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Treatment Of IgA Nephropathy

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Abstract:

Although IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide, our understanding of the pathogenesis of this complex disease remains limited. IgA nephropathy may appear with a variety of clinical presentations, a number of different clinical and histopathologic risk factors for progressive renal disease, and a very variable course over time. Thus, it is not surprising that a single therapeutic treatment plan has not been established. Many of the studies dealing with IgAN are retrospective, lack statistical significance, or have confounding designs, which hinder their general acceptance. Nevertheless, a number of well-designed studies have been performed. This paper reviews currently available therapeutic options for IgAN. It attempts to address several important questions: Why do we treat patients with IgAN? How do we decide which patients should be treated? What are the general treatment guidelines for all IgAN patients? What is the role of specific therapy such as fish oils, tonsillectomy, and immunosuppression in the treatment of patient with IgAN? It also addresses several on-going trials and goals for future therapeutic studies for IgAN patients.

Introduction :

Immunoglobulin A nephropathy (IgAN) is the most common pattern of idiopathic glomerulonephritis in all countries where renal biopsy is widely practiced. It is an
important cause of end-stage renal disease (ESRD) at all ages, and therefore treatment strategies to reduce the risk of IgAN progressing to ESRD would have substantial health benefit. There are, however, few well-designed randomized controlled trials (RCTs) to inform the treatment of this condition. The reason for this is in part the slow rate of progression of IgAN,
IgA nephropathy usually doesn't cause symptoms in the early stages. The disease can go unnoticed for decades and is sometimes first suspected when routine tests reveal protein and red blood cells in your urine that can't be seen without a microscope (microscopic hematuria).

Signs and symptoms of IgA nephropathy when kidney function is impaired include:

- Cola- or tea-colored urine (caused by red blood cells in the urine)
- Repeated episodes of cola- or tea-colored urine, sometimes even visible blood in your urine, usually during or after an upper respiratory or other type of infection
- Pain in the side(s) of your back below your ribs (flank)
- Swelling (edema) in your hands and feet
- High blood pressure

Immunoglobulin A (IgA) is an antibody that plays a key role in your immune system by attacking invading pathogens and fighting infections. But in IgA nephropathy, this antibody collects in the glomeruli, causing inflammation (glomerulonephritis) and gradually affecting their filtering ability.

Researchers don't know exactly what causes IgA deposits in the kidneys. [1]

Discussion :

WHY DO WE TREAT IgAN?

IgAN is a very frequent glomerular disease. It accounts for approximately 30–40% of patients undergoing renal biopsy in Asia, 15–20% in Europe, and 5–10% in North America. It is unclear if these differences are related to true genetic susceptibility differences or geographic differences in urinalysis screening practices and selection differences in indications for renal biopsy. Clearly, preventing renal failure has been the major focus of therapy for nephrologists treating patients with IgAN. Although the exact proportion of
patients who progress to renal failure is very variable, many series report that a significant percentage of patients will develop ESRD by 10 years. The percentage increases to25–30% by 20 years and is likely to be significantly higher at30 years. Many patients with IgAN are young at clinical presentation. Renal survival rates of 30 years and longer are very reasonable concerns for patients with this disease. Thus, preventing progressive renal disease is a valid concern for everyone dealing with the disease.[1]

WHICH PATIENTS DO WE TREAT?

The patient who is most likely to progress to chronic kidney disease and ultimately ESRD may be the patient most likely to derive the most benefit from therapy. This is especially true if the potential therapies have offsetting side effects that must be carefully weighed into the benefit–risk ratio. A number of epidemiologic, clinical, and histologic features have been associated with a more progressive course in IgAN. Some have been integrated into formulae to predict renal outcome. Clinical features at either presentation or at time of renal biopsy predictive of progression include higher degrees of proteinuria, reduced GFR, persistent microhematuria, and presence of hypertension For example, one long-term study followed 298 IgAN patients with a mean baseline serum creatinine of 1.54 mg/dl, creatinine clearance of 76 ml/min, and initial urinary protein excretion of 2.3 g/day.4 Only two of 10 variables by multivariate analysis independently predicted progression of renal disease: higher mean blood pressure (BP) and greater amounts of proteinuria. The change in GFR in ml/min/year decreased by _0.2 for each 1mm Hg increase in mean arterial pressure above 97mm Hg and by _0.3 for each 200 mg/day increase in urinary protein excretion above 200 mg/day.4 Other investigators have found greater value in evaluating certain clinical features after 1 year of maximal therapeutic intervention, rather than at the time of presentation. In two study populations, the Mayo Clinic group found that the degree of proteinuria and reduction in GFR at 1 year were highly predictive of progressive renal disease.5 Thus, patients with proteinuria of 0.5–1 g/day at 1 year fared far worse than those with less than 0.5 g/day, and those with greater amounts did even worse.[2]

GENERAL TREATMENT RECOMMENDATIONS FOR ALL IGAN PATIENTS

Certain therapeutic interventions have appeared beneficial in almost all reported trials in IgAN. As hypertension is a risk factor for progression in IgAN and virtually all renal diseases, optimal control would be ideal. A reasonable goal is to aim for BPs p125/75 _130/80mm Hg. A 3-year randomized controlled trial found that IgAN patients with a mean BP of 136/76mm Hg had reductions in creatinine clearance over 3 years, whereas those with a mean BP of 129/70mm Hg

maintained stable renal function over the same time.7 Likewise, a number of trials have shown that blockade of the RAS with either ACE inhibitors (ACEI) or angiotensin II receptor blockers (ARB) is beneficial in IgAN patients. In a retrospective study of IgAN patients in the Toronto registry, use of ACEI to control hypertension lowered the annual loss
of renal function to the same level as normotensive IgAN patients. In contrast, those treated with other antihypertensive drugs had a greater annual loss of GFR.8 Further evidence of the renoprotective effect of ACEI is provided bya recent randomized controlled trial, which demonstratedimproved renal survival in IgAN patients receiving enalaprilcompared to those receiving other antihypertensive drugs despite equivalent BP control (o140/90mm Hg). The primary end point of 50% increase in baseline serum creatinine was reached in only 13% of the patients treated with enalapril compared to 57% of those patients treated with alternate medications.[3]

