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Common Threads in Pediatric Inflammatory Diseases: Insight into Personalized Medicine

Trusha T. Patel, MD[1], **Maire A. Conrad, MD**[1], **Judith R. Kelsen, MD**[1]

[1]Division of Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia

Pediatric inflammatory diseases include a spectrum of complex interactions among host genomics, immune response and environmental exposures. Despite this common thread, alterations in these interactions lead to different disease phenotypes and are often approached by each individual sub-specialty in isolation. In actuality, these different diseases often share causative pathways and subsequently may have common therapeutic targets. Indeed, in this era of precision medicine, integration of the expertise among different disciplines will allow us to identify therapies that are more precise and effective. By learning from one another's successes and failures, we can develop a personalized approach to each patient, guided by the phenotype and disease severity.

In this issue of *JAMA Pediatrics*, Basu et al demonstrate a targeted approach through use of Rituximab as primary therapy in patients with severe nephrotic disease. Nephrotic syndrome is the most common pediatric primary glomerular disease, and the majority of children respond favorably to corticosteroids.[1–3] Unfortunately, some children develop steroid-dependent nephrotic syndrome that is often refractory to medications. Up to 50% of these children progress to end-stage renal disease within 10 years.[4] Histological features frequently seen in kidney biopsies of patients with steroid-resistant nephrotic syndrome are consistent with focal segmental glomerulosclerosis (FSGS). Presence of FSGS is associated with 33% risk recurrence of nephrotic syndrome rapidly after kidney transplant indicating that this disease is not inherent to the native kidney alone but also has circulating factors.

The etiologic hypotheses of nephrotic syndrome have evolved over time from a primary T cell dysfunction, to T regulatory cell dysfunction, and currently are thought to involve B cell derived factors. The developing insight into the disease mechanism has led to changes in therapy. Tacrolimus a calcineurin inhibitor, the initial therapeutic approach following steroid failure, primarily functions through inhibiting IL-2 production and T lymphocyte activation. Additionally, it affects broader cytokine production in addition to IL-2, as well as growth and differentiation of B lymphocytes.[5,6] Rituximab, on the other hand, is an anti-CD20 antibody that depletes B cells. More subjects with refractory nephrotic syndrome had longer disease free response to rituximab compared to tacrolimus in this paper, which may point to improved targeting of the mechanism of disease.

Correspondence: Judith R. Kelsen, MD, 7NW, Division of Pediatric Gastroenterology, 3400 Civic Center Blvd, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, Tel: 215-590-7423, Fax: 215-590-5326, Kelsen@email.chop.edu.

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The success of the authors' strategy highlights the shift in patient care that is already a reality in some inflammatory conditions. Traditional treatment algorithms are evolving to include immunomodulatory and biologic therapies previously not employed. While there are different mechanisms of inflammation that lead to specific organ involvement, such as the gut, lung, kidney, skin, brain, and joints, the overall process of many of these disorders involves similar immune mediated pathways, allowing for a shared therapeutic approach. Thus, our understanding of the "conventional" therapeutic approach for many conditions is dramatically changing.

Regardless of the specific manifestation, inflammatory diseases involve a breach in an otherwise coordinated and eloquent immune response. The immune attack involves a uniform approach of antigen recognition, tagging and effective killing. The innate immune system includes dendritic cells, (DCs), macrophages and lymphocytes among other components. Within each organ, DCs recruit neutrophils upon sensing a pathogen. Complement directly binds to potential pathogens, which are recognized by neutrophils and macrophages and can then be subsequently phagocytosed. Additionally, cytolytic activity, including natural killer cells, allow for killing and clearance of viral mediated processes. The adaptive immune response is then called into action, with a T cell and B cell mediated response depending on the pathogen. A defect in any component of this process can lead to inflammation and disease and is a potential therapeutic target.

Indeed, the current biologic therapies, and those in development, are aimed at these immune targets and thus may have multiple indications. These can range from inflammatory bowel disease, rheumatoid arthritis and psoriasis to systemic lupus erythematosus, immune thrombocytopenia and ANCA-associated vasculitis. Application of therapies in one disease often informs the potential use in a similar immune mediated disease. For example, anti-Tumor Necrosis Factor alpha (TNF) therapies such as infliximab, adalimumab, and golimumab have FDA approval for use in inflammatory bowel disease, rheumatoid arthritis, psoriasis/psoriatic arthritis and ankylosing spondylitis. Given similar production of TNF in Bechet's disease and non-infectious uveitis, it is not surprising that it has been used successfully with these diseases as well.[7 8] Rituximab, has FDA approval for management of some low grade or follicular CD20+ Non-Hodgkin's Lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis as well as other autoimmune diseases. Aside from improving the target precision with biologic agents, advances in utilizing pharmacokinetics through therapeutic drug monitoring have further improved subjects' clinical response and the long term success with these therapies.

As we understand more about the genomic drivers of disease and immune dysfunction, targeted therapy will become even more attainable. This has been seen in specific Mendelian diseases as well as monogenic forms of complex inflammatory disease, such as very early onset inflammatory bowel disease. This is also true of nephrotic syndrome, in which the role of monogenic defects causative for certain disease phenotypes has been increasingly recognized. The positive response to rituximab in this study's population could be related to the similar genetic and ethnic background of the subjects enrolled. Previous studies demonstrate clear geographical variation in the incidence of nephrotic syndrome and

variation in response to medications.[9] New technology in genetic sequencing may allow us to be even more precise. Identifying causative genes has implicated the glomerular podocytes and slit membranes as the primary site of disease. So far, 53 genes have been identified in young children diagnosed with steroid resistant nephrotic syndrome (SRNS) and next generation sequencing technology, including whole exome sequencing, have allowed for continued exploration of the genetic background of SRNS.[10,11] The major implication of identifying monogenic defects in SRNS, and inflammatory diseases in general, is the ability to detect the disease drivers in order to improve clinical outcomes. Therefore, refractory disease may be the result of an underlying genetic or immunological causative or contributory defect. Further investigation to elucidate the etiology may lead to the true diagnosis and definitive therapy.

Through the integration of genomic and clinical data, we will find that seemingly different disease processes, in fact, are mechanistically very similar with overlapping drug targets. Thus, going forward we will be able to expand our arsenal of therapeutics in order to improve our precision medicine approach.

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