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IgA Nephropathy: Are We Doing Enough?

Jose Lucas Daza[1], Yaroslad de la Cruz[1], Luis Puello[1], Gerardo Gutierrez[1], Alexander Ariza[2], Antonio Vasquez[3], Orlando Ariza[4]

[1]Department of Internal Medicine, Nephrology, University of Buenos Aires, Buenos Aires, Argentina
[2]Department of Internal Medicine, Hematology, University of Buenos Aires, Buenos Aires, Argentina
[3]Department of Internal Medicine, University of Buenos Aires, Buenos Aires, Argentina
[4]Department of Internal Medicine, Cardiology, University of Buenos Aires, Buenos Aires, Argentina
Email: montelucaz@gmail.com

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Abstract

Immunoglobulin A nephropathy (IgAN) was first identified and described as a disease by Berger and Hinglais in 1968. It is the most common primary glomerulopathy worldwide [1], most prevalent in East Asians and Caucasians and rare in black individuals. There are four key elements that contribute to IgAN, which determine the severity, course, and prognosis of the disease: circulating IgA immunocomplexes that favor mesangial deposition, the efficiency of the reticuloendothelial system, mesangial cell affinity and reaction to mesangial accumulation of poorly glycosylated IgA1, and the renal tendency to glomerulosclerosis and interstitial fibrosis. Clinical manifestations among patients with IgAN include hematuria, approximately 40% to 50% of cases present with one or more episodes of hematuria, usually preceded by upper respiratory tract infections. Between 30% and 40% present with hematuria and non-nephrotic range proteinuria that may be associated with arterial hypertension and impaired renal function. The TESTING study reveal a significant decrease in outcomes such as the risk of a 40% decrease in glomerular filtration rate or the need for renal replacement therapy in the group treated with steroids. The decrease in renal function compared to the group treated in the previously mentioned STOP-IgAN trial was 4 times less than in the TESTING study. *Are we doing enough?* Obviously, more trials are required with the use of adequate nephroprotection measures. We present 3 patients with a diagnosis of IgA nephropathy who attend the follow-up consultation and voluntarily decide to take part in the review.

Keywords

Immunoglobulin A Nephropathy (IgAN), Inhibition of the Renin-Angiotensin System (ACEI/ARA II), End-Stage Renal Disease (ESRD)

1. Introduction

Immunoglobulin A nephropathy (IgAN) was first identified and described as a disease by Berger and Hinglais in 1968. It is the most common primary glomerulopathy worldwide [1], most prevalent in East Asians and Caucasians and rare in black individuals [2]. In a Chinese study of 13,519 kidney biopsies, IgAN accounted for 45% of all cases of primary glomerulopathy [3]. An international survey on kidney biopsies found that IgAN accounted for 22% and 11% of glomerular disease diagnoses in Europe and North America, respectively [4].

The disease can be present at any age, with a peak incidence in the second and third decades of life. There is a 2:1 male-to-female predominance in North American and Western European populations in both adults and children, although the sexes are equally affected among East Asian populations [5].

The initiating event in the pathogenesis of IgA nephropathy (IgAN) consists of mesangial deposits of IgA, mainly polymeric IgA of the IgA1 subclass. Coexistent deposits of immunoglobulin G (IgG) and complement C3 are also frequently seen and may contribute to disease severity. Mesangial deposits of secretory IgA have also been reported, but the pathogenic significance of these deposits is unclear [6].

There are four key elements that contribute to IgAN, which determine the severity, course, and prognosis of the disease [7].

- Generation of circulating IgA immunocomplexes with chemical and biological characteristics that favor mesangial deposition;
- The ability of the reticuloendothelial system to effectively clear potentially pathogenic IgA immune complexes or poorly glycosylated IgA1 aggregates from the circulation;
- Mesangial cell affinity and reaction to mesangial accumulation of poorly glycosylated IgA1;
- The renal tendency, which when suffering an injury responds with glomerulosclerosis and interstitial fibrosis regardless of whether the inflammatory process is resolved.

The characteristics of pathogenic IgA are [8]: Overproduction of anionic IgA and lambda light chains in the blood, increased amount of polymeric IgA in the serum, large increase of poorly galactosylated IgA, IgA1 alterations due to sialylation.

