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Review Article

Novel therapeutic approaches for steroid-resistant nephrotic syndrome in paediatric patients: a comprehensive review

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ABSTRACT

Steroid-resistant nephrotic syndrome poses a significant therapeutic challenge in paediatric nephrology. Previously exact cause of steroid-resistant nephrotic syndrome was mostly unknown. Recently, advancements in diagnostic intervention, they are found to be a heterogeneous entity having an immune basis and genetic aetiology. With a better understanding of the pathogenesis of SRNS, leading to the development of novel therapeutic strategies. Novel therapeutic options include extracorporeal therapy, monoclonal antibodies, stem cell therapy, ACTH and galactose. The aim of this study was to provide an overview of emerging therapies for SRNS in paediatric populations.

Keywords: SRNS, Extracorporeal therapy, Galactose, ACTH

INTRODUCTION

Idiopathic nephrotic syndrome (NS) is a renal condition defined by the presence of significant proteinuria, hypoalbuminemia, and/or oedema. The prevalence of Idiopathic nephrotic syndrome (NS) in children is 1.15-16.9 per 100,000 and it varies based on geography and ethnicity.[1] Around 85% of patients get complete remission of proteinuria after receiving daily oral prednisolone/prednisone (PDN) treatment at standard doses and duration. Individuals who fail to achieve remission after 4-6 weeks of treatment are considered to have steroid-resistant nephrotic syndrome (SRNS).

Steroid-resistant nephrotic syndrome (SRNS) is linked to an unfavourable renal prognosis, with 36-50% of patients developing end-stage kidney disease within a decade.[2] SRNS poses a significant therapeutic challenge in paediatric nephrology due to its resistance to conventional treatment regimens.[3] Previously, the exact cause of SRNS is still mostly unknown. Now, it is believed that a malfunction of T cells caused the production of certain factors that increased the permeability of the glomerulus to serum proteins, leading to the condition.[4] SRNS is currently also attributed to Mendelian genetic aetiology.

A subset of difficult cases of secondary SRNS following initial steroid sensitivity is immunologically mediated and attributed to an unidentified circulating factor.[5] Recent years have seen considerable advancements in understanding the pathogenesis of SRNS, leading to the development of novel treatment strategies. This comprehensive review aims to provide an overview of emerging therapies for SRNS in paediatric populations.

EXTRACORPOREAL THERAPY

The role of circulating factors in the pathogenesis of nephrotic syndrome has generated considerable interest in extracorporeal therapies, including plasma exchange, immunoadsorption, and low-density lipoprotein apheresis.[6] Among the different extracorporeal treatments,

plasma exchange (PE) therapy has been extensively researched and is the most commonly used intervention.[7] It has been postulated that PE therapy can quickly eliminate the permeability factor in the bloodstream, resulting in a reduction in proteinuria and an improvement in kidney function.[8] In a study by Dall'Amico et al out of the 11 patients who had treatment with plasmapheresis and cyclophosphamide, proteinuria was successfully reversed in 9 patients and 7 patients achieved sustained remission.[9] Immunoadsorption is the semi-selective system that is popularly being used in the treatment of SRNS, especially FSGS. It is a type of plasma exchange in which specific ligands are used in high-affinity absorption columns to selectively remove circulating components from plasma. The ligands utilized in this context are either protein A derived from the cell wall of Staphylococcus aureus or a synthetic peptide called GAM, which exhibits a strong binding affinity for antibodies, particularly IgG.[10]

Low-density lipoprotein apheresis (LDL-A) is one of the major extracorporeal systems that has been extensively researched in SRNS, especially FSGS. LDL-A is effective in reducing proteinuria and helps in recovery, also enhances the effectiveness of steroid and immunosuppressive treatment.[11] Using highly negative-charged dextran sulfate-carrying beads, lipoproteins containing apolipoprotein B can be selectively adsorbate from plasma using LDL-A.[12] Another way to eliminate low-density lipoproteins is through a technique called LDL-apheresis, which involves the use of heparin extracorporeal LDL precipitation (HELP) and direct adsorption lipoproteins (DALI).[13]

Several theories have been postulated by researchers regarding specific mechanisms of LDL apheresis. The reduction in LDL levels leads to the recovery of macrophage function which counteracts the lipotoxic effect on the glomeruli and interstium as well. Additionally, it improves intracellular drug transport, resulting in a more effective response to steroid and immunosuppressive therapy. LDL-A has a beneficial effect on endothelial dysfunction. In addition, LDL-A reduces the levels of vascular permeability factor and also has anti-inflammatory effects by reducing LDL oxidation, C-reactive protein, intercellular adhesion molecule-1, and p-selectin.[14] In a study done by Hattori et al on 11 patients with SRNS, 7 of whom experienced remission of nephrotic syndrome, five of them obtained complete remission within four weeks after starting prednisone therapy with LDL-A. Out of the two patients who experienced partial remission, one patient had consistent renal function throughout the 4.5-year follow-up period, whereas the other patient saw a steady deterioration in renal function and eventually developed end-stage renal failure.[15]