THE ROLE OF TONSILLECTOMY AND FISH OILS IN IGA NEPHROPATHY

Several retrospective studies have analyzed the role of tonsillectomy in the treatment of IgAN. Most contain a small number of patients, are non-randomized uncontrolled trials, and provide conflicting data. A retrospective study from Germany reviewed the renal outcome in 55 patients with IgAN, 16 of whom had a prior tonsillectomy. Tonsillectomy did not have an independent impact on renal survival 10 years after biopsy.14 A Japanese study of 329 patients with IgAN found tonsillectomy to be an independent factor in predicting remission of clinical findings and lack of renal progression.15 A more recent retrospective study from Japan analyzed 118 patients with IgAN followed over 20 years.16 Forty-eight of these patients had a prior tonsillectomy. Renal survival at 240 months was 90% for the tonsillectomy group and 64% for the group without tonsillectomy. By multivariate analysis, tonsillectomy had a significant impact on renal outcome. However, renal survival curves only diverged between the two groups at greater than 10 years from biopsy. It is clear that none of these studies contain populations large enough for epidemiologic analysis, none are randomized controlled or prospective, and they may only apply to patients within a given geographic area. At present, there is insufficient data to recommend tonsillectomy for IgAN patients. Those with recurrent bouts of tonsillitis may benefit, but if so, only at some time in the distant future. The role of fish oils in preventing progressive renal disease in IgAN remains no less controversial. Fish oils have been shown to possess a number of potential benefits in preventing cardiovascular events in high-risk populations. There is good rationale for the use of fish oils in IgAN: they have been shown to inhibit cell growth and proliferation, inhibit renal inflammation, reduce serum lipids, decrease BP, and reduceproteinuria and glomerular injury in several animal modelsof glomerular disease.17 However, they do have a number ofdetracting side effects including a fishy odor, inconvenience of large medication dosages, and expense. Moreover, they
may delude patients into feeling that they are definitively treating their renal disease at the expense of instituting othermore effective therapies. A number of studies have evaluated the role of fish oils in IgAN. A Japanese study of 20 patients followed for 1 year demonstrated stabilization of renalfunction with fish oil use.18 Conversely, an Australian study of 37 patients found no benefit on the renal outcome over 2 years.19 A controlled, meticulously performed, randomized trial of 32 patients with IgAN and moderately reduced GFR from Sweden found that fish oils led to greater reduction inGFR than corn oil (placebo).[4]

WHAT IS THE ROLE OF CORTICOSTEROIDS AND OTHER IMMUNOSUPPRESSIVES?

A number of studies have examined the role of corticosteroids in patients with IgAN. Corticosteroids have provided
dramatic remissions of the nephrotic syndrome in those IgAN patients with normal appearing glomeruli, only mesangial IgA deposits, and diffuse foot process effacement on electron microscopy. These patients with the so-called 'IgAN minimal change disease' clearly have a very differentdisease than most IgAN patients, and are really a minimal change disease variant. In other IgAN populations, corticosteroids have given mixed results. Some studies have suggested benefit, whereas others have not. Most of the studies are not prospective, randomized, or controlled, and have not provided conclusive results. One randomized controlled trial examined 90 IgAN patients (baseline serum creatinineo1.5 mg/dl) randomized to receive either oral prednisone tapered over 2 years or placebo.24 Renal survival was identical (85%) at 84 months, although the proteinuria declined more
in the steroid group.[5]

Table 1 | Treatment recommendations for IgAN according to clinical features

Clinical presentation	Recommended treatment
Recurrent macroscopic hematuria with preserved renal function	No specific treatment – no role for antibiotics or tonsillectomy
Proteinuria <1 g/24 h ± microscopic hematuria	No specific treatment
Proteinuria >1 g/24 h ± microscopic hematuria	Combined renin–angiotensin blockade with ACE inhibitor and ARB
Acute renal failure	
Acute tubular necrosis	Supportive measures
Crescentic IgAN (with little or no chronic damage)	
Induction (~8 weeks)	Prednisolone 0.5–1 mg/kg/day Cyclophosphamide 2 mg/kg/day
Maintenance	Prednisolone in reducing dosage Azathioprine 2.5 mg/kg/day
Nephrotic syndrome	
With minimal change on light microscopy	Prednisolone 0.5–1 mg/kg/day for up to 8 weeks
With structural glomerular changes	No specific treatment
Hypertension	Target BP 125/75 mm Hg if proteinuria >1 g/24 h ACE inhibitors/ARB first choice agents

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; IgAN, IgA nephropathy.

In ***Conclusion***, Corticosteroids and otherimmunosuppressive drugs are basically the major treatment that is used right now for igAN but there are other factors and drugs that can help to treat the disease according to many studies such as tonsillectomy and fish oils.

Recommendation :

- the treatment of this disease remains a dilemma because the pathogenesis remains unknown so we recommend to do studies and researches about the pathogenesis of this common disease.

- The only way for your doctor to confirm a diagnosis of IgA nephropathy is with a kidney biopsy and unfortunately in Libya kidney biopsy is not an option so we hope that one day this diagnostic method of the commonest nephron disease will be an option .

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