Clinical manifestations among patients with IgAN include hematuria, approximately 40% to 50% of cases present with one or more episodes of hematuria, usually preceded by upper respiratory tract infections. Between 30% and 40% present with hematuria and non-nephrotic range proteinuria that may be associated with arterial hypertension and impaired renal function. Nephrotic syndrome is an infrequent presentation, only 5% of cases, severe lesions (glomerular sclerosis, crescents, tubular atrophy, interstitial fibrosis, and vascular compromise) can be found in the renal biopsy, as well as mild mesangial proliferation and fusion of the podocytes, similar to a minimal change lesion. Neph-

ritic syndrome is between 8% and 10% of cases. Acute renal failure, between 5% to 8% of cases, may be due to two causes: IgA nephropathy superimposed on extracapillary glomerulonephritis, with non-nephrotic range proteinuria and dysmorphic microhematuria in most cases and acute kidney injury that can occur during episodes of macro hematuria, usually due to infectious presentations of main respiratory cause, or by tubular obstruction by erythrocyte casts with histological lesions of acute tubular necrosis, induced by the release of iron by lysis of red blood cells [9] [10].

The treatment of primary IgAN is mainly based on general measures such as sodium restriction, weight control, smoking cessation, physical activity, and blood pressure control.

In patients with proteinuria greater than or equal to 0.5gr/day, the renal prognosis improves with the blockade of the renin-angiotensin-aldosterone system with the ACEI and ARA II associated with modifying the lifestyle of the patients.

Among patients who do not reach the goal of proteinuria with an ACEI or ARB II at the maximum recommended dose for at least three and up to six months, whose blood pressure does not reduce to levels associated with symptoms, the addition of other antiproteinuric therapies is recommended or renoprotective such as an SGLT2 inhibitor rather than combination therapy with an ACE inhibitor and ARB II [11].

In patients at high risk of progression; For those with proteinuria ≥ 1 g/day despite at least three to six months of optimized management, immunosuppressive treatment primarily with glucocorticoids has been shown to improve outcomes in patients with IgAN but with significant acute and chronic adverse events (particularly at high doses administered for prolonged periods) [12].

A targeted-release oral formulation of the glucocorticoid budesonide (delayed/directed-release budesonide) has been designed to deliver the drug in the distal ileum in patients with immunoglobulin A nephropathy (IgAN) to target the presumed site of time aberrant galactosylated IgA1 production. It limits the systemic absorption of glucocorticoids. The efficacy and safety of this agent were evaluated in a randomized phase 3 trial of 199 patients with IgAN and persistent proteinuria despite optimized renin-angiotensin system blockade. [1] [13] Treatment with targeted-release budesonide, compared with placebo, gave resulted in a greater reduction in proteinuria from baseline and a slower estimated rate of decline in glomerular filtration rate at nine months; although the rates of adverse events were similar between the groups, the rates of adverse events leading to treatment discontinuation were higher in the budesonide group. Longer-term results are expected with budesonide, for now, initial treatment with oral systemic glucocorticoids plus supportive non-pharmacological measures is still suggested for IgAN patients at high risk of disease progression. Regarding the prognosis of patients with IgAN with proteinuria less than 0.5 gr/day, they have a low risk of progression. However, progressive proteinuria and renal function deterioration develop in a high number of patients over the long term [14].

Among patients who develop persistent proteinuria > 1 g/day and/or elevated serum creatinine, progression to end-stage renal disease (ESRD) is approximately 15% to 25% at 10 years and 20% at 20 years [15].

