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Should we really STOP treating patients with IgA nephropathy with steroids?

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IgA nephropathy (IgAN) is the most common primary glomerulonephritis all over the world. Once considered as a benign disease, today the scientific community is aware that a significant percentage of patients eventually progress to end-stage kidney disease (ESKD). The rate of progression is often very slow. Since 1980s, several therapeutic attempts have been made with steroids. Despite different molecules, doses, and lengths of treatment, the majority of uncontrolled and controlled studies found benefits in terms of proteinuria reduction and reduction of the risk of ESKD. This was obtained with reasonable safety and tolerability, especially when steroids are given at relatively low dose and for a period not exceeding 6 months. Recently, two randomized controlled trials have questioned the efficacy and safety of steroid therapy in IgAN. However, these trials have many drawbacks that are to be considered when interpreting the findings.

Keywords: IgA nephropathy, proteinuria, steroids, progression, end-stage kidney disease, budesonide

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis all over the world, being particularly frequent in the Asian-Pacific areas (9) and in males (21).

It is characterized by predominant IgA deposition in the mesangial area of the glomerulus. Clinically, it may present with variable symptoms and/or lab exams, going from hematuria (either microscopic or macroscopic) or proteinuria to nephritic or nephrotic syndrome.

IgAN has been considered as a benign disease for many years, since many patients maintain stable kidney function over time. However, when the follow-up is extended to 20 years or more, up to 40% of the patients progress to end-stage kidney disease (ESKD), even with optimal blood pressure control and treatment with renin–angiotensin–aldosterone system (RAAS) blockade.

Hematuria has always been underestimated as a sign of active disease (5). Conversely, proteinuria is the most important prognostic factor for disease progression (1, 6, 11, 13, 14). Accordingly, the patients who maintain proteinuria levels below 1 g/day during follow-up have a better outcome, regardless of baseline proteinuria (30). Then, proteinuria is not only a mere marker of disease, but is also an index of disease activity and response to treatment (30).

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Physiopathology of IgAN

IgAN is triggered by an alteration in galactosylation (and sialylation) of the glycans of IgA_1, which accounts for about 90% of IgA. Human IgA_1 has a unique mucin-like structure in its hinge region. It can carry up to six sugar chains called O-linked glycans. In IgAN patients, IgA_1 molecules have an aberrant structure of their O-glycans, characterized by abbreviated glycans that are composed of N-acetylgalactosamine either with or without sialic acid (33). This aberrant glycosylation of IgA_1 can be recognized as an autoantigen that generates the synthesis of glycan-specific autoantibodies. The binding of antibodies to antigens forms circulating immune complexes. These can accumulate in the mesangium and stimulate activation of mesangial cells, production of extracellular matrix, and release of proinflammatory cytokines and chemokines, which can initiate and perpetuate the glomerular injury (2). The complement activation via the alternative or the lectin pathways also plays an important role (20).

The First Uncontrolled Studies of Corticosteroids in IgAN

Until recently, many nephrologists have used only symptomatic therapy in IgAN, mainly based on RAAS inhibitors. This attitude was mainly based on the belief that IgAN is an indolent disease and on the lack of information about its pathogenesis. However, it is now clear that a substantial number of patients with IgAN may eventually progress to ESKD. Moreover, the pathogenesis of the disease has been partly elucidated.

As specified above, different factors contribute to the pathophysiology of IgAN. These pathogenic events may theoretically benefit by the anti-inflammatory and immunosuppressive effects of corticosteroids (23).

An early attempt with corticosteroids in IgAN patients and proteinuria of ≥2.0 g/day was made by Kobayashi et al. (16).

They used prednisolone at an initial dose of 40 mg/day and then tapered to a maintenance dose of 15 mg/day for 1–3 years. The patients, who had a creatinine clearance of ≥70 ml/min, maintained stable kidney function over time, but 1 out of 15 patients had developed ESKD after a follow-up of 74 months. Conversely, in the group with creatinine clearance <70 ml/min, the rate of creatinine clearance decline was not modified by steroid treatment. Among adverse effects, avascular necrosis of the femoral head and duodenal ulcer were reported in two patients.

In another uncontrolled trial, the same group studied IgAN patients with proteinuria of 1–2 g/day (17). About 18 subjects were placed on a similar prednisolone regimen for a period of 2 years and were compared with the other 42 subjects, who were given either indomethacin or dipyridamole. Again, patients with creatinine clearance <70 ml/min did not respond to therapy, whereas patients with creatinine clearance ≥70 ml/min remained stable in both the treatment and control groups.

