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Severe Adverse Effects Associated With Corticosteroid Treatment in Patients With IgA Nephropathy

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Introduction: Few data are available on the risk of SAEs in corticosteroid users in IgAN populations. We describe the prevalence and risk factors of corticosteroid-related SAEs in a Chinese cohort.

Methods: A total of 1034 IgAN patients were followed up in our renal center from 2003 to 2014. Prevalence of corticosteroid use and corticosteroid-related SAEs were noted. Logistic regression was used to search for risk factors of SAEs in corticosteroid users.

Results: Of the 369 patients with steroids therapy, 46 patients (12.5%) with 58 events suffered SAEs, whereas only 18 patients (2.7%) without corticosteroids suffered SAEs (OR: 5.45; 95% CI: 3.07–9.68; $P < 0.001$). SAEs included diabetes mellitus ($n = 19$, 5.1%), severe or fatal infection ($n = 18$, 4.9%), osteonecrosis of the femoral head or bone fracture ($n = 6$, 1.6%), cardiocerebral vascular disease ($n = 4$, 1.1%), cataract ($n = 3$, 0.8%), and gastrointestinal hemorrhage ($n = 1$, 0.3%). Multivariable logistic regression analysis revealed that advanced age (OR: 1.05; 95% CI: 1.02–1.07; $P < 0.001$) and hypertension (OR: 1.04; 95% CI: 1.01–1.06; $P = 0.009$) were risk factors for corticosteroid-related SAEs. Impaired kidney function (estimated GFR: OR: O.98; 95% CI: 0.96–0.99; $P = 0.036$) was a risk factor for severe infection. Accumulated dosages of corticosteroids were not identified as a risk factor of SAEs (OR: 1.09; 95% CI: 0.91–1.30; $P = 0.365$).

Discussion: Corticosteroid use is associated with a high risk of SAEs in IgAN patients, especially those who are older, have hypertension, or impaired renal function. Current guidelines on corticosteroid regimens in IgAN should be reviewed with regard to safety.

Kidney Int Rep (2017) **2,** 603–609; http://dx.doi.org/10.1016/j.ekir.2017.02.003
KEYWORDS: adverse events; corticosteroid; diabetes mellitus; IgA nephropathy

IgA nephropathy (IgAN) is a glomerulonephritis mediated by immune complexes.[1–3] IgAN is characterized by a highly variable course ranging from a totally benign incidental condition to rapidly progressive renal failure. However, most affected individuals develop chronic, slowly progressive renal injury, and many patients develop end-stage renal disease (ESRD).[4]

Each year, about 1% to 2% of all patients with IgAN develop ESRD from the time of diagnosis.[5] About 15% to 20% of patients with apparent-onset IgAN develop ESRD within 10 years, and 30% to 40% within 20 years.[6–8] Lowering of blood pressure as well as inhibition of the renin-angiotensin system remains the cornerstone of IgAN management. However, a substantial number of patients progress to ESRD even with this regimen (especially those with persistent proteinuria).

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the treatment of glomerulonephritis suggest that IgAN patients with a persistent proteinuria >1 g/d despite 3 to 6 months of optimized supportive care receive a 6-month course of corticosteroids.[9] Several small clinical trials have suggested the potential renoprotective capabilities of corticosteroids in IgAN.[10–12] One meta-analysis of 9 clinical trials suggested that 6-month corticosteroid therapy could reduce the prevalence of renal failure by 68%.[13] However, these trials comprised a small number of patients, and adverse outcomes (AEs) were poorly

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Received 1 November 2016; revised 18 January 2017; accepted 3 February 2017; published online 10 February 2017

reported (especially serious adverse events [SAEs] with clinical relevance). The recently completed Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study (262 participants) found that this renoprotective benefit came at a high cost with regard to SAEs (clinicaltrials.gov no. 01560052).[14] Thus, the safety of corticosteroids in IgAN patients needs further evaluation. We evaluated the safety of corticosteroids and their risk factors in Chinese IgAN patients.