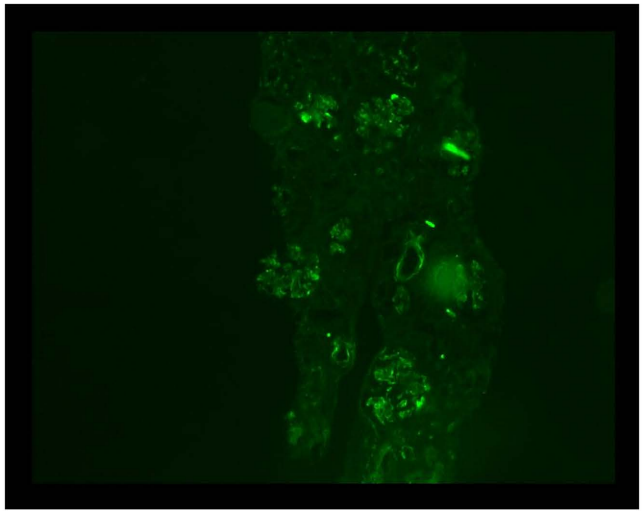
2. Case Reports

CASE 1. A 53-year-old male patient with a medical history of arterial hypertension, hyperlipidemia, obesity and renal lithiasis presented a 3 months history of intermittent macroscopic hematuria related to flu-like symptoms, associated with pain in the right renal fossa, she consulted the emergency service on several occasions, and the symptoms were attributed to renal colic. Physical examination with blood pressure of 140/90mmHg HR 87 bpm weight 105 kg height 1.79 mts. Paraclinical findings with creatinine of 1.7 mg/dl (reference range, 0.6 a 1.1) and proteinuria of 1.6 g/day (reference range, less than 150 mg/day), LDL 205 mg/dl (reference range, less than 100), urinary sediment with glomerular hematuria, negative immunoserology and viral serology, renal and urinary tract ultrasound with 4-mm lithiasis in middle calyceal group of the right kidney. A renal biopsy was performed without complications with findings of IgAN M1E0S0T1C0 (**Figure 1**).

Treatment was started with irbesartan 150 mg every 12 hours, spironolactone 25 mg per day, dapagliflozin 10 mg per day, liraglutide 3 mg sc per day, and budesonide 18 mg per day. Follow-up was carried out for 12 months, reaching complete remission (**Table 1**).

CASE 2. A 32-year-old male patient, with no pathological history, consulted the emergency department due to a 3-day evolution of predominantly holocranial headache, self-medicated with NSAIDs with supra-therapeutic doses. On admission high blood pressure figures BP 170/90mmHg weight 76 kg height 1.76 mts. Paraclinical tests showed acute renal failure with creatinine of 2.1 mg/day, urinalysis with proteinuria and microhematuria. Nephrology evaluation was requested, urinary sediment was performed showing glomerular hematuria and 24-hour proteinuria of 1.9 g/day. Serological tests and viral serologies were requested with normal results. He began treatment with prednisolone at a dose of 40 mg per day for 30 days, a renal biopsy was performed with evidence of IgA M1E1T0S1C1 nephropathy. Prednisolone was suspended and treatment with budesonide 18 mg per day was indicated. Dapagliflozin 10 mg per day, spironolactone 12.5 mg per day and valsartan 160 mg every 12 hours were added to the treatment. Follow-up was carried out for 12 months, reaching complete remission (**Table 2**).

CASE 3. A 48-year-old male patient with a history of hyperlipidemia, controlled arterial hypertension, grade II obesity and 1st-degree relatives of father on dialysis at 48 years of unclear etiology presented ad admission. His usual medication is losartan 50 mg every 12 hours, amlodipine 5 mg every 12 hours, atorvastatin 40 mg daily. He presented with headache and palpitations, which is why he consulted with cardiology, which evidenced stage II hypertension 170/90mmHg



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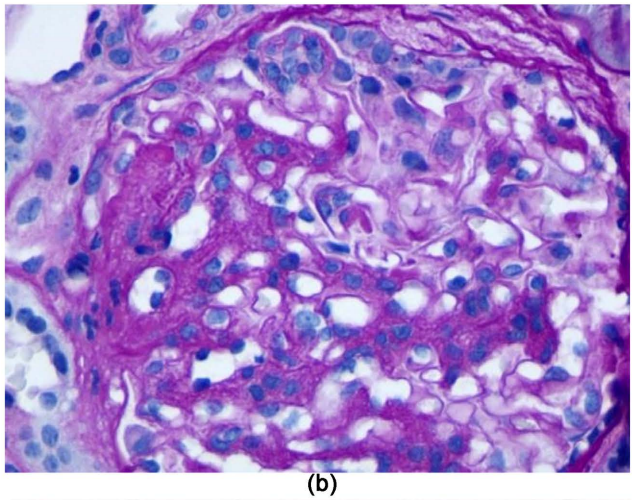

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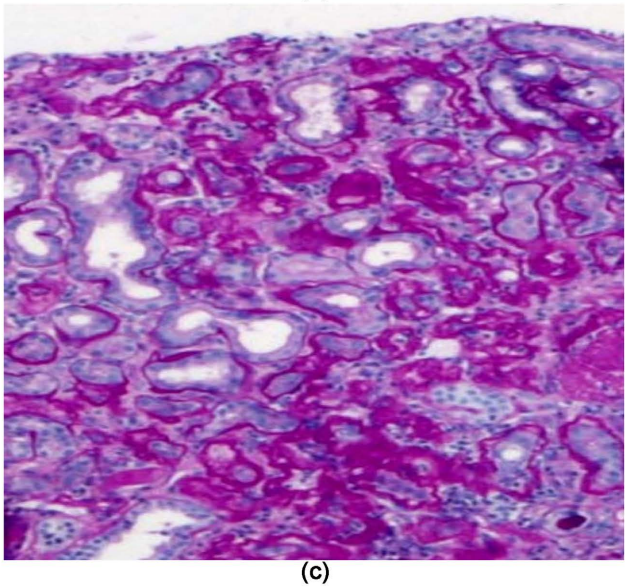