A small, controlled trial failed to demonstrate any benefit of corticosteroids at lower doses overall, even if efficacy was found in the subgroup with IgAN and nephrotic syndrome with minimal glomerular lesions at biopsy (18).

In order to reduce the potential toxicity of steroids, an alternate-day steroid therapy was proposed. In an uncontrolled trial, children with IgAN and proteinuria of more than 1 g/day were given prednisolone at a dose of 60 mg/m^2 every other day for a period of 2–4 years (using historical controls). This therapy normalized urine abnormalities, preserved

glomerular filtration rate (GFR), and resulted in a fall in the glomerular activity score in repeated renal biopsies. No steroid toxicity was observed (no increase in the incidence of hypertension, cataracts, growth retardation, infections, or bone disease) (37).

In a retrospective study of 45 adults with IgAN and proteinuria between 0.5 and 2.0 g/day, 23 patients were given steroids and the remaining 22 patients received symptomatic therapy. During the follow-up of 3 years, urinary protein excretion did not change in the control group, but mean urinary protein excretion decreased significantly in the steroid group. Seven patients in the control group and two patients in the steroid group reached the endpoint (defined as a 50% increase in serum creatinine concentration from baseline). A second biopsy was performed in 20 patients who had received steroid therapy. Mesangial cell proliferation, mesangial matrix increase, and cellular crescents were significantly reduced in the second biopsy compared to the first biopsy specimens (36).

Randomized Controlled Trials in IgAN

In an open-label, randomized controlled study, 86 adults with IgAN, serum creatinine levels ≤1.5 mg/dl, and proteinuria of 1–3 g/day were randomized either to symptomatic treatment or to a 6-month course of steroid therapy (three methylprednisolone pulses at the beginning of months 1, 3, and 5, followed by oral prednisone 0.5 mg/kg every other day) (28). Patients who were assigned to steroid treatment showed a significant reduction in the risk of reaching the endpoint of the doubling of the serum creatinine (28). Indeed, the 10-year renal survival was significantly better in the corticosteroid than in the control group (97% vs. 53%). The median value of daily proteinuria has also significantly decreased in the corticosteroid arm and increased in the control group. One steroid-treated participant developed diabetes; no other serious side effects were reported. Interestingly, the changes in proteinuria during follow-up predicted the outcome better than the absolute proteinuria values at baseline (26).

Another multicentre trial randomly assigned 97 participants with IgAN, proteinuria >1 g/day, and creatinine clearance >50 ml/min/1.73 m^2 to ramipril alone or to combined therapy with ramipril and a 6-month course of prednisone (0.8–1 mg/kg/day for 2 months tapered to 0.2 mg/kg/day). Combined treatment increased the probability of not reaching the primary outcome measure of the doubling of the serum creatinine or ESKD (85.2% vs. 52.1%); it also significantly reduced the proteinuria (22). Adverse events were mild in both groups. These findings were confirmed in another larger trial of 207 patients, who were randomized to corticosteroids along with azathioprine or corticosteroids alone and followed for a median follow-up of 5 years (27). Both treatments significantly reduced proteinuria; however, azathioprine did not add additional benefit to steroids alone and was less tolerated.

More recently, a systemic review of nine randomized controlled trials, including more than 500 participants, demonstrated that a course of corticosteroids was more effective in reducing the risk for renal function deterioration in comparison with supportive therapy alone in IgAN (4). According to these data, the Kidney Disease Improving Global Outcome (KDIGO) guidelines recommended the use of RAAS inhibitors as the initial approach in patients with IgAN, followed by a course of corticosteroids in those with an estimated GFR (eGFR) of >50 ml/min/1.73 m^2 and persisting proteinuria if >1 g/day, despite 3–6 months of optimized supportive care including (RAAS) blockers (15).

After the publication of the KDIGO guidelines, corticosteroids have been widely used in IgAN patients with these characteristics. Conversely, during the preparation of the KDIGO

guidelines, the evidence about the effectiveness and safety of corticosteroids (and immunosuppressive therapies) was scanty in the more advanced phases of IgAN and chronic kidney disease (CKD).

More recently, some large cohort studies and new, randomized controlled trials have provided conflicting messages about the benefits of corticosteroid treatment with regard to supportive care alone (mostly based on optimized RAAS blockers use). More importantly, concerns were raised about the safety of corticosteroids use in IgAN. Therefore, confusion and incertitude were generated (mainly on corticosteroids use), even in IgAN patients with significant proteinuria and progressive disease.

