Robert J. Wyatt · Ronald J. Hogg

Evidence-based assessment of treatment options for children with IgA nephropathies

Abstract We present an evidence-based evaluation of published data on therapy for children with various presentations of the IgA nephropathies – idiopathic IgA nephropathy (IgAN) and Henoch-Schönlein purpura nephritis (HSPN). Particular attention has been paid to the outcome markers used in the studies reviewed, with the best evidence provided by markers highly associated with progressive renal failure. No treatment modality for either IgAN or HSPN in pediatric patients has been shown to be effective by a properly designed and administered randomized controlled trial (i.e., the highest level of evidence – level 1). Lower levels of evidence support the use of a variety of corticosteroid regimens, often in combination with other agents, although there are some conflicting studies in this area. No convincing evidence has been published to date to support the use of fish oil, angiotensin-converting enzyme inhibitors or tonsillectomy for the treatment of children with IgAN or HSPN. Well designed randomized controlled trials in children with the IgA nephropathies need to be undertaken.

Keywords IgA nephropathy · Evidence-based assessment · Henoch-Schönlein purpura nephritis

Introduction

The concept of evidence-based medicine was developed in the early 1990s [1, 2] and subsequently a standard methodological approach has been developed for assessment of therapy for a broad range of diseases [3, 4]. However, principles of evidence-based medicine have only recently been used to systematically evaluate therapy for glomerular disease in adult patients [5] and have not yet been applied to pediatric studies of treatment for IgA nephropathy (IgAN) or Henoch-Schönlein purpura nephritis (HSPN).

In this report, we provide an evidence-based approach to the evaluation of therapy in children with varying presentations of the IgA nephropathies. This approach incorporates treatment experience for the prevention and treatment of HSPN as well as the treatment of idiopathic IgAN, including some relatively uncommon presentations. It is important from the outset to emphasize that most pediatric patients who have progressive IgAN will not reach end stage renal disease (ESRD) until they become adults [6, 7]. Thus, pediatric studies of patients with IgAN may differ markedly from adult studies with respect to the apparent risk of progressive disease and hence the need for therapy. Virtually all studies of adult patients addressing prognosis in IgAN include a significant proportion of patients who have impaired renal function at the time of identification and subsequently develop chronic renal insufficiency (CRI) and ESRD [8]. Fortunately, such patients are less common in pediatric studies.

It is likely that therapeutic intervention early after the onset of clinically apparent disease will provide the best opportunity for improving the outcome of patients with IgAN and thus reducing the number of patients who develop CRI or ESRD. However, due to the long time period from clinical onset of disease until progression to ESRD, surrogate markers of outcome must be used to evaluate efficacy of therapy for IgAN in both adult and pediatric trials. Unfortunately, validation of these surrogate markers may be lacking, resulting in the potential for inappropriate conclusions with regards to therapeutic efficacy.

In this review, we will focus on published reports that describe the results of therapeutic approaches to the IgA
nephropathies when they occur in childhood and adolescence. Adult trials will be briefly discussed when the findings are based upon well-designed randomized-controlled trials or if the findings differ significantly from the pediatric experience. Whenever possible, we will indicate how the pediatric experience with each treatment under review compares to the recent evidence-based conclusions drawn from adult studies by Nolin and Courteau [9]. We will attempt to align our approach with that taken by these latter authors in order to facilitate comparison between pediatric and adult recommendations for the management of this common disorder.

Clinical course of children with untreated idiopathic IgAN

Although most early studies concluded that childhood IgAN was a benign disorder [10–12], some recent pediatric series have included a higher percentage of patients with progression to ESRD [6, 7, 13–15]. Data from three pediatric studies of kidney survival [6, 7, 14] showed the 5-year predicted renal survival to be 94–98%. They also showed the survival at 20 years to be only 70% in the U.S. study as compared to 82% and 89% in two Japanese studies. It is therefore evident that IgAN in childhood is not always benign. It is also apparent that when progressive disease is seen, it is often quite insidious. This combination results in considerable problems when the effects of therapeutic interventions are evaluated.

Treatment trials

While the most convincing end point for treatment failure in patients with IgAN is ESRD, the period from diagnosis to ESRD in patients with onset in childhood may be over many decades. Thus, most studies of therapy for pediatric IgAN have used surrogate end points, such as change in the rate of deterioration of renal function, improvement or stability of renal biopsy findings, or decline in the amount of proteinuria and/or hematuria. Significant deterioration in renal function [i.e., 50% reduction of glomerular filtration rate (GFR) or doubling of serum creatinine concentration] is the surrogate end point most closely associated with progression to ESRD.

Methods for evaluation of treatment efficacy

For evaluation of treatment efficacy, we have used the same guidelines that were recently utilized for adult glomerular disease, including IgAN [5, 9]. The level of evidence (LOE) is used to determine the strength of the recommendation [5, 16]. In order to utilize data from the numerous pediatric reports with surrogate end points, we have modified the scale to provide a penalty for the reliance on such end points. Thus, in this report, if the outcome measure employed does not correlate highly with the primary outcome of progression to ESRD, the LOE will be followed by an “S” to designate the employment of a relatively weak surrogate outcome marker. The following definitions for LOE are used:

Level 1
The highest level or “gold standard” of evidence is a randomized controlled trial (RCT) that demonstrates a statistically significant difference for the primary outcome measure. The primary outcome measure must be stated before the study begins and a surrogate marker for outcome is not acceptable unless it correlates highly and unequivocally with the true outcome of progression to ESRD. A study fails at this level if the sample size is adequate to detect a difference in outcome with sufficient power (usually 0.8) and significance (usually α<0.05, two-tailed) is not achieved.

Level 2
An RCT that does not reach the standards set for level 1. Often this is a small trial with uncertain results and a moderate to high risk of error. A trial with an interesting positive trend that is not statistically significant (α error) or one that, due to small numbers of subjects, concluded that an outcome was not significant when it would have been with a larger sample size (β error) could support this level of evidence.

Level 3
A non-randomized concurrent cohort comparison between treated patients and contemporaneous patients who received no therapy or another form of therapy.

Level 4
A non-randomized historical comparison between currently treated patients and former patients who received no therapy or another form of therapy. The control patients may be from the same study site, from another institution(s), or from the literature.

Level 5
A case series of at least ten patients without controls.

Level 6
A case series of less than ten patients without controls.

Recommendations for treatment range from grades A to D, with grade A representing the highest recommendation (5). In virtually all instances, one or more studies at level 1 are required to support the grade A recommendation. The grade B recommendation is supported by at least one level 2 study. The grade C recommendation is supported by at least one level 3 study. The grade D recommendation is supported by lower (lesser) levels of evidence and may include expert opinion. Evidence from level 4, 5, and 6 studies is not obligated to support any recommendation for treatment.

In this review only data published in peer-reviewed articles have been considered. Articles were selected using a