(c)

Figure 1. Renal biopsy. (a) Intense and diffuse mesangial immunostaining IGA; (b) Hematoxylin, eosin staining shows mesangial proliferation with increased mesangial matrix; (c) Hematoxylin, eosin staining tubular atrophy.

Table 1. Evolutionary monitoring of patient treatment.

Laboratory/Month	1st month	3rd month	5th month	7th month	9th month	12th month
Creatinine mg/dl	1.7	1.5	1.4	1.2	1.1	1.1
24-hour proteinuria (g/day)	1.6	1.45	1.1	0.67	0.76	0.34
Acanthocytes	+	+	+	-	+	-
LDL	205	145	100	87	62	55
Weight (kg)	105	96	90	87	85	83
BP (mm/Hg)	140/90	110/60	120/50	110/70	120/60	110/65
Liraglutide	+	+	+	+	+	+
Budesonide mg/day	18	18	18	18	18	-

Table 2. Evolutionary monitoring of patient treatment.

Laboratory/Month	1st month	3rd month	5th month	7th month	9th month	12th month
Creatinine mg/dl	2.1 mg/dl	1.5	1.36	1.23	1.25	1.31
24-hour proteinuria (g/day)	1.9	0.9	0.71	0.54	0.45	O.41
Acanthocytes	+	+	+	+	-	-
Weight (kg)	72	70	72	71	73	71
BP (mm/Hg)	170/90	120/60	110/60	120/50	110/60	120/60
Budesonide mg/day	-	18	18	18	18	-
Prednisolone	40 mg	-	-	-	-	-

with evidence of proteinuria 1.8 g/day, weight 116 kg, height 1.95 meters, creatinine 1.96 mg/dl and microhematuria. He is referred to nephrology.

Urine sediment was performed with the presence of glomerular hematuria (**Figure 2**), TGL 789 mg/dl, TC 389 mg/dl (reference range, less than 200), LDL 278 mg/dl HBA1C 6.4% uric acid 9.3 mg/dl (reference range, 3.5 to 7.2), negative serologies and negative viral serology. A renal biopsy was performed with a diagnosis of IgA nephropathy M1E1S0T0C1. It was initially managed with budesonide 18 mg/day, spironolactone 25 mg/day, valsartan 160/amlodipine 5 mg once every 12 hours, evolucumab 140 mg sc every 15 days, rosuvastatin 40 mg, ezetimibe 10 mg/day, dapagliflozin 10 mg/day, liraglutide 3 mg subcutaneously/day. A weight reduction of more than 10% was achieved over 12 months of treatment, and she also achieved complete remission and is still in clinical follow-up (**Table 3**).

In the Global Study of IgA Nephropathy (TESTING Low Dose Study) in which immunosuppressive therapy with steroids is evaluated, more than 700 patients with proteinuria greater than 1 gr/day and different degrees of renal function