A retrospective analysis from the European Validation Study of the Oxford Classification of IgAN (VALIGA) confirmed that corticosteroids reduce the risk of progression of renal damage in IgAN patients and showed a possible great advantage of corticosteroids in those with severe histologic lesions (34). This suggests that the predictive value of pathology is reduced in patients who had received immunosuppressive therapy (mainly corticosteroids).

In 2015, the randomized controlled STOP-IgAN study tested the hypothesis that immunosuppressive therapy (corticosteroids in combination or not with alkylating/antimetabolite agents) and comprehensive supportive care would be superior to supportive care alone (29). The primary endpoints were full clinical remission, defined as urinary protein/creatinine <0.2 mg/mg with stable eGFR or decrease of eGFR more than 15 ml/min/1.73 m^2. Eligible patients had proteinuria >0.75 and <3.5 g/day and hypertension or eGFR between 30 and 90 ml/min/1.73 m^2. During a 6-month run-in phase, a rigorous supportive therapy was implemented, including moderate protein intake restriction, cholesterol control with statins, avoiding of smoking and nephrotoxic drugs and RAAS inhibitors, which were titrated to attain a strict blood pressure target (<125/75 mmHg). The run-in phase was completed by 309 of 337 patients. The randomization excluded 34.4% of patients who responded to supportive care (proteinuria < 0.75 g/day) and 12.3% of patients at high risk of renal function deterioration (proteinuria >3.5 g/day, eGFR <30 ml/min/1.73 m^2 or decreased by >30% during the run-in phase). Then, the remaining 162 patients were either randomized to continued supportive care alone or assigned to receive corticosteroid/immunosuppression with two very different protocols: 55 patients with eGFR of >60 ml/min/1.73 m^2 received corticosteroids for 6 months (three intravenous pulses of methylprednisolone of 1 g each at months 1, 3, and 5 and oral prednisolone of 0.5 mg/kg on alternate days); 27 patients with eGFR >30 and <59 ml/min/1.73m^2 received 1.5 mg/kg/day of cyclophosphamide for 36 months, followed by 1.5 mg/kg/day of azathioprine and 40 mg/day of oral prednisolone waning over 36 months.

After 3 years, 5% of the patients in the supportive-care group versus 17% in the immunosuppression group had full clinical remission ($p = 0.001$). However, no difference between the two groups was found in the decrease of eGFR >15 ml/min/1.73 m^2 (28% vs. 26%). The patients in the corticosteroid/immunosuppression group had significantly lower mean proteinuria than those in the supportive-care group after a 1-year follow-up, but the difference was no longer significant at 3 years, mostly because of an increase in proteinuria in patients with advanced CKD. Microscopic hematuria disappeared more frequently in the corticosteroid/immunosuppression group ($p = 0.004$). More patients receiving corticosteroids monotherapy than those receiving combination immunosuppressive therapy had remission of proteinuria, hematuria, or both (probably because those receiving only steroids have a milder disease). The serious adverse events had similar frequency in the two study groups, but the patients treated with immunosuppression had reported more cases of infection, impaired

glucose metabolism, and body-weight gain. Of note, one patient died of sepsis and two others had malignant neoplasms during combined immunosuppression. As expected, the side effects occurred more frequently in the patients who had lower renal function and were treated with the combination of corticosteroids and immunosuppressive drugs.

The authors of the STOP-IgAN concluded that additional immunosuppressive therapy does not provide substantial kidney-related benefits in patients with high-risk IgAN, since there was no difference in the rate of decrease in eGFR (although corticosteroid/immunosuppressive therapy induced more frequently than supportive care alone complete remission of proteinuria).

The supportive care adopted in the STOP-IgAN trial was very rigorous and the results were impressive. However, not all the participants enrolled in the trial were at high risk. Patients with proteinuria >3.5 g/day or progressive loss of eGFR were excluded, whereas participants with proteinuria <1 g/day (proteinuria >0.75 g/day) and mild eGFR decline (mean decline of 1.6 ml/min/year) were included. A 3-year follow-up for patients with such a slow-progressive disease was likely to be insufficient to detect any beneficial effect of corticosteroids. This is also considering that the sample size was already halved by the end of the run-in phase. Another limitation of the study is that two small groups of patients with different characteristics and corticosteroid/immunosuppressive regimens were pooled together. In the corticosteroid monotherapy group, proteinuria at 1 year dropped below 1 g/day and remained stable till the third year, with full remission in 30% of the cases. Conversely, in the immunosuppressive combination therapy group, which included patients with eGFR <60 ml/min/1.73 m^2, proteinuria slightly decreased at 1 year but increased again above 1.2 g/day at the end of the follow-up. Only 11% of these patients went into full remission. The two groups had different anti-proteinuric responses and thus the effects on eGFR decline on the long-term course were different as expected (24).

