuria is one of the most potent predictors of end-stage renal disease in IgA nephropathy.[25,26] Usually, clinically significant proteinuria is arbitrarily defined as a proteinuria level above 1 g of urinary protein excretion per day[3]; however, there is also evidence that in IgA nephropathy, a proteinuria level above 0.5 g of urinary protein excretion per day is a predictor of adverse renal outcomes.[27] These epidemiologic data must be interpreted with caution because the investigators for this study[27] did not analyze a comprehensive supportive care approach that was adjusted on the basis of proteinuria among the patients who entered their registry, as we did in our trial. Thus, the choice of the proteinuria threshold of 0.75 g of urinary protein excretion per day appears to be clinically justified, especially since approximately 80% of our patients who underwent randomization had a baseline proteinuria level above 1 g of urinary protein excretion per day.

Our results do not apply to patients who have a proteinuria level above 3.5 g of urinary protein excretion per day at baseline; such patients have a very high risk of progression and have been reported to have a particularly good response to glucocorticoids.[26,28] Our run-in cohort included only 23 patients (7%) with a persistent urinary protein excretion rate above 3.5 g per day at baseline. Similarly, our study excluded the patients who had a very rapid decrease in the eGFR during the run-in phase (8 patients [2.5%]). Thus, our findings cannot be extrapolated to such patients, who have a poor prognosis with or without immunosuppression.[29] Similarly, we cannot comment on patients with very advanced disease (i.e., with an eGFR lower than 30 ml per minute per 1.73 m^2) for whom immunosuppression is discouraged unless they have a vasculitic course of IgA nephropathy.[3]

The lack of positive effects of immunosuppression on the decrease in eGFR in our trial differs from the findings in various prior randomized, controlled trials that showed benefits of immunosuppression.[6-9,11] It is unlikely that our study was underpowered because the results with respect to a decrease in the eGFR in the supportive-care group and the immunosuppression group virtually overlapped, with more than 20 patients in each group reaching the end point of fast progression (i.e., a decrease in the eGFR of at least 15 ml per minute). The major difference between prior studies and our study is that our study included a run-in phase with comprehensive supportive care and selection of a homogeneous, high-risk population before the addition of immunosuppressive therapy. In the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial, mean blood pressure was approximately 126/78 mm Hg, which was substantially lower than that in previous reports.[7,11] A small 3-year trial involving patients with IgA nephropathy also showed that GFR was preserved when the blood pressure was 129/70 mm Hg, whereas GFR decreased by 15% when the blood pressure was 136/76 mm Hg.[30]

Low blood pressure may not be the only explanation for the lack of a benefit of immunosuppression with respect to eGFR in our study. In two randomized, controlled trials, eGFR was better preserved with immunosuppression added to angiotensin-converting–enzyme inhibition, despite blood pressures in the range of 120/75 mm Hg.[8,9] Both of these trials are notable for a rapid progression of chronic kidney disease in the control group that received angiotensin-converting–enzyme inhibitors alone; the annual decrease in eGFR was 7.6 ml per minute per 1.73 m^2 in one trial,[8] and in the other trial, almost 50% of the patients had a decrease in eGFR of more than 25%.[9] These data contrast with an annual decrease in the eGFR of 1.6 ml per minute per 1.73 m^2 in the supportive-care group in our study and suggest that our comprehensive supportive-care approach may have been effective in retarding the progression of IgA nephropathy. One may speculate that an increase in the dose of renin–angiotensin system blockers even when

the blood-pressure target was reached, frequent dual renin–angiotensin system blockade, or both were determining factors. Furthermore, in both prior randomized, controlled trials,[8,9] patients were younger than those in the STOP-IgAN trial by more than 10 years, and the baseline eGFR was approximately 100 ml per minute per 1.73 m^2.

Some randomized, controlled trials have noted long-lasting effects of glucocorticoids on proteinuria.[7,31] In our study, immunosuppression resulted in a significant reduction of proteinuria over that observed with supportive care. However, this effect was transient. Similarly, another randomized, controlled trial noted that after 6 months of immunosuppression or angiotensin-converting–enzyme inhibitor therapy alone, no difference in proteinuria was observed beyond 2 years.[8] Data from controlled trials on the use of glucocorticoids for substantially longer than 6 months are lacking.

