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Effectiveness of use of rituximab in treatment of steroid-resistant nephrotic syndrome

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ABSTRACT

Childhood nephrotic syndrome is a challenging and often persistent renal disorder, and its incidence varies between different ethnicities and regions. Corticosteroids have been the main treatment for decades and are effective in most children with idiopathic NS, although 10–15% of these children become steroid resistant. Furthermore, some initially steroid sensitive children follow a steroid dependent or frequently relapsing course and are therefore at increased risk for developing steroid toxicity. In such children, alternative immunosuppressive medications are used to induce and/or maintain remission of NS. One such drug, rituximab, is a monoclonal antibody directed against the B lymphocyte CD20 marker which induces depletion of B cells, and has shown promising results in the management of NS in children. In this review, we summarize recent studies on the efficacy and safety of rituximab in the different types of childhood nephrotic syndrome, the known and potential mechanisms of action of rituximab, its possible complications and side effects, and the available and potential biomarkers of rituximab activity.

1. Introduction

Nephrotic syndrome (NS) is a challenging and often persistent renal disease in children, with an average incidence of 2–16.9 per 100,000 children worldwide, and large variability in incidence between different ethnicities and regions [1– 3]. For example, NS is six times more common among Asian children than Caucasian children in the United Kingdom, with an overall incidence of 16 new cases per 100,000 children per year [4]. In contrast, NS is relatively less common in children of African ethnicity, in whom steroid resistant focal segmental glomerulosclerosis (FSGS) is more common [5]. Corticosteroids are the mainstay for treatment of idiopathic NS (INS). Children with complete resolution of proteinuria with daily prednisone (2 mg/kg/d or 60 mg/M2/d; maximum = 60 mg/d) for 6 weeks are labeled as having steroid sensitive NS (SSNS) and usually have a good clinical outcome. However, at least 50% will develop multiple relapses and may develop steroid dependent NS (SDNS; defined as two consecutive relapses during steroid tapering or within 14 days of cessation of therapy) or frequent relapsing NS (FRNS; defined as at least four relapses per year or at least two relapses within 6 months of initial presentation). These children are often treated with alternative immunosuppressive agents such as cyclophosphamide,

mycophenolate mofetil (MMF) and calcineurin inhibitors (CNIs) to improve their clinical course. Response rates to those agents varies among studies, but have been promising in particular for MMF [6] which is generally well-tolerated. In contrast, children who fail to respond to a 4–8 week course of daily corticosteroids are diagnosed with steroid resistant NS (SRNS), at which point CNIs are the main immunosuppressive agents used for treatment [6]. For children failing to respond to CNIs, additional alternative immunosuppressive agents are often employed, including MMF, prolonged and/or high-dose intravenous pulse corticosteroids, among other options.

2. CONCLUSION

Rituximab is an effective and increasingly used treatment option to induce or prolong clinical remission in children with NS. Rituximab may very well-exert its beneficial effects through multiple mechanisms of action. There is now growing evidence to support its efficacy and safety in children with SDNS or FRNS in inducing prolonged remission, enabling reduced corticosteroid exposure and side effects. In children with SRNS, there is evidence of beneficial effects in a smaller but sizable percentage of children. Rituximab is generally well-tolerated in these children, but it requires close monitoring for possible side effects which can be serious or fatal in some cases. With continued efforts to standardize rituximab treatment regimens within the pediatric nephrology community, combined with systematic prospective data collection regarding treatment doses and courses, outcomes, and complications, the use of rituximab can almost certainly be made both more efficacious and safer for children with NS in the future.

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