CJASN ePress. Published on July 10, 2020 as doi: 10.2215/CJN.06400420

COVID-19 in Children with Nephrotic Syndrome on Anti-CD20 Chronic Immunosuppression

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CJASN 15: ●●●–●●●, 2020. doi: https://doi.org/10.2215/CJN.06400420

Children seem to have a lower incidence and milder clinical course of coronavirus disease 2019 (COVID-19) (1), but data regarding disease susceptibility in specific categories of pediatric patients on chronic immunosuppression are limited (2). Decisions to reduce immunosuppression or delay redosing of B cell–depleting therapy are currently being considered as the spread of this pandemic advances and the effect of COVID-19 is feared by patients who are immunosuppressed and their physicians.

B-cell anomalies play a fundamental role in the pathogenesis of several immune disorders. In the last 2 decades, the chimeric anti-CD20 antibody rituximab emerged as a valuable therapy to safely improve the natural history of several kidney disease and systemic autoimmune disorders, including multirelapsing or steroid-dependent nephrotic syndrome, membranous nephropathies, vasculitis, SLE, rheumatoid arthritis, and neurologic disorders. Furthermore, recent evidence supported the use of fully humanized anti-CD20 antibody ofatumumab as a valid alternative to rituximab. Despite the relatively safe profile (3), the administration of rituximab and ofatumumab is usually correlated with safety concerns, requiring careful evaluation and intensive surveillance in early detection of serious infection events.

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which rapidly spread to pandemic proportions and has resulted in >6 million positive cases worldwide (www.who.int), may represent an important and reliable infective stress test for these therapies.

We have prospectively followed up a cohort of 159 pediatric patients (127 children [≤18 years] and 32 young adults [19–28 years]) on chronic immunosuppression due to multirelapsing nephrotic syndrome on therapy with anti-CD20 antibodies. These patients had been enrolled in a single-center, randomized controlled trial comparing the safety/efficacy profile of two B cell–depleting antibodies, rituximab and ofatumumab (NCT02394119) (4). Written informed consent for the use of medical records was obtained at enrollment.

All patients were living in Italy, in areas of high incidence of SARS-CoV-2. From February 24 to April 7, 2020, all patients were interviewed weekly for 7 consecutive weeks to assess their health status and the health status of cohabitants. Patients were also interviewed at 8 weeks of follow-up. Of note, subjects who were asymptomatic may have been missed.

Data were collected using an *ad hoc* database and reviewed by two investigators independently.

At the time of the initial interview, 54 (34%) patients were on chronic immunosuppression with steroids, calcineurin inhibitors, and/or mycophenolate mofetil (Table 1). All patients had received B cell–depleting therapy at a median time of 18 months since last infusion. Of the patients, 74 (46%) had circulating IgG below the normal range. Of the remaining patients, 19 (22%) received anti-CD20 no longer than 12 months prior and 20 (23%) were on chronic immunosuppression (Table 1). A total of 32 (20%) patients had proteinuria and two were in treatment with renin-angiotensin-aldosterone system inhibitors.

None of the 159 patients reported clinical symptoms for COVID-19, including fever (>37°C), cough, sore throat, fatigue, ageusia, or gastrointestinal disorders (Table 1). We detected six subjects whose cohabitants, with symptoms for COVID-19, tested positive for SARS-CoV-2 by nasopharyngeal swab. Four cohabitants remained in the same house, but isolated in a single room until a negative swab test was obtained. The remaining two were hospitalized and later died due to COVID-19 lung complications. Four of the six patients of the cohort at high risk presented reduced levels of serum IgG and circulating $CD19^+$ B cells. Despite the close contact, none of the six subjects reported any symptoms, neither during nor at the end of the incubation period of 14 days. These patients were not tested for SARS-CoV-2 because they did not develop any symptoms. One patient with a positive cohabitant was tested due to hospitalization for the management of nephrotic syndrome relapse and the test was negative for SARS-CoV-2. The two patients with cohabitants who died of COVID-19 were later tested for anti–SARS-CoV-2 antibodies 4 and 6 weeks after initial exposure, respectively, but both IgM and IgG antibodies were negative.

This report documents that chronic immunosuppression does not increase the risk of COVID-19 in children and young adults in areas where SARS-CoV-2 incidence is high, provided that regular measures for disease prevention are followed. Strict prevention is strongly recommended in the case of positive cohabitants.

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Table 1. Epidemiologic characteristics, therapy, and immune phenotype of 159 patients in Italian areas with a high incidence of COVID-19

Characteristics	Value
Age, yr	
Median (range)	12.5 (2–28)
Sex, *n* (%)	
Male	108 (68)
Female	51 (32)
Median of months since last anti-CD20 Ab administration (range)	18 (1–63)
Median of total anti-CD20 infusions, *n* (range)	2 (1–11)
Ongoing immunosuppressive therapies, *n* (%)	
None	105 (66)
Steroids	18 (11)
CNI	14 (9)
MMF	9 (6)
Steroids and MMF	7 (4)
Steroids and MMF and CNI	6 (4)
Proteinuria (g/24 h)	
Median (range)	1.5 (0.1–6.8)
RAASi, *n* (%)	2 (1)
IgG (mg/dl), median (range)[a]	675 (79–1425)
Pts with IgG ≤650 mg/dl, *n* (%)	74 (46)
Circulating CD19$^+$ B cells (/μl)[b]	
Median (range)	328 (0–1275)
CD4/CD8 T cells, median (range)[c]	1.5 (0.4–2.5)
Neutrophils ($\times 10^3/\mu$l), median (range)[d]	4.5 (1.6–9.1)
Natural killer (%), median (range)[e]	9.2 (1–23)
Pts with natural killer ≤6%, *n* (%)	64 (40)

COVID-19, coronavirus disease 2019; Ab, antibody; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; RAASi, renin-angiotensin-aldosterone system inhibitor; Pts, patients.
[a]Normal range for IgG: 650–2400 mg/dl.
[b]Normal range for CD19$^+$ B cells: 140–900/μl.
[c]Normal range for CD4/CD8: 0.9–3.5.
[d]Normal range for neutrophils: 2.1–6.4 $\times$ $10^3/\mu$l.
[e]Normal range for natural killer cells: 6%–27%.

Cytokine storm triggered by SARS-CoV-2 might be responsible for severe and fatal complications in COVID-19 (5). Thus, immunosuppressive treatment may be suggested to lower the host immune response, with consequent attenuation of the hyperinflammatory reaction. We suggest not altering the immunosuppressive therapy in children with nephrotic syndrome, even if exposed to close contact with individuals who have COVID-19.

B cell–depleting therapies were also found to be safe in this large cohort of young patients with nephrotic syndrome, which might represent an important observation not only for patients affected by nephrotic syndrome and chronic autoimmune and inflammatory disease, but also for individuals with hematologic disorders.

Disclosures

All authors have nothing to disclose.

Funding

G.M. Ghiggeri was supported by Ricerca Finalizzata (Italian Ministry of Health) grant 2016:WFR: PE-2016-02361576 for the trial (NCT02394119).

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Published online ahead of print. Publication date available at www.cjasn.org.