

Original Research Article

Short-term and long-term efficacies of combined use of irbesartan and calcitriol for the treatment of IgA nephropathy

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Abstract

Purpose: To determine the efficacy and safety of irbesartan plus calcitriol in the treatment of IgA nephropathy, and its effect on inflammatory injury and complement system

Methods: Differences in renal function, inflammatory response, immune function, complement factor levels, clinical efficacy, and incidence of adverse reactions between IgA nephropathy patients treated with irbesartan (control, n = 50) and those treated with irbesartan + calcitriol (study group, n = 50) after 2 and 12 months, were retrospectively analyzed. As treatment progressed, protein in 24-h urine, and creatinine and BUN in both groups were gradually reduced.

Results: The serum levels of complement factors C1q and C3 in both groups gradually increased, while C4 level gradually decreased. Relative to pre-treatment, at 2- and 12-months post-treatment, serum levels of C1q and C3 in both groups were raised, while C4 level decreased ($p < 0.05$). Relative to control, serum C1q and C3 in the study group were raised, while C4 level was decreased ($p < 0.05$). Relative to the control group, total treatment effectiveness in the study group increased at 2- and 12-months post-treatment ($p < 0.05$). There was no significant difference in the incidence of adverse reactions between the control and study groups during the treatment.

Conclusion: Treatment with irbesartan + calcitriol significantly improves renal function in patients with IgA nephropathy, reduces inflammatory response, and improves immune function and clinical effectiveness with high safety profile. More clinical trials should be carried out to validate the findings of this study.

Keywords: Irbesartan, Calcitriol, IgA nephropathy, Renal function, Inflammatory response, Immune function

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INTRODUCTION

Immunoglobulin A (IgA) nephropathy, a very common primary glomerular disease

characterized by deposition of IgA and C3 in the mesangial area of the glomerulonephritis, occurs frequently in children and young people [1]. Immune response or inflammatory response is

an important cause of IgA nephropathy [2]. The progression of the disease leads to end-stage renal failure, and inflammatory response increases the risk of adverse clinical outcomes. Hypertension, proteinuria, renal function injury, and renal tubular atrophy are important indicators that lead to poor prognosis in IgA patients [3]. Urinary protein plays a major role in the deterioration of renal function in patients with IgA nephropathy. It may directly damage the normal function of renal tubules and glomeruli, enhance extracellular matrix deposition and inflammatory cell infiltration, and eventually lead to renal interstitial fibrosis [4]. Therefore, clinical research has focused on effective reduction of urinary protein levels in IgA patients, as well as the prevention and treatment of IgA nephropathy.

Angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists have been used in the treatment of IgA nephropathy, with excellent results [5]. Irbesartan is a type of angiotensin II receptor antagonist which is used in management of essential hypertension and type 2 diabetic nephropathy complicated with hypertension [6]. Calcitriol plays an anti-nephropathy role by effectively regulating T cell multiplication and secretion of cytokines, thereby inhibiting mesangial cell proliferation and podocyte loss, and preventing glomerular and tubulointerstitial fibrosis [7]. However, not much is known about the effect of irbesartan plus calcitriol on renal function, immune function, complement system, and other factors in patients with IgA nephropathy.

This research focused on retrospectively analyzing short-term and long-term outcomes of using irbesartan alone and irbesartan + calcitriol on IgA nephropathy, as well as the differences in renal function, inflammatory response, immune function, complement system factors, and incidence of adverse reactions. This was with a view to providing an understanding of the effectiveness and harmlessness of combined application of irbesartan + calcitriol in improving the quality of life of IgA nephropathy patients.

METHODS

General data

Immunoglobulin A (IgA) nephropathy patients treated in Lin'an District People's Hospital, Zhejiang Province, China from June 2020 to September 2021, were enrolled in this study. This research was approved by the Ethical Committee of Lin'an District People's Hospital (approval no. LDPHH002) and conducted in line

with the guidelines of the Declaration of Helsinki promulgated in 1964 as amended in 1996 [8].

The enrolled subjects were patients with IgA nephropathy confirmed via immunology, urine, and renal function tests; patients with systolic blood pressure less than 140 mmHg and diastolic blood pressure less than 90 mmHg before treatment; patients who did not receive treatments through other methods prior to the study, and patients with good treatment compliance and normal communication ability.

Inclusion and exclusion criteria

Patients with cognitive dysfunction or disturbance of consciousness; those with secondary glomerulonephritis; patients with serious cardiac, hepatic and brain diseases; cancer patients, subjects with autoimmune diseases; those who were allergic to the therapeutic drugs used in the study, and patients with incomplete clinical data, were excluded.