Immunosuppression was associated with substantial side effects, the most disconcerting of which were infections, which resulted in one sepsis-related death. Infections were more infrequent in other trials,[11] but a study of IgA nephropathy in 2008 also noted several deaths from pulmonary infections during therapy with mycophenolate mofetil.[32] Other common adverse events related to glucocorticoid use were weight gain and impaired glucose tolerance.

One limitation of our trial is its open-label nature. Given the complex immunosuppressive treatment regimens, a blinded study did not seem possible; however, all end points were based on objectively measured laboratory values that reduced the chance for bias. Furthermore, the trial design that included two different immunosuppressive treatment regimens raises a statistical power issue for the data analysis, but this should not be a confounding factor. A second limitation is that our end points were based on eGFRs derived from creatinine measurements. Glucocorticoids can have long-lasting effects on muscles and can reduce the rate of creatinine generation, which can result in an erroneous assumption of a higher eGFR. To exclude this possibility, we verified our findings using measurements of creatinine clearance that are independent of rates of creatinine generation. A third limitation is the 3-year study duration, which is relatively short, even in a population with high-risk IgA nephropathy. Indeed, in prior trials, patients with IgA nephropathy were followed for up to 10 years to detect the effects of immunosuppression on the rate of renal failure.[7-9,33] However, in contrast to trials that showed significant differences in eGFR slopes independent of the analyzed period,[8] we did not observe a difference — not even a trend toward a difference — in eGFR between the two study groups, which suggests that the data might not have been altered by a longer study duration. Nevertheless, we cannot exclude the possibility that, for example, the patients who received additional immunosuppressive therapy and had a full clinical remission might have a better outcome with respect to preservation of renal function with a much longer follow-up.

In conclusion, our trial showed that the addition of immunosuppression to ongoing comprehensive supportive care was not beneficial in patients with IgA nephropathy that was characterized by moderate proteinuria and chronic kidney disease stages 1 through 3.

Supported by a grant (GFVT01044604) from the German Federal Ministry of Education and Research.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the trial centers and patients who participated in this trial; Natalie Luetzeler for data monitoring; Sabine Ernst, M.Sc., and Diana Ackermann, M.Sc., for support with data handling and statistical analyses; Anna Bolte and Elena Hristodorova for help with data entry and handling; and the data and safety monitoring board (Eberhard Ritz, Karl-Martin Koch, Ulf Janssen, and Walter Lehmacher).

APPENDIX

The authors' affiliations are as follows: the Division of Nephrology and Clinical Immunology (T.R., F.E., J.F.) and Department of Medical Statistics (C.F., R.-D.H.), RWTH Aachen University, Aachen, Bayer Pharma, Kidney Diseases Research, Wuppertal (F.E.), Department of Nephrology, University of Heidelberg, Heidelberg (C.S., M.Z.), Internal Medicine D, Department of Nephrology, Hypertension and Rheumatology, University Hospital Muenster, Muenster (B.O.), University Medical Center Hamburg-Eppendorf, Hamburg (U.P.), Department of Nephrology and Dieter Scheffner Center for Medical Education, Charité Campus Mitte, Charité-Universitätsmedizin Berlin, Berlin (H.P.), Department of Medicine V, University Medical Center Mannheim, University of Heidelberg, Mannheim (U.B.), Department of Nephrology and Hypertension, Diabetes and Endocrinology, Otto-von-Guericke University, Magdeburg (P.R.M.), Medical Clinic III, Central Hospital Bremen, Bremen (U.K.), Department of Nephrology, University Hospital Essen, University of Duisburg-Essen, Essen (O.W.), Clinic for Nephrology and Rheumatology, University Medical Center Goettingen, Goettingen (O.G.), and Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV, Klinikum der Ludwig-Maximilians-Universität (V.V.), and Department of Nephrology, Hypertension and Rheumatology, Munich General Hospital (J.F.E.M.), Munich — all in Germany.

