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Difficult-to-Treat Nephrotic Syndrome in Childhood–Global Depletion of B-Cells

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Idiopathic nephrotic syndrome (iNS) is the most common glomerular disease in childhood and there are clear and generally accepted treatment strategies for initial and follow-up treatment. In general, pediatric nephrologists feel confident about the diagnosis and treatment of iNS.

The problem is the chronic relapsing course of the disease in about 80% of patients, of which more than half of the cases develop frequent relapses and steroid dependency. This requires repeated therapy with glucocorticoids accompanied with several side effects, or the use of steroid-sparing alternatives, and puts the affected families under considerable pressure. Some patients even develop multidrug-dependent or multidrug-resistant nephrotic syndrome. International clinical practice recommendations guide the management of such situations.[1,2] However, do we really know what we are doing? Despite countless mechanistic and therapy-optimizing studies, the pathogenesis of nephrotic syndrome in childhood is not only elusive, but also simply not yet understood. It remains to be seen whether the current enthusiastic discussion regarding the role of antinephrin antibodies in the development of nephrotic syndrome will turn iNS into an antibody-mediated nephrotic syndrome. The same uncertainty exists with regard to the effectiveness of the drugs used. The most common justification for their use is simply their clinically proven efficacy in the majority of cases.

At this point, we realize that the cause of iNS is multifactorial, including membrane selectivity, oxidative stress, circulating factors, complement, interleukins, immune cells, antibodies, and regulatory immunoglobulins.[3] With that in mind, it does not sound conceivable that 1 single form of therapy can help all patients.

Recently, the chimeric monoclonal anti-CD20 antibody rituximab has gained great attention, especially when complicated courses of iNS cannot be controlled by other steroid-sparing agents.[2,4] The treatment effect is temporary, and many children require additional courses of rituximab. A series of well-performed studies even propose rituximab as first line steroid-sparing option.[5] Rituximab depletes all circulating B-cell subsets (but not the bone-marrow resident plasma cells), and B-cell recovery is associated with the risk of relapse.[4] Currently, it is not clear, if newer humanized anti-CD20 antibodies such as ofatumumab or obinutuzumab may have superior efficacy compared to rituximab in children with iNS.[6]

In a recent issue of Kidney International Reports, Angeletti *et al.*[7] address the aspect of antibody-mediated disease and report on their experience with a combined rituximab and daratumumab treatment in a cohort of multidrug-resistant and multidrug-dependent patients suffering from nongenetic nephrotic syndrome. Daratumumab is a fully human monoclonal anti-CD38 antibody, depleting long-lived CD38 positive plasma cells that are not affected by rituximab. Combined therapy results in profound depletion of the entire B-cell spectrum and causes prolonged reduction in serum IgM that is supposed to play a pathogenic role in nephrotic-range proteinuria *via* classical complement activation.[3,8] The reported clinical success is impressive: 6 out of 7 multidrug-resistant patients went into partial ($n = 2$) or complete remission ($n = 4$) and the relapse-free survival after 12 months doubled in multidrug-dependent patients despite withdrawal of oral immunosuppressive drugs. Not less important is the absence of infectious complications and only 1 significant hypogammaglobulinemia in the follow-up period of 9 to 28 months. Thus, global depletion of B cells may be a promising treatment attempt in difficult-to-treat cases of

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nongenetic nephrotic syndrome. In this respect, the real-life character of the study, which included a very heterogeneous patient population of different ages (aged 3 to 24 years), different histologies, different disease courses and previous therapies, is to be seen as a strength. However, we are aware that only a very small group of patients with iNS is candidate for global B-cell depletion as most patients respond to steroid-sparing immunosuppressive therapy and those requiring rituximab as rescue show a satisfactory response in 30% to 90% of the cases.

However, the study leaves a number of questions unanswered, which require further clarification in the future.

1. Rituximab is supposed to generate a disease-modifying effect[4] that seems to increase with repeated doses and might be irrespective of B-cell recovery. In the present study, a subset of patients had already been treated with rituximab before and it remains unclear whether this could have had an effect on the clinical outcome.
   Could the sustained effect also be true for daratumumab alone? Could the combination of both agents result in an even more pronounced sustained effect? What would this mean for potential further dosing when plasma cells and IgM levels recover? Is recovery of target cells a helpful finding in decision-making for repeated dosing at all? Could maintenance mycophenolate mofetil treatment following global B-cell depletion induce long-term disease remission as has been shown for rituximab alone[9]?

2. We cannot yet assess the extent to which antibodies contribute to the development of the disease.
   In the present study, the recovery of IgM levels was associated with a higher risk of relapse.
   Would the complement activating property of IgM antibodies open the door for complement blockade? Unfortunately, no kidney biopsies were available from all patients at baseline and none after the start of treatment that could provide information on glomerular IgM deposits and local complement activation. The rising IgM levels could merely be a surrogate parameter of the recurring CD38 positive plasma cells.
   Do we have enough mechanistic evidence to indicate global B-cell depletion?
   This leads to the next aspect that is of special concern for pediatric nephrologists.

3. Is global B-cell depletion safe in pediatric patients?
   There were no safety concerns in the present study; but the cohort was rather small. There is some evidence supporting the view that rituximab is safe for most children; however, we fear the rare and potentially serious adverse events such as lung injury, multifocal leukoencephalopathy, or viral reactivations.[4]
   How is the risk of especially young children to develop sustained neutropenia and hypogammaglobulinemia in global B-cell depletion?

4. How should we assess the finding that antinephrin antibody levels were not affected by global B-cell depletion in the present study? The finding might be due to an analytical problem. Assuming it was a reproducible result, would that call into question the impact of antinephrin antibodies and the indication for B-cell depleting therapy in total? Do we need more data on immune cell profiles and their signaling dynamics in iNS?

We have come a long way and yet somehow, we are still at the beginning. That is no reason to despair; it is an absolute motivation to keep going. It currently seems to be an exciting time because we can expect groundbreaking research into the pathophysiology and treatment of childhood INS in the near future.

DISCLOSURE

All the authors declared no competing interests.

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