The clinical data of 100 patients with IgA nephropathy were included. The patients were assigned to control and study groups ($n = 50/\text{group}$), based on treatment method. Irbesartan alone was given to control subjects. Patients in control group comprised 31 men and 19 women aged 30-65 years (mean age = 51.6 ± 4.8 years). The disease duration ranged from 2 to 9 years, with an average of 4.2 ± 1.1 years. There were 18 cases of membranous nephropathy, 13 cases of minimal change nephropathy, and 19 cases of mesangial proliferative nephropathy. The mean body mass index (BMI) of patients in control group was $21.3 \pm 2.6 \text{ kg/m}^2$. Patients in study group were treated with irbesartan + calcitriol. This group comprised 33 men and 17 women aged 28-66 years, with mean age of 49.1 ± 5.3 years. The disease duration was in the range of 6 months - 8 years (mean duration = 3.8 ± 1.3 years), with 16 cases of membranous nephropathy, 15 cases of minimal change nephropathy, and 19 cases of mesangial proliferative nephropathy. The mean BMI was $21.8 \pm 1.7 \text{ kg/m}^2$. Both groups were comparable with respect to basic data. Approval for this investigation was received from the ethical authority of Lin'an District People's Hospital, China (approval no. LDPH2020002), and it was carried out in line with Helsinki Declaration [9].

Treatments

All patients received a low-salt, low-fat, high-quality, low-protein diet, and regular dipyrindamole tablets (Changzhou Kangpu Pharmaceutical Co.

Ltd.; specification: 100 x 25-mg tablets; approval no. H32022164) at a dose of 150 mg/day. In addition, patients in control group received irbesartan (Sanofi, Hangzhou; specification: 7 x 0.15-g tablets; approval no. H20040494) alone, at a dose of 150 mg/day. The study group received irbesartan tablets (dose:150 mg/day) and calcitriol capsules (Shanghai Roche Pharmaceutical Co. Ltd; specification: 10 x 0.25- μ g capsules; approval no. H20140598) at a dose of 0.25 μ g/day. Patients with elevated blood pressure were given non-angiotensin-converting-enzyme inhibitor antihypertensive medications at their discretion. Patients in both groups received 8 weeks of treatment, and all patients were followed up for at least 12 months.

Evaluation of parameters/indices

Treatment effectiveness

The clinical outcome in patients was determined at 2 and 12 months of treatment. If edema, proteinuria, and other clinical symptoms and signs disappeared, and urine red blood cell (RBC) count was normalized, the clinical outcome was classified as *cured* (C). If the above signs became better in the patient, and the urine RBC count decreased by 90 – 100 %, the treatment outcome was considered *markedly effective* (ME). The treatment result was adjudged *effective* (E) when the above signs were favorable in the patients, and the urine RBC count was reduced by 50 – 90 %. However, if these signs were not improved, or if they became worsened, and the urine RBC count decreased by less than 50 %, the treatment was deemed *ineffective*. Total treatment effectiveness was obtained by summing up the numbers of patients who were in the *cured*, *markedly effective* and *effective* treatment categories shown in Eq 1.

$$TE = (C+ME+E/N)100 \dots\dots\dots (1)$$

where TE is the *total treatment effectiveness* (%), N is *total number of patients*.

Renal function

Fasting venous blood (5 mL) was collected in duplicate, from patients before treatment, and also at 2 and 12 months of treatment. One sample was left to stand and centrifuged, and the supernatant (serum) was used for determination of levels of Cr and BUN using enzyme-linked immunosorbent assay. In addition, 24-h urine of patients was collected and mixed with 1 mL of 40% formaldehyde solution. The level of protein in 24-h urine was determined using automatic biochemical analyzer. The second blood sample

was placed in a sodium citrate anticoagulant tube to obtain plasma used for evaluation of inflammatory response and IgM, IgG, and IgA.

Inflammatory response

The plasma levels of IgA, IgG, and IgM were determined using automatic protein analyzer. Moreover, plasma concentrations of TNF- α , IL-6 and hs-CRP and were assayed using colloidal gold method kits purchased from Shanghai Upper Biomedical Co. Ltd.

Levels of complement factors

The serum levels of C1q, C3, and C4 were determined using an automatic protein analyzer.

Adverse reactions

The total incidence of nausea and vomiting, gastrointestinal discomfort, rash, and other adverse reactions were recorded.

