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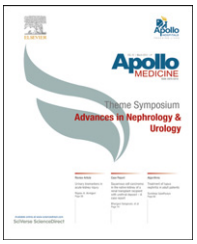

Review Article

An update on the treatment of glomerulonephritis

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ABSTRACT

Glomerulonephritis (GN) is a common cause of end stage renal disease (ESRD). Some of these entities are responsive to immunosuppressive agents and other therapies. There have been recent advances in the treatment options, notably the benefit shown with the use of rituximab in some forms of GN. Moreover, the KDIGO guideline on the management of glomerulonephritis has recently been published which has consolidated the available evidence on the management of this heterogeneous group of disorders. Though there are significant risks and side-effects involved, the treatment of some of the forms of GN can be very gratifying while others progress relentlessly to ESRD. This review summarizes some of the key recommendations from the KDIGO guideline along with a brief discussion of the supporting evidence.

1. Introduction

Glomerulonephritis (GN) is the third most common cause of end stage renal disease (ESRD). The incidence of some forms of primary GN, like IgA nephropathy, is increasing worldwide. Some of them respond well to treatment, hence avoiding the morbidity and cost associated with dialysis or renal transplantation. This article reviews the recent evidence for the treatment of the common types of GN in adults. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for glomerulonephritis has recently been published.[1] Newer drugs such as rituximab are now available which has increased the options available to treat this challenging group of disorders. Salient aspects of the KDIGO recommendations are highlighted and a brief discussion of the supporting evidence follows the recommendations.

The grading of the recommendations stated and their supporting evidence is according to the KDIGO clinical practice guideline for glomerulonephritis. The strength of recommendation followed by the level of supporting evidence is mentioned within parenthesis after each guidance.

The strength of recommendation is indicated as Level 1 ("recommend"), Level 2 ("suggest"), or Not Graded, and the quality of the supporting evidence is shown as A, B, C, or D.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

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2. Minimal change disease (MCD)

2.1. Treatment of initial episode of adult MCD

Corticosteroids are recommended for the initial treatment of nephrotic syndrome (1C).

The following treatment measures are suggested:

Prednisolone as a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg) (2C).

The initial dose of prednisolone is to be maintained for a minimum period of 4 weeks in those achieving complete remission, and for a maximum period of 16 weeks in those that don't achieve complete remission (2C).

In patients who remit, taper steroids slowly over a period of up to 6 months (2D).

Cyclophosphamide or calcineurin inhibitors (CNIs) are to be considered in patients with contraindications or intolerance to high-dose corticosteroids (2D).

Up to 3 relapses a year can be treated with corticosteroids (2D).

There are no randomized controlled trials (RCTs) to guide the therapy of relapse in adult MCD. But relapses can usually be managed with a more rapid taper of corticosteroids. Much of the recommendations for the treatment of adults with MCD with steroids is based on extrapolation from studies in children.[2]

A complete remission (CR) is a reduction in proteinuria to 300 mg/day. Glucocorticoid or steroid-resistance (SR) refers to little or no reduction in proteinuria after 16 weeks of adequate steroid therapy. Patients are considered frequent relapsers (FR) if they have more than three relapses per year.

2.2. In the frequent relapser (FR)/steroid dependant (SD) patient the following treatment measures are suggested

Oral cyclophosphamide 2–2.5 mg/kg/d for 8 weeks (2C).

CNI (cyclosporine 3–5 mg/kg/d or tacrolimus 0.05–0.1 mg/kg/d in divided doses) for 1–2 years for patients with FR/SD MCD who elapsed despite cyclophosphamide, or for those concerned about the risk of infertility (2C).

Mycophenolate mofetil (MMF) 500–1000 mg twice daily for 1–2 years for patients intolerant of corticosteroids, cyclophosphamide, and CNIs (2D).

Re-evaluate corticosteroid-resistant patients for other causes of nephrotic syndrome (Not Graded).

Response to steroids is usually abrupt with response being of the "all or none type". More than half of adult MCD patients will relapse and up to a third of them may be frequent relapsers or corticosteroid-dependent. Corticosteroid therapy leads to complete remission in over 80% of adults with MCD. Adults with MCD take longer to respond compared to children, with only 50% responding by 4 weeks.[3] Many observational studies have reported the efficacy of cyclosporine with remission rates of 70–90%.[4] Cyclosporine may have the additional benefit of lower exposure to corticosteroids as it permits earlier steroid withdrawal.[5] Cyclosporine is a possible alternative in patients who continue to relapse after an initial course of cyclophosphamide, who are steroid-dependent, or in whom avoidance of the toxicity of cyclophosphamide (eg, gonadal toxicity) is important.[6]

70 and 90 percent of glucocorticoid-dependent or frequently relapsing patients, respectively, could undergo complete or partial remission when treated with cyclosporine at a dose of 4–6 mg/kg per day in divided doses.[7] Tacrolimus is similar in efficacy to cyclosporine in inducing complete remission.[8] All patients in this study were able to discontinue corticosteroids. Therapeutic levels for CNI's have not been defined in adult patients with MCD. CNI dose should be gradually reduced to the lowest level that maintains remission.

There is very scant evidence to recommend the use of MMF in adults. Other agents that have shown anecdotal benefit in MCD are levamisole, azathioprine and rituximab. In situations of resource constraints, it is worthwhile remembering that prednisone and cyclophosphamide are considerably less expensive than CNIs and MMF.

3. Focal and segmental glomerulosclerosis

3.1. Initial treatment of FSGS

It is recommended that corticosteroid and immunosuppressive therapy be used only in patients with idiopathic FSGS with the nephrotic syndrome (1C).

The following measures have been suggested-

Prednisolone be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg) (2C).

The initial dose of steroids be given for a minimum of 4 weeks; and continued up to a maximum of 16 weeks, if tolerated, or until complete remission has been achieved, whichever is earlier (2D).

Corticosteroids are to be tapered slowly over a period of 6 months after achieving complete remission (2D).

CNIs are to be considered as first-line therapy for patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis) (2D).

3.2. Treatment for relapse

Relapse of nephrotic syndrome is treated as per the recommendations for relapsing MCD in adults (2D).

3.3. Treatment for steroid-resistant FSGS

The following measures have been suggested:

Cyclosporine use at 3–5 mg/kg/d in divided doses be given for at least 4–6 months.

If there is a partial or complete remission, cyclosporine could be continued for at least 12 months, followed by a slow taper (2D).

In patients with steroid-resistant FSGS, who do not tolerate cyclosporine, a combination of mycophenolate mofetil and high-dose dexamethasone could be tried (2C).

Partial remission refers to a reduction of proteinuria to 0.3–3.5 g/d (300–3500 mg/g [30–350 mg/mmol]), urine creatinine and stable serum creatinine (change in creatinine <25%) **OR** Reduction of proteinuria to 0.3–3.5 g/d (300–3500 mg/g [30–350 mg/mmol]), urine creatinine and a decrease >50%