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EDITORIAL

The horizon of the 21st century in pediatric nephrology: Clinical trials and personalized medicine☆

El horizonte del siglo XXI en nefrología pediátrica: ensayos clínicos y medicina personalizada

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In the field of nephrology, treatment options have been very limited until the early XXI century, when the pathophysiological mechanisms of numerous renal diseases started to be elucidated, leading to the identification of potential therapeutic targets. It was not until 2007, when the European Union Paediatric Regulation was introduced, mandating performance of paediatric clinical trials in the drug development process, that research advances started to translate into treatments in paediatric nephrology. Since 2007, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have collaborated closely in paediatric development plans and paediatric strategies, allowing the pursuit of a single, aligned paediatric investigation plan (PIP).[1]

Conducting a literature search for clinical trials in paediatric nephrology yields at least 77 hits just from the past year. Autoimmune diseases with heterogeneous presentations, such as lupus nephritis, require a more personalised approach with identification of individual risk factors and characterization of the immune profile of patients, and there are now clinical trials of drugs that target specific biological pathways and may achieve better response rates. Currently underway are 3 phase I trials (anifrolumab, tocilizumab and eculizumab), 3 phase II trials (obinutuzumab, dapirolizumab and atacicept) and 1 phase III trial (abatacept) that accept paediatric patients who do not achieve complete remission with conventional treatment.[2]

Patients with primary glomerulonephritis have also benefitted from recent advances in pharmacology and genetics. For instance, in the case of nephrotic syndrome, the most frequent form of chronic glomerulonephritis in children, there has been an exponential increase in the detection of genetic changes that cause the disease, to the point that in some series the proportion of monogenic cases is as low as 30%, and the number of patients assessed by means of whole-genome exome sequencing has been increasing. These findings are important to avoid treatments that could have severe side effects. Patients with steroid-resistant nephrotic syndrome with negative genetic test results that progress to end-stage renal disease in childhood are at high risk of recurrence after renal transplantation, so treatment efforts should be maximised, while patients with genetic mutations do not experience relapse in the graft, which calls for reducing the number of drugs that have frequent or severe adverse effects especially given that, on the other hand, the likelihood of a response is minimal no nonexistent.[3]

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Eighty percent of patients with nephrotic syndrome respond to first-line treatment (steroid therapy), but 50% of them experience a course of disease with numerous relapses (frequently relapsing nephrotic syndrome, FRNS) or become steroid-dependent (steroid-dependent nephrotic syndrome, SDNS). The treatment options for nephrotic syndrome in the late XX century were limited to steroids, alkylating agents and ciclosporin, all of which have significant and frequent adverse effects, including Cushing syndrome, osteoporosis, delayed growth, sterility, and an increased risk of cardiovascular disease, tumours, infection and kidney failure.

The new therapeutic armamentarium includes tacrolimus, mycophenolate mofetil, rituximab and levamisole, as well as their combinations and their combination with conventional treatment, chiefly steroids. Rituximab is a chimeric anti-CD20 monoclonal antibody that inhibits B cell proliferation and differentiation mediated by CD20. It was originally developed to treat patients with B-cell non-Hodgkin lymphoma. This monoclonal antibody is currently used to treat various autoimmune diseases, such as rheumatoid arthritis, Wegener granulomatosis and microscopic polyangiitis. Benz et al.[4] were the first to report that a 4-dose course of rituximab induced long-term remission in CDNS complicated by idiopathic thrombocytopenic purpura in a male patient aged 16 years. This was the first report that hinted at the efficacy of rituximab for treatment of complicated FRNS or SDNS. Later on, Gilbert et al.[5] reported that 4 cycles of rituximab were effective for maintaining remission in patients with complicated childhood-onset FRNS or SDNS. Ravani et al.[6] carried out the first clinical trial of rituximab for children with steroid and calcineurin inhibitor-dependent nephrotic syndrome (complicated SDNS) and found urine protein levels that were 70% lower in the rituximab group compared to the group that received conventional treatment, as well as a lower relapse rate. However, there are also drawbacks of treatment with rituximab, as the drug has been associated with severe adverse events, including fatal hepatitis due to reactivation of the hepatitis B virus and progressive multifocal leukoencephalopathy. In children with FRNS or SDNS, the most frequently described adverse events are pulmonary fibrosis, fulminant myocarditis, *Pneumocystis* pneumonia, immune-mediated ulcerative colitis and agranulocytosis. Following treatment with rituximab, hypogammaglobulinemia persist in most patients who had low immunoglobulin G (IgG) levels before treatment, so it is important to conduct a long follow-up in these patients.[7]

Different rituximab protocols are used in Europe for management of steroid-dependent or frequent-relapsing patients in clinical practice, which do not modify the established dose of 375 mg/m^2 per infusion, but rather the number of doses, as it was observed that some patients maintained low or undetectable CD19+ cell counts without relapsing for a long time after only 1 or 2 doses, which also minimised the adverse effects of rituximab. Guzmán et al. published their experience supporting this approach, as only 1 of their patients received 4 cycles, while 6 received 2 and 1 a single dose. The authors observed a decrease in the number of relapses per year after treatment, which allowed a reduction in the dosage of steroid and immunosuppressant drugs and offered their patients, who had undergone chronic treatment for years, a treatment option that maintained them free of disease and without treatment for a long time.[8]

Clinical trials for nephrotic syndrome currently underway focus on finding combinations of drugs that would allow reducing their dosage to prevent adverse events, and genetics studies on establishing the predisposition to develop disease and predicting the response to drugs. As paediatricians, we must never forget that our duty is not limited to protecting child health in the present, but also to work towards future health and wellbeing, which requires that we stay up to date and promote advances in science.

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