Statistical analysis

Data analysis and processing were done with the SPSS 19.0 software package. Measured data are presented as mean \pm standard deviation (SD) and 2-group comparison was done with *t*-test. Count data are presented as frequencies, and were compared using χ^2 test. Statistical significance was fixed at $p < 0.05$.

RESULTS

Renal function indices

A comparison was made on 24 h-protein, Cr, and BUN between the two groups. It was found that as treatment progressed, the concentrations of these parameters in the two groups were gradually reduced. Relative to pre-treatment, at 2- and 12-months post-treatment, the concentrations of these indices were markedly reduced in both groups, but the levels in study group were markedly lower than those in the control group ($p < 0.05$; Figure 1).

Levels of inflammatory factors

With treatment, the plasma concentrations of IL-6, hs-CRP, and TNF- α were gradually decreased in the 2 groups. However, relative to pre-treatment, the serum concentrations of these indices were markedly decreased in the two groups at 2 months and 12 months of treatment, but with lower concentrations in the study group patients ($p < 0.05$; Figure 2).

Serum concentrations of IgA and IgG in the two groups gradually increased, but IgM levels gradually decreased. Relative to pre-treatment, the serum IgA and IgG levels in both groups were raised, while levels of IgM were reduced at 2- and 12-months post-treatment. Relative to control group, IgA and IgG levels in study group were raised, while IgM level was decreased ($p < 0.05$; Figure 3).

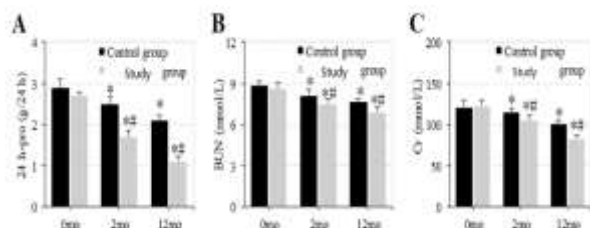


Figure 1: Comparison of levels of renal function indicators between the 2 groups of patients. (A) 24 h-protein, (B) BUN, (C) Cr, 0 mo: before treatment; 2 mo: 2 months after treatment; 12 mo: 12 months after treatment. * $P < 0.05$, compared with the same group before treatment; # $p < 0.05$, relative to control at the same time point

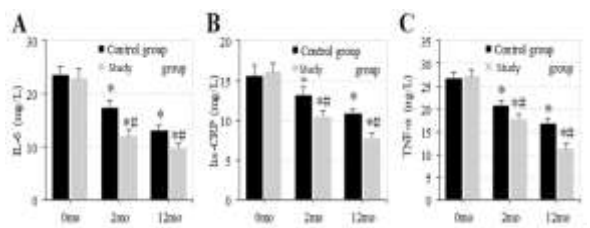


Figure 2: Serum levels of inflammatory factors in both groups of patients. (A) IL-6, (B) hs-CRP, and (C) TNF- α . 0 mo: before treatment; 2 mo: 2 months after treatment; 12 mo: 12 months after treatment. * $P < 0.05$, compared with the same group before treatment; # $p < 0.05$, relative to control at the same time point

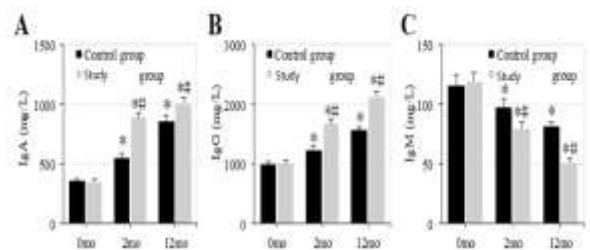


Figure 3: Serum levels of serum immune function indices in patients. (A) IgA, (B) IgG, and (C) IgM. 0 mo: before treatment; 2 mo: 2 months after treatment; 12 mo: 12 months after treatment. * $P < 0.05$, compared with the same group before treatment; # $p < 0.05$, relative to control at the same time point

Levels of complement factors

The plasma levels of complement factors C1q and C3 in both groups were gradually increased,

while C4 level was gradually decreased. Relative to pre-treatment, at 2- and 12-months post-treatment, serum levels of C1q and C3 in both groups were raised, while C4 level was decreased. Relative to control, the amounts of C1q and C3 in serum in study group were raised, while C4 level was decreased ($p < 0.05$; Figure 4).