REFERENCES

1. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med 2013;368:2402-14.
2. Floege J. The pathogenesis of IgA nephropathy: what is new and how does it change therapeutic approaches? Am J Kidney Dis 2011;58:992-1004.
3. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl2012; 2:142. abstract.
4. Coppo R, Peruzzi L, Amore A, et al. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. J Am Soc Nephrol 2007;18:1880-8.
5. Praga M, Gutiérrez E, González E, Morales E, Hernández E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. J Am Soc Nephrol 2003;14:1578-83.
6. Pozzi C, Bolasco PG, Fogazzi GB, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet 1999;353: 883-7.
7. Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol 2004; 15:157-63.
8. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. Nephrol Dial Transplant 2009;24:3694-701.
9. Lv J, Zhang H, Chen Y, et al. Combination therapy of prednisone and ACE inhibitor versus ACE-inhibitor therapy alone in patients with IgA nephropathy: a randomized controlled trial. Am J Kidney Dis 2009;53:26-32.
10. Eitner F, Floege J. Glomerular disease: ACEIs with or without corticosteroids in IgA nephropathy? Nat Rev Nephrol 2010; 6:252-4.
11. Ballardie FW, Roberts IS. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. J Am Soc Nephrol 2002;13:142-8.
12. Floege J, Feehally J. Treatment of IgA nephropathy and Henoch-Schönlein nephritis. Nat Rev Nephrol 2013;9:320-7.
13. Eitner F, Ackermann D, Hilgers RD, Floege J. Supportive Versus Immunosuppressive Therapy of Progressive IgA nephropathy (STOP) IgAN trial: rationale and study protocol. J Nephrol 2008;21:284-9.
14. Parikh SV, Haddad NJ, Hebert LA. Retarding progression of kidney disease. In: Freehally J, Johnson RJ, Floege J, eds. Comprehensive clinical nephrology. 5th ed. St. Louis: Saunders, 2015:931-41.
15. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
16. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.
17. International Conference on Harmonisation E9 Expert Working Group. ICH harmonised tripartite guideline: statistical principles for clinical trials. Stat Med 1999;18:1905-42.
18. Phillips A, Fletcher C, Atkinson G, et al. Points to consider on multiplicity issues in clinical trials. Pharm Stat 2002;12:255-9.
19. Ruggenenti P, Perticucci E, Cravedi P, et al. Role of remission clinics in the longitudinal treatment of CKD. J Am Soc Nephrol 2008;19:1213-24.
20. Yoshikawa N, Ito H, Sakai T, et al. A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. J Am Soc Nephrol 1999;10: 101-9.
21. Yoshikawa N, Honda M, Iijima K, et al. Steroid treatment for severe childhood IgA nephropathy: a randomized, controlled trial. Clin J Am Soc Nephrol 2006;1:511-7.
22. Shima Y, Nakanishi K, Hama T, et al. Spontaneous remission in children with IgA nephropathy. Pediatr Nephrol 2013; 28:71-6.
23. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. Am J Kidney Dis 2014;63:820-34.
24. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 2014; 311:2518-31.
25. Reich HN, Troyanov S, Scholey JW, Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol 2007;18:3177-83.
26. Tesar V, Troyanov S, Bellur S, et al. Corticosteroids in IgA nephropathy: a retrospective analysis from the VALIGA study. J Am Soc Nephrol 2015;26:2248-58.
27. Nam KH, Kie JH, Lee MJ, et al. Optimal proteinuria target for renoprotection in patients with IgA nephropathy. PLoS One 2014;9(7):e101935.
28. Kim JK, Kim JH, Lee SC, et al. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. Clin J Am Soc Nephrol 2012;7:427-36.
29. Lv J, Yang Y, Zhang H, et al. Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. J Am Soc Nephrol 2013;24:2118-25.
30. Kanno Y, Okada H, Saruta T, Suzuki H. Blood pressure reduction associated with preservation of renal function in hypertensive patients with IgA nephropathy: a 3-year follow-up. Clin Nephrol 2000;54:360-5.
31. Pozzi C, Andrulli S, Pani A, et al. Addition of azathioprine to corticosteroids does not benefit patients with IgA nephropathy. J Am Soc Nephrol 2010;21:1783-90.
32. Lv J, Zhang H, Cui Z, Su T, Zhang Y, Wang H. Delayed severe pneumonia in mycophenolate mofetil-treated patients with IgA nephropathy. Nephrol Dial Transplant 2008;23:2868-72.
33. Tang SC, Tang AW, Wong SS, Leung JC, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgA nephropathy. Kidney Int 2010;77:543-9.