According to the data of the Toronto's Registry (30), the remission of proteinuria <1 g/day is a predictor of a better renal survival; this finding is not evident before 5 years of follow-up. Similarly, the VALIGA study showed that the protective effect of proteinuria decline >0.5 g/day on the combined endpoint of the 50% decline of eGFR and/or ESKD was detected after 10 years of follow-up (34). The data analysis of the STOP-IgAN trial is further complicated by an unusual endpoint, i.e., the loss of eGFR of >15 ml/min/1.73 m^2 (i.e., a 25% loss roughly). This does not allow a direct comparison with previous studies. Thus, we can speculate that a positive effect of corticosteroids in the steroid monotherapy group may be observed if these patients had been followed up for longer than 3 years.

The role of corticosteroids in IgAN has been further investigated by the Therapeutic Evaluation of Steroids in IgAN (TESTING) (19), which enrolled 262 patients with biopsy-proven IgAN, proteinuria >1 g/day, and eGFR 20–120 ml/min/1.73 m^2. The participants were randomized either to oral methylprednisolone 0.8 mg/day for 2 months then weaned over 6–8 months or matching placebo. The TESTING trial found that methylprednisolone could significantly reduce the time-averaged proteinuria and the decline of kidney function. However, the trial was stopped earlier because of excess serious adverse events, in particular infections (two deaths in the steroids group vs. one in the control group). In this regard, it is important to underline that the dosage of oral methylprednisolone was higher and the length of the treatment was longer than that commonly used to treat IgAN patients in everyday clinical practice and in previous controlled trials.

Budesonide is a slow release corticosteroid with local activity (enteric Peyer's patches). Positive effects of budesonide in IgAN have been reported by the NEFIGAN trial (8). Even if

budesonide is supposed to act only on the intestinal mucosa, when given at high dose, the drug can cause some systemic side effects.

Main Side Effects of Corticosteroids and Their Prevention

Corticosteroids may be responsible of a large number of side effects, including infections, diabetes, hypertension, hyperlipidaemia, metabolic syndrome, hypercoagulability, cardiovascular disease, psychiatric reactions, myopathy, tendon rupture, osteoporosis, aseptic bone necrosis, obesity, cataract and glaucoma, peptic and colonic ulcer, hypoadrenalism, growth retardation in children, frail skin, and aesthetic changes, such as acne, *striae rubrae*, moon facies, and Bateman's purpura.

In most cases, these adverse events are dose- and time-dependent. The type of corticosteroid, the time and modality of administration, and a careful use of other concomitant drugs may also influence the toxicity of corticosteroids.

Short-acting corticosteroids (such as prednisone, prednisolone, and methylprednisolone) are the drugs of choice for chronic treatments. Indeed, long-acting molecules (betamethasone and dexamethasone) may favor the atrophy of adrenal tissues and hypoadrenalism crisis at steroid cessation or at too rapid dose decrease (24).

The time of day to administer corticosteroid is critical. Endogenous cortisol levels increase early in the morning, decline through the day, and become low during sleep onset. Thus, it is recommended to give the daily dosage of a short-acting glucocorticoid in a single-morning administration, between 7 and 9 a.m., in order to mimic the circadian rhythm of natural corticosteroids. Administration of synthetic glucocorticoids twice or thrice a day cannot replicate the circadian rhythm of cortisol and can increase the risk of infections and metabolic disorders (7, 12).

It is important to remind that the anti-inflammatory and immunosuppressive effects of corticosteroids mainly depend on its genomic effects. Steroids bind to their receptor in the cytosol, form a new complex that enter the nucleus and bind to the glucocorticoid-response elements, and eventually activating anti-inflammatory genes (transactivation) or repressing transcription factors (transrepression). These genomic effects may require 4–24 h. Differing with genomic effects, non-genomic effects may develop within few minutes. These effects are probably mediated by membrane receptors. Even if not completely proved, it is likely that the intravenous administration of short-term corticosteroids (namely methylprednisolone) may activate non-genomic effects, maximizing their efficacy while reducing side effects in comparison with high-dose oral prednisone (3, 32).