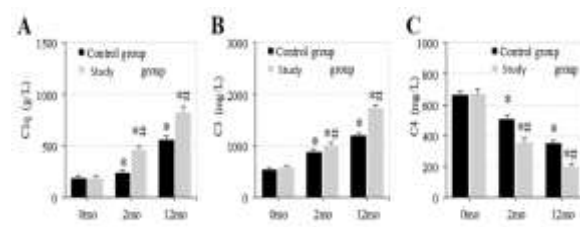


Figure 4: Serum levels of complement factors in patients. (A) C1q, (B) C3, and (C) C4. 0 mo: before treatment; 2 mo: 2 months after treatment; 12 mo: 12 months after treatment. * $P < 0.05$, compared with the same group before treatment; # $p < 0.05$, relative to control at the same time point

Clinical treatment efficacy

At 2 months of treatment, the total treatment effectiveness in the control and study groups were 74.0 and 88.0 %, respectively. Following 12 months of treatment, the total effectiveness values were 82.0 and 94.0 %, respectively. Relative to control patients, total treatment effectiveness in the study patients was increased at 2- and 12-months post-treatment ($p < 0.05$; Figure 5).

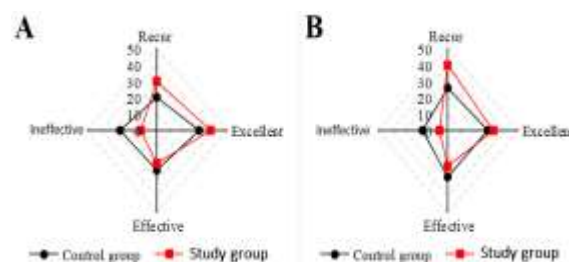


Figure 5: Clinical treatment effectiveness in the 2 groups of patients. (A) Clinical efficacy at 2 months of treatment, (B) Clinical efficacy at 12 months of treatment

Incidence of adverse reactions

In the control group, there was 1 case of gastrointestinal discomfort, in addition to 1 case of rash, but no cases of nausea and vomiting were seen. The total adverse reaction rate was 4.0 %. In study group, nausea and vomiting occurred in 1 patient, while gastrointestinal discomfort occurred in 1 patient, and rash was seen in 1 case. The total adverse reaction rate was 6.0 %. The incidence of adverse reactions

was comparable in the control and study groups during the treatment (Figure 6).

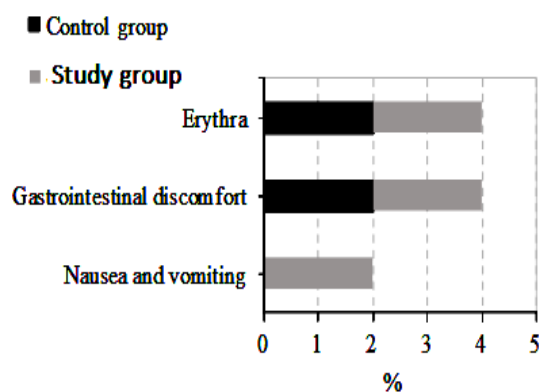


Figure 6: Adverse reaction rates in the 2 groups during treatment

DISCUSSION

Immunoglobulin A (IgA) nephropathy is an autoimmune disease with an increasing incidence. As IgA disease gradually develops, the damage to basement membrane tissue in the glomerulus or nephron of patients is aggravated, and the filtration rate or reabsorption capacity of the glomerulus is impaired [10]. A decrease in serum Cr level may enhance the repair of renal tubular epithelial cells, reduce the level of renal interstitial fibrosis, and play a protective role in glomeruli [11]. The main treatment goals in IgA nephropathy are blood pressure control, reduction of urinary protein level, and alleviation of damage to renal function. The results obtained in this study indicate that 24-h urine protein, BUN, and Cr were markedly decreased in patients with IgA nephropathy following treatment with irbesartan alone or irbesartan + calcitriol. However, compared with irbesartan alone, BUN, 24-h urine protein, and Cr in patients with IgA nephropathy treated with irbesartan + calcitriol were clearly reduced.

Calcitriol is the active form of vitamin D3 which is applied in the treatment of renal bone diseases such as osteoporosis and hypoparathyroidism. Calcitriol + irbesartan effectively reduced the state of glomerular hypertension, hyperperfusion and hyperfiltration, and decrease the deposition of extracellular matrix. Therefore, treatment with irbesartan + calcitriol synergistically improved the therapeutic outcome in IgA nephropathy.