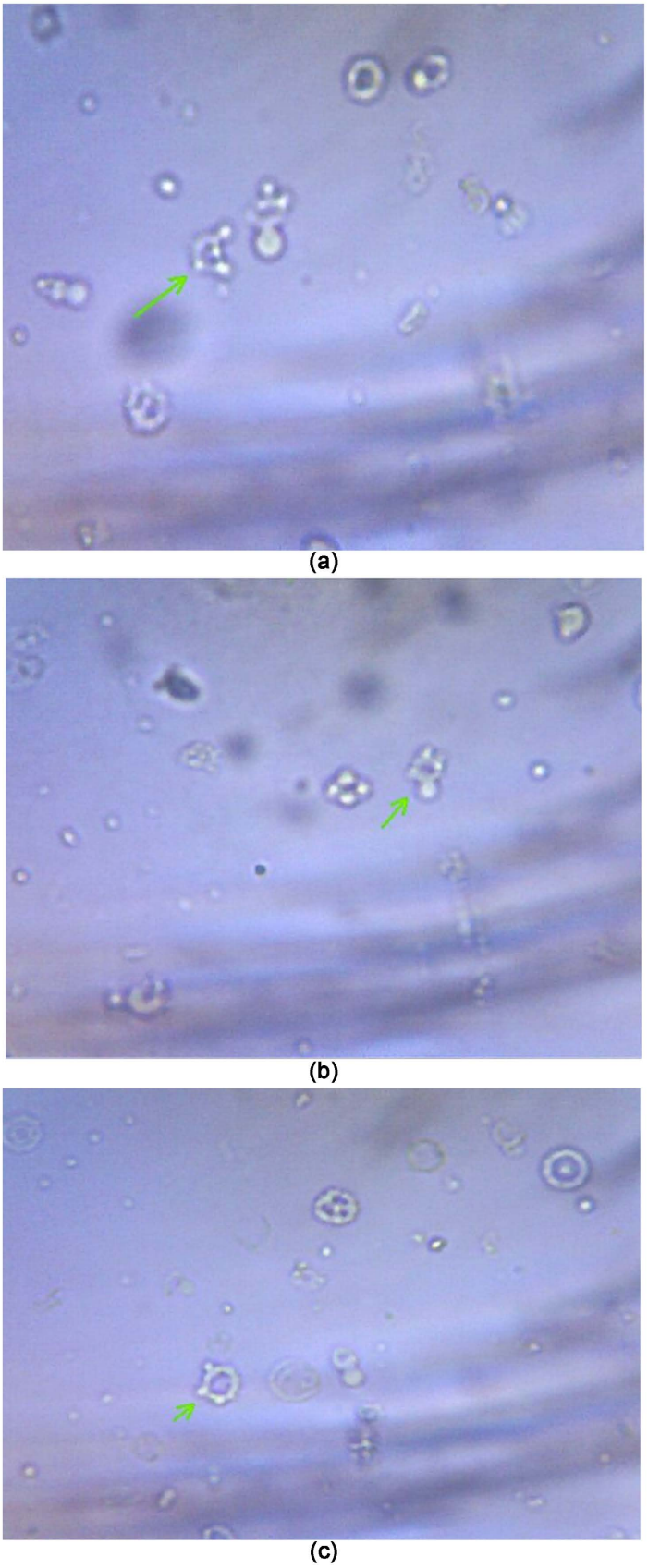

Figure 2. Urinary sediment prior to treatment in case, 40×.

Table 3. Evolutionary monitoring of patient treatment.

Laboratory/Month	1st month	3rd month	5th month	7th month	9th month	12th month
Creatinine mg/dl	1.96	1.92	1.54	1.43	1.41	1.42
24-hour proteinuria (g/day)	1.8	1.76	0.8	0.56	0.43	0.39
Acanthocytes	+	+	+	+	-	-
Weight (kg)	116	114	105	100	97	98
BP (mm/Hg)	170/90	130/60	110/60	110/70	120/60	110/70
LDL	278	210	154	-	110	90
Triglycerides	789	320	210	-	180	176
Evolucumab	+	+	+	+	-	-
Liraglutide	+	+	+	+	+	+
Budesonide mg/day	18	18	18	18	18	18

were randomized over a period of 6 months, in the study design, 136 patients were treated with prednisone (0.6 - 0.8 mg/kg/ for 2 months) and 126 patients in the placebo group, finding that the number of renal events (end-stage renal disease, death of renal cause and 40% decrease in filtration) was significantly lower in those treated, p = 0.03. [16] During follow-up, an interim analysis was performed that revealed serious infectious events, for which it was determined to end the trial early, complications included lethal pneumonia due to Pneumocystis Jirovecii.

Subsequent analyzes of the TESTING study reveal a significant decrease in outcomes such as the risk of a 40% decrease in glomerular filtration rate or the need for renal replacement therapy in the group treated with steroids. The decrease in renal function compared to the group treated in the previously mentioned STOP-IgAN trial was 4 times less than in the TESTING study, which may suggest a population at higher risk and that the support measures (nephroprotection) were different. Likewise, in the expected benefits in the TESTING study, there was no difference in filtrations greater or less than 50 ml/min, very similar phenomena in other trials [17] [18] [19] [20].

The question that remains with the cases exposed and the evidence supported to date is: *Are we doing enough?* Obviously, more trials are required with the use of adequate nephroprotection measures in conjunction with immunosuppression schemes in patients at risk of progression in this pathology in order to have a strong impact on its incidence and prevalence.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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