When infused in a peripheral vein over 30–60 min, methylprednisolone is generally safe. Severe complications, including seizures, cardiac arrhythmias, and anaphylaxis, have been reported exceptionally and occurred when the steroid was injected rapidly and/or was given through a central venous line in critically ill patients.

Concomitant treatments may influence the activity and toxicity of corticosteroids. Many physicians use long-term proton pump inhibitors to protect from the ulcerogenic effect of glucocorticoids. However, the prolonged use of these drugs may deteriorate renal function in some patients (35, 38). Corticosteroids are metabolized by cytochrome P450 (CYP450) enzymes. Although the regulation of CYP450 is a complex process involving multiple mechanisms, some drugs, such as erythromycin, clarythromycin, tienilic acid, and ketoconazole, inhibit the activity of CYP450 enzymes and can reduce the ability of the liver to

metabolize glucocorticoids. This may lead to an increase in their circulating levels and side effects. Conversely, drugs such as phenobarbital, phenytoin, and rifampicin activate CYP450 with consequent increased breakdown of glucocorticoids and reduction in their blood levels (10). Glucocorticoid effects on warfarin can vary, requiring a strict monitoring of coagulation parameters (10).

A correct lifestyle is critical to prevent adverse events. Handwashing is the best way to prevent infections. Regular teeth brushing and flossing can prevent parodontopathy and reduce the risk of cardiovascular disease. Patients receiving continuous steroid treatment should follow a low-caloric diet to prevent excessive body weight increase, diabetes, and hyperlipidemia. Limited salt intake is also recommended to prevent hypertension and water retention. Physical activity is warranted when feasible to prevent myopathy, osteopenia, and obesity. Smoking cessation, mild alcohol intake, and strict control of blood pressure can also prevent cardiovascular disease.

A supplementation of vitamin D together with bisphosphonate in high-risk patients is suggested to reduce the risk of osteoporosis.

If steroid is discontinued after a long-term treatment, the adrenal tissues may be unable to respond, having atrophied during the period of disuse. Symptoms of acute adrenal insufficiency include irritability, nausea, arthralgia, dizziness, and hypotension. The risk of hypoadrenalism depends on the duration and type of treatment; the use of single-morning administration of short-acting corticosteroids may prevent or reduce the symptoms of hypoadrenalism. A further important measure consists in the gradual withdrawal of corticosteroids, tapering the doses over weeks or months to allow the atrophied cortex to regain functional status.

Conclusions

Whether to treat or not IgAN is still an open question, despite years of clinical trials, since many patients may remain asymptomatic and stable for years. Thus, it is important to recognize the patients who are likely to progress. At present, the best indicator of outcome is the time-averaged proteinuria; the lower it is, the higher is the renal survival. This prognostic role is maintained in patients with severe renal insufficiency. Other prognostic factors are hematuria, serum creatinine and 24 h proteinuria at baseline, and blood pressure increase during follow-up. In the presence of indicators of poor outcome, the use of corticosteroids is the treatment of choice. Randomized controlled trials and large cohort studies unanimously demonstrated that a 6-month course of corticosteroids may reduce proteinuria and protect from kidney function deterioration. Nonetheless, the STOP-IgAN (29) and TESTING (19) trials warned against the risk of infection with corticosteroid treatment. However, these trials have many drawbacks. For instance, the TESTING trial does not give detailed information about the clinical conditions of participants and how the corticosteroids were administered. In our own experience, the use of corticosteroids proved to be very effective and safe in IgAN. According to the Pozzi–Locatelli schedule (28), and as already proposed by Ponticelli et al. (25) in membranous nephropathy, we believe that a 6-month course of corticosteroids is the most effective and safest therapy for reducing time-averaged proteinuria and improving renal survival.

While the association with RAAS inhibitors is recommended, there is no evidence that the combination of corticosteroids with alkylating/antimetabolites drugs is more effective than corticosteroids alone (27, 31). Moreover, this association can expose to increased risk of

side effects and should be avoided, especially in patients with impaired renal function. Potential positive effects have been reported with budesonide, an oral corticosteroid with local intestinal efficacy. However, systemic side effects have also been reported. A larger trial testing budesonide over a longer follow-up has been designed for validating these preliminary positive results.

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