It is known that IL-6, hs-CRP, TNF- α , and other cellular inflammatory factors are important indices that exacerbate nephropathy, induce glomerular damage and impair the reabsorption function of renal tubules in patients [12]. In the

early stage of IgA nephropathy, inflammatory injury stimulates glomerular mesangial cells to produce and secrete inflammatory factors, leading to precipitation of large amounts of immune complexes in the kidney [13]. The results obtained in this research revealed that the serum concentrations of proinflammatory factors in patients with IgA nephropathy who were treated with irbesartan alone and irbesartan + calcitriol were significantly reduced. However, relative to irbesartan alone, the pro-inflammatory factor levels in subjects with IgA nephropathy treated with irbesartan + calcitriol were significantly decreased. Irbesartan + calcitriol significantly reduced the degree of inflammatory response in patients with IgA nephropathy. This has the potential of improving the prognosis of patients.

Normal human serum contains IgA, IgG, and IgM, but the level of IgG is the highest. The urine of patients with nephropathy contains large amounts of proteins. Thus, the serum IgG level is significantly lower than that of normal people. Other studies have confirmed that IgA level is lower in nephropathy patients, a situation which possibly is related to the local inflammatory response of glomeruli [14]. Patients with nephropathy characteristically exhibit immune dysfunction which leads to dysfunction in immunoglobulin conversion, and hinders the conversion of IgM to IgA and IgG. Therefore, serum IgM levels are abnormally increased, and IgA and IgG levels are decreased in patients with nephropathy [15]. In this study, the treatment of IgA nephropathy with irbesartan alone or irbesartan + calcitriol resulted in significant decreases in serum IgM levels, while IgA and IgG levels were significantly raised. However, compared with irbesartan alone, the serum IgM level of IgA nephropathy patients treated with irbesartan + calcitriol was significantly decreased, while IgA and IgG levels were clearly increased. These results suggest that irbesartan + calcitriol may improve the therapeutic effect on IgA nephropathy by improving the immune function of patients.

The complement is an enzyme-like active globulin distributed in the blood or on the surface of cell membrane, and it participates in immune function. The complement system is important in the etiology of IgA nephropathy. When complex precipitation occurs in the immune circulation system of the patient, it activates the complement system and reduces the levels of serum complement C3 and C4 [16]. In a study by Pan *et al* [17], it was shown that the decreased level of serum complement C3 may serve as an index for prediction of IgA nephropathy, and that

the activated level of serum complement C3 is closely correlated with the level of urinary protein and the deterioration of renal function.

In another study, Bi *et al.* [18] reported that elevated serum C4 level is related to the clinicopathological prognosis of patients with IgA nephropathy and that it may serve as an independent risk factor for the prediction of IgA nephropathy. Complement 1q (C1q), a glycoprotein subunit of complement C1, belongs to the initiation factor of the classical pathway of complement activation. Recent studies have demonstrated that complement C1q is associated with immune diseases, atherosclerosis, cardiovascular diseases, and other diseases. It has been reported that C1q reduced the activation of stromal cells and inflammatory response induced by secretory IgA.

In the present study, the level of complement C3 in IgA nephropathy patients treated with irbesartan alone or irbesartan + calcitriol was evidently lower, while C1q and C4 levels were evidently higher. However, compared with irbesartan alone, C3 in IgA nephropathy patients treated with irbesartan + calcitriol was markedly decreased, while C4 and C1q levels were markedly raised. Relative to the use of irbesartan alone, the clinical effectiveness of irbesartan + calcitriol in IgA nephropathy improved significantly, but there were no obvious differences in the incidence of adverse reactions. These results suggest that C1q, C3, and C4 are involved in IgA nephropathy and that treatment with irbesartan + calcitriol may improve the function of the complement system in IgA nephropathy patients, thereby improving the clinical treatment outcome. Moreover, the combined treatment had an excellent safety profile.

Limitations of the study

The clinical effect of irbesartan + calcitriol in IgA nephropathy was analyzed, but the sample size was small, and risk factors for the prognosis of IgA patients were not analyzed.

CONCLUSION

The short-term and long-term clinical effects of irbesartan alone and irbesartan + calcitriol in patients with IgA nephropathy are excellent, with high safety and effectiveness. Irbesartan plus calcitriol treatment improves renal function of patients, reduces inflammatory response, and improves immune function and function of the complement system. However, additional clinical

trials are required prior to its use in clinical practice.

DECLARATIONS

Acknowledgements

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Funding

None provided.

Ethical approval

This study was approved by the Ethical Committee of Lin'an District People's Hospital, China (approval no. LDPHH002).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication. Laming Li conceived and designed the study, Laming Li collected and analyzed the data. Yan Jiang wrote the manuscript.

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