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LETTER TO THE EDITOR

Should mycophenolate mofetil be administered prior to cyclosporine A as a steroid-sparing agent to children with steroid-dependent nephrotic syndrome?

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Sir,

We read with great interest the review article titled, "Mycophenolate mofetil for sustained remission in nephrotic syndrome" by Querfeld et al. [1]. Based on the recommendations in the recent clinical practice guidelines, the authors conclude that mycophenolate mofetil (MMF) is a valuable steroid-sparing agent that does not exert a nephrotoxic effect on children with frequent-relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS). They also recommend the administration of MMF for several years to achieve sustained remission of nephrotic syndrome (NS) because many studies have reported rapid relapse of NS after MMF discontinuation. Although recent randomized controlled trials have demonstrated that MMF is less effective than cyclosporine A (CsA), currently, there is no consensus regarding the first-line steroid-sparing agent for children with FRNS or SDNS. In this regard, we previously reported in *Pediatric Nephrology* that MMF can be an alternative treatment for patients with chronic nephrotoxicity who have undergone long-term CsA treatment [2]. In contrast, severe infections may develop in some children with FRNS or SDNS who receive such immunosuppressive agents for a long period, resulting in NS relapse and hospitalization. However, there is limited information regarding the adverse events in these patients at the time of febrile infections.

Based on our experience at a single center, we would like to comment on the risk factors for NS relapse and hospitalization during the course of infections in children with SDNS who received steroid-sparing agents, such as MMF and CsA. Between 2005 January and 2016 December, we retrospectively reviewed 203 episodes of febrile infections (> 37.5 °C) in 83 patients with childhood-onset SDNS (median age, 6.9 years) who were treated with various immunosuppressive agents (CsA in 106, MMF in 71, mizoribine [MZR] in 27, and cyclophosphamide [CPM] in 9 patients) at Saitama Children's Medical Center [3]. Of the 203 episodes (47 due to influenza virus, 7 due to streptococcal infections, 3 due to adenovirus, 3 due to mycoplasma pneumoniae, 12 due to others, and 131 due to unknown pathogens) NS relapse and hospitalization because of severe infection was observed in 15 (7.4%) and 15 patients (7.4%), respectively. There were no differences in the clinical characteristics, such as age at febrile infection, and use of CsA or CPM between the patients with and without NS relapse. However, the use of MZR (40 vs. 11%, $p < 0.01$) and prevalence of influenza virus infection (47 vs. 21%, $p < 0.05$) were significantly higher in patients with NS relapse than in those without relapse. However, the use of MMF in patients with NS relapse was significantly lower than in those without relapse (7 vs. 32%, $p < 0.05$). There were no differences in the clinical characteristics, such as use of MZR or CPM, and prevalence of influenza virus infection between hospitalized and non-hospitalized patients. However, the use of CsA (20 vs. 50%, $p < 0.05$) and mean age at febrile infection (6.8 vs. 8.2 years, $p < 0.05$) were significantly lower in patients requiring hospitalization than in those without hospitalization. In addition, the use of MMF was significantly higher in hospitalized patients than in non-hospitalized patients (53 vs. 28%, $p < 0.05$).

In this retrospective study of 83 children with SDNS who received various immunosuppressive agents at the time of febrile infections, MMF inhibited NS relapse more effectively than MZR. Moreover, compared to the use of CsA, the use of MMF at the time of febrile infections was

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a risk factor for hospitalization, especially in younger patients. In a German randomized, open-label, crossover study that compared MMF and CsA in 60 children with FRNS over a 2-year period, Gellerman et al. reported that prior CsA therapy was associated with higher MMF efficacy in the second year of treatment, potentially due to a carryover effect from the first year of CsA treatment. Thus, we prefer to administer CsA prior to MMF, especially in younger patients and prescribe MMF only if FRNS or SDNS persists even after long-term use of CsA, while this treatment strategy may improve chronic nephrotoxicity by the antifibrotic actions of MMF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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