METHODS

Study Design and Participants

We reviewed the medical records of a large database of IgAN patients based at Peking University First Hospital. This cohort was established in 2003 and recruited patients mainly from northern China. A total of 1750 patients were registered from 2003 to 2014, and 1052 participants had follow-up data for ≥1 year or ≥3 times. The follow-up interval is generally scheduled at once a month thereafter for 3 months and then once every 3 to 6 months depending on patients' status or treating physician. Among them, 387 patients were screened for corticosteroid use, and 18 patients were excluded because corticosteroids had been used for less than 3 months. Thus, 1034 patients formed the study cohort. Among them, 369 patients (35.7%) received a single corticosteroid ($n = 150$) or corticosteroids plus other immunosuppressive agents ($n = 219$) for ≥3 months (Supplementary Figure S1).

The study protocol was approved by the Ethics Committee of Peking University First Hospital (approval number 2016[1142]; Beijing, China). All participants provided written informed consent for the IgAN cohort study.

Treatment Protocol

We usually considered steroid therapy in patients with persistent proteinuria >1 g/d after supportive therapy for >3 months, which was consistent with current KDIGO guidelines. Patients with a relative amount of crescents on a kidney biopsy or nephrotic syndrome (with serum albumin <30 g/l) might consider adding corticosteroids directly, which was determined by the treating physician. Other immunosuppressive agents were considered if patients presented with crescentic IgAN (cyclophosphamide and mycophenolate mofetil), persistent nephrotic syndrome (tacrolimus, cyclosporine A, or leflunomide), or progressive decline in renal function (cyclophosphamide and mycophenolate mofetil) after corticosteroid therapy. Initially, patients used prednisone or prednisolone (0.8–1 mg/kg/d; maximum, 60 mg/d) for 2 months, which was tapered to 5 mg every 2 weeks and stopped within 6 to 8 months. Another regimen of steroid pulse therapy was bolus injections (i.v.) of methylprednisolone (500 mg) for 3 days each at 1, 3, and 5 months, followed by prednisone (30 mg, p.o.) on alternate days for 6 months.[12] The option of these 2 corticosteroid regimens depended on the physician and the patients' intention. All medications used during the study period were recorded. Baseline characteristics including age, sex, blood pressure, hemoglobin, albumin, triglyceride, total cholesterol, proteinuria, serum creatinine, and estimated glomerular filtration rate ([eGFR] according to the Chronic Kidney Disease Epidemiology group [CKD-EPI] equation for Chinese[15]) were recorded.

Definition of SAEs

This was a retrospective study, and to minimize the selection bias, only patients with AEs necessitating hospitalization or treatment changes were considered as SAEs in the study. SAEs of interest were as follows: (i) all-cause mortality; (ii) severe infection necessitating hospitalization or fatal infection; (iii) osteonecrosis of the femoral head or bone fracture; (iv) gastrointestinal hemorrhage or gastrointestinal perforation; (v) new-onset diabetes mellitus (DM); (vi) new-onset cataract; (vii) major cardiocerebral vascular disease (including fatal/nonfatal myocardial infarction, fatal/nonfatal stroke, and heart failure). All adverse effects were recorded according to the clinical diagnoses. The relationship between these SAEs was adjudicated by 2 investigators (QC, JL) to ascertain whether the AE was related to the study drug.

Statistical Analyses

Continuous variables are expressed as the mean and SD or median with 25th and 75th centiles (as appropriate) for data distribution. Categorical variables are summarized as frequencies with percentages. Significance of differences between groups was dependent on distribution of data (normal or nonnormal) and so was determined from the independent sample t test or Mann-Whitney test as appropriate (for comparison of continuous scores between 2 groups) and the chi-squared test with continuity correction (for comparison of proportions between 2 groups). We analyzed relevant covariates that might associate with SAEs with multivariable logistic regression and reported odds ratios (ORs) with 95% confidence intervals (CIs) and P values of Wald χ^2 test. Covariates included in the analysis were age, sex, mean arterial pressure, proteinuria, eGFR, and corticosteroid or corticosteroid plus immunosuppressant therapy. To evaluate cumulative corticosteroid dosages on the risk of SAEs, we used the propensity-score matching patients with and without SAEs using the following 6 potential confounders: age,