ACTH

SRNS poses a therapeutic challenge in paediatric nephrology, as some patients do not respond well to traditional corticosteroid therapy. Adrenocorticotropic hormone (ACTH) has become a promising alternative for treating SRNS, as it can help induce remission and reduce the likelihood of disease relapse. ACTH functions by inducing the synthesis of corticosteroids. More recently, numerous case studies of patients with steroid and multidrug-resistant nephrotic syndrome showed that ACTH was beneficial in generating and sustaining illness remission and improving GFR, indicating that ACTH has effects beyond steroidogenesis.[16]

ACTH binds to melanocortin receptor 5 (MCR5) and acts as an antagonist. MCR has been detected in various cell types in the body, including podocytes, glomerular cells, and numerous immune cells. ACTH binds directly to the receptor on podocytes, contributing to the stability of a particular protein termed synaptopodin. This leads to a decrease in foot process effacement and an enhancement in glomerular function. ACTH also has immunomodulatory properties since it binds to hyperimmune cells and aids in the downregulation of the proinflammatory pathway, reducing the inflammatory response.[17] In a study conducted by Wang et al ACTH in combination with other medications effectively lowers the maintenance dose of prednisone and prevents disease relapses in children with SRNS.[18]

STEM CELL THERAPY

Children diagnosed with SRNS are at risk of end-stage renal disease. Additional therapeutic alternatives are required for these patients. Stem cell therapy has emerged as a promising strategy for treating SRNS, offering the potential to repair renal damage, modulate immune dysregulation, and induce disease remission. Mesenchymal stromal cells (MSCs) are a type of non-hematopoietic stem cell that can differentiate into multiple cell types. They possess various immunomodulatory features and are increasingly being used in clinical settings. MSCs limit monocytes and macrophages' antigen-presenting and phagocytic activity while increasing their production of interleukin (IL)-10 and programmed cell death.[19] MSCs regulate the development of dendritic cells and their release of pro-inflammatory cytokines. Additionally, they restrict the growth and pro-inflammatory characteristics of CD4+T helper (Th)1 and Th17 cells, while promoting the proliferation of regulatory T cells. It restricts growth, release of cytokines, and the ability to kill cells of CD8+T cells; prevents the development, growth, and release of antibodies by B-cells and promotes the production of cell subsets that produce IL-10.[20] The study conducted by Morello W et al. is currently in phase II clinical trial. The results indicate that out of the 11 patients involved in the trial, 3 patients experienced either partial or total remission.[21]

Galactose

Proteinuria in FSGS (SRNS) is linked to a permeability factor (PF) in certain cases. Studies have demonstrated that

galactose has the ability to attach to PF and hinder its interaction with podocyte glycocalyx. Furthermore, the oral intake of galactose may result in a decrease in proteinuria.[22] However, a recent phase II clinical trial demonstrated that three out of seven patients with FSGS who were given oral galactose experienced a minimum 50% decrease in proteinuria after 6 months of treatment, and this effect lasted for 3-12 months even after stopping galactose. This suggests that galactose could be a beneficial additional treatment for SRNS.[23]

Adalimumab

Adalimumab is a monoclonal antibody that specifically targets and blocks the action of tumor necrosis factor-alpha (TNF-α), a protein involved in inflammation. By binding to TNF-α, adalimumab inhibits it from activating its receptors. Tumor necrosis factor-alpha (TNF-α) released by mononuclear cells in patients with focal segmental glomerulosclerosis (FSGS) has the ability to cause proteinuria in animals. Conversely, the administration of a TNF-α antagonist can decrease proteinuria in experimental models of FSGS.[24] The first FONT study was a phase 1 experiment conducted to assess the safety, tolerability, and pharmacokinetics of adalimumab. Out of 10 patients, four experienced a decrease in UP/C greater than 50% and 56% of patients had stabilization of eGFR, defined as a reduced negative slope of the line plotting eGFR versus time.[25]

Abatacept

Abatacept, also known as CTLA-4-Ig, is an inhibitor of the T-cell co-stimulatory molecule B7-1 (CD 80). Podocyte B7-1 expression is detectable in patients with specific glomerular diseases but is absent in normal human kidney podocytes. Those patients with SRNS who were positive for B7-1 showed a response to abatacept.[26] In a study done by Greka A et al on 5 patients, nephrotic range proteinuria was resolved in all 4 patients who were rituximab-resistant recurrent FSGS and 1 patient of primary glucocorticoid resistant FSGS.[27] Undoubtedly, further data from a randomized trial are required to assess the effectiveness of abatacept in FSGS.

CONCLUSION

The landscape of treatment options for steroid-resistant nephrotic syndrome in pediatric patients is rapidly evolving, with the emergence of novel therapeutic approaches like plasma exchange, complement inhibitors, ACTH analogues, galactose, abatacept, TNF inhibitors, and stem cell therapy represent promising avenues for improving outcomes in this challenging condition. Furthermore, progress in the utilization of genetic tools, the investigation into focused therapeutics using small molecules and monoclonal antibodies, and the establishment of extensive clinical trials will also have a significant effect on the management and therapy choices for SRNS.

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