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LETTER TO THE EDITOR

Profound effect of post-rituximab mycophenolate mofetil administration for persistent hypogammaglobulinemia in young children with steroid-dependent nephrotic syndrome

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To the Editor,

Although immunoglobulin serum levels are usually not affected after rituximab (RTX) administration because CD20 is not expressed on mature plasma cells, recent studies have revealed that post-RTX hypogammaglobulinemia may develop, particular in young patients with steroid-dependent nephrotic syndrome (SDNS) [1, 2] However, the mechanism and risk factors of persistent hypogammaglobulinemia after B-cell recovery remain unclear. Based on our retrospective analyses, we wish to discuss the characteristics of patients with SDNS who develop hypogammaglobulinemia after a single infusion of RTX.

Total 74 Japanese patients with SDNS (median age at RTX administration, 13.8 years) who had received RTX treatment (total 178 doses) at Saitama Children's Medical Center between February 2008 and June 2017 were enrolled in this study [3]. After a single infusion of RTX (375 mg/m^2), maintenance therapy with immunosuppressive agent (IS), such as cyclosporine (CsA) or mycophenolate mofetil (MMF), was continued for preventing post-RTX relapse [4]. If NS relapse occurred after CD19+ cells recovery ($\geq 1\%$ of total lymphocytes) in the peripheral blood despite IS maintenance therapy, a single dose of RTX was added. To detect potential drug toxicity, clinical and laboratory parameters, including complete blood count and levels of immunoglobulins, were regularly measured at least once a month during B-cell depletion periods. At 6 months after RTX administration, 20 episodes of hypogammaglobulinemia (serum IgG level < 500 mg/dL) were detected during 178 RTX treatments (11%). We compared the patient characteristics of those with ($N = 20$) and without hypogammaglobulinemia ($N = 158$) at 6 months after RTX administration. No significant differences were observed in the clinical characteristics, such as sex, number of RTX infusions, and type of IS administered after RTX, of the groups. However, median age at RTX administration was significantly lower in patients with hypogammaglobulinemia than in those without hypogammaglobulinemia (6.1 vs. 14.4 years, $p < 0.05$). In addition, the median serum IgG levels before RTX were significantly lower in patients with hypogammaglobulinemia than in those without hypogammaglobulinemia (426 vs. 656 mg/dL, $p < 0.05$). Among the 15 patients with hypogammaglobulinemia at 6 months after RTX administration, we compared the patient characteristics of those with ($N = 9$; 449 mg/dL) and without persistent hypogammaglobulinemia ($N = 6$; 650 mg/dL) at 12 months after the previous episode of hypogammaglobulinemia. No significant differences were observed in the clinical characteristics, such as sex, age at RTX administration, number of RTX infusions, number of NS relapse, and serum IgG levels before RTX (391 vs. 345 mg/dL) or at 6 months after RTX (415 vs. 428 mg/dL), of the groups. However, the rate of post-RTX MMF administration was significantly higher in patients with persistent hypogammaglobulinemia than in those without persistent hypogammaglobulinemia (78 vs. 17%, $p < 0.05$). Among seven patients with persistent hypogammaglobulinemia who received post-RTX MMF administration, severe infection with varicella zoster virus requiring hospitalization developed in one patient. Furthermore, regular intravenous immunoglobulin (IVIG) administration was required in three patients because of severe persistent hypogammaglobulinemia (< 100 mg/dL). In contrast, severe infection and requirement of IVIG administration did not develop in two patients with persistent hypogammaglobulinemia who received post-RTX CsA administration.

Similar to the results of recent retrospective studies conducted in France and Italy [1, 2], our data also demonstrated that younger children were more likely to develop hypogammaglobulinemia at 6 months after a single infusion of RTX,

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especially in patients with pre-existing low serum IgG levels. This may reflect the immaturity of the immune system in young children having a lower percentage of memory B cells. Furthermore, patients who received sequential therapy with MMF after RTX were more likely to have persistent hypogammaglobulinemia for > 12 months after B-cell recovery. We speculate that the depletion of naïve and memory B cells and inhibition of both T- and B-cell proliferation with the combination therapy of RTX and MMF may explain the profound effect on persistent hypogammaglobulinemia [5]. Taken together, our results raise the possibility that the pre-existing intrinsic immunodeficiency could be aggravated by the treatment strategy, particularly in young children with SDNS. Thus, we conclude that persistent hypogammaglobulinemia due to post-RTX MMF administration should be taken into consideration in this cohort. A larger prospective study is required to clarify the mechanism and risk factors of persistent hypogammaglobulinemia after B-cell recovery in RTX-treated children with complicated SDNS.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and/or National Research Committee at which the study was conducted (approval number 2019-01-003) with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in this study.

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