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Efficacy and Safety of Subcutaneous Rituximab in Idiopathic Nephrotic Syndrome

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INTRODUCTION

Idiopathic nephrotic syndrome is a rare disease characterized by edema, nephrotic-range proteinuria, and hypoalbuminemia. Although corticosteroids induce remission in almost 90% of patients, approximately 40% to 60% of cases develop frequent relapses and become steroid-dependent. These patients are often treated with steroid-sparing agents, to manage frequently relapsing or steroid-dependent nephrotic syndrome (SDNS).[1]

Rituximab is a chimeric anti-CD20 monoclonal antibody depleting B cells that was initially approved for the treatment of hematological diseases. Several clinical studies have demonstrated that i.v. rituximab is effective in achieving sustained remission in children with SDNS, providing a viable option as a steroid-sparing agent.[2–4]

However, i.v. administration of rituximab requires prolonged infusions (3–8 hours), with associated costs and potential risks of infusion-related reactions.[5] Children receiving i.v. rituximab administration often require hospitalization due to the challenges in securing stable vascular access and the requirement for intensive monitoring. This further increases the logistical challenges and healthcare expenses.

To simplify logistics, shorten rituximab administration time, and reduce costs, a subcutaneous (SC) formulation of rituximab has been developed that can be completed in only 5 to 6 minutes.[6] To reduce the injection volume, SC rituximab formulation has a 12-fold higher concentration than the i.v. formulation. It contains recombinant human hyaluronidase, which enhances drug diffusion and absorption by temporarily hydrolyzing interstitial hyaluronic acid fibers, thus minimizing swelling and pain.[7] So far, numerous hematological clinical trials have been conducted to prove the efficacy and safety of SC rituximab.[8] To the best of our knowledge, no studies have reported the administration of SC rituximab in nephrological conditions.

RESULTS

In the present prospective-cohort study, we included consecutive patients with SDNS with nephrotic syndrome recurrence who had previously received at least 1 course of i.v. rituximab. We aimed at comparing, within the same subjects, the efficacy in preventing disease relapses, safety, and costs of SC rituximab versus previous i.v. rituximab administrations. The primary end point was the occurrence of disease relapse within 12 months of follow-up after treatment. As per Kidney Disease: Improving Global Outcomes guidelines,[9] we defined SDNS as the occurrence of 2 consecutive relapses while on corticosteroid therapy, or within 15 days after steroid withdrawal.

SC rituximab (Roche, Basel, Switzerland) was administered as a single dose of 1 g or 1.4 g according to the body surface area $<$ or $>$ to the arbitrarily established threshold of 1.5. Previous i.v. rituximab (Sandoz, Basel, Switzerland) was administered as a single dose of 375 mg/m^2 diluted in saline. In accordance with drug indications,[6] SC rituximab was administered only in subjects who well-tolerated prior i.v. rituximab. For both SC and i.v. treatments,

Table 1. Main baseline parameters subjects at administration of subcutaneous or i.v. rituximab

	i.v.	s.c.	*p*
Gender	9 M / 4 F		
Ethnicity	13 Caucasian		
Age, yr	12.1 ± 3.8	14.5 ± 4.1	0.03
Serum creatinine, mg/dl	0.4 ± 0.3	0.5 ± 0.3	n.s.
Serum albumin, g/dl	3.1 ± 0.6	3.2 ± 0.4	n.s.
Proteinuria, g/24 h	0.2 ± 0.1	0.1 ± 0.1	n.s.

F, female; M, male; n.s., not significant; s.c., subcutaneous.

patients received a premedication as described in the Supplementary Methods.

We enrolled a total of 13 consecutive patients with SDNS immediately after achieving remission with steroids for recent recurrence. All the patients received i.v. rituximab in the previous relapse episodes. SC and i.v. treatments were administered immediately after having achieved remission. Patients presented comparable baseline clinical characteristics at SC and i.v. treatment, as summarized in Table 1.

Single SC and i.v. rituximab administration resulted in similar relapse-free time after treatment (Figure 1a). Circulating total $CD19^+$ B cells were similar at baseline (before treatment) and followed almost identical trends after treatment in both groups: they were fully depleted at 3 months, and fully recovered at 12 months after treatment (Figure 1b). The other major B cell subpopulations, including total memory B cells (not shown) and plasma blasts, followed similar trends (Figure 1b).

No minor or major infusion reactions were observed during SC injections nor during i.v. treatment. During the 12 months after either single SC or i.v. rituximab administration, we did not observe any adverse events, including episodes of severe hypogammaglobulinemia (IgG serum levels $<$ 400 g/dl).

We performed a cost analysis taking the perspective of healthy service providers in the Italian Public Health System, and the costing method determined the direct health care costs associated with each treatment schedule. All resource use was valued at 2024 Euro prices. Costs for drugs and hospitalization were obtained from the Hospital Economy Department. Indirect costs were not considered.

Cost for 0.1 g of SC and i.v. rituximab is €188.00 ($203.96) and €330.71 ($359.04), respectively. SC rituximab was administered as a 1 g dose in 3 patients and as a 1.4 g dose in 10 patients, at the total cost of €31,942.4 ($34,653.67). i.v. rituximab was administered at a single dose of 1 g in 9 patients and as a 0.5 g in 4 patients, at the total cost of €36,378.98 ($39,467.32). SC injections were performed as outpatient in all cases, whereas i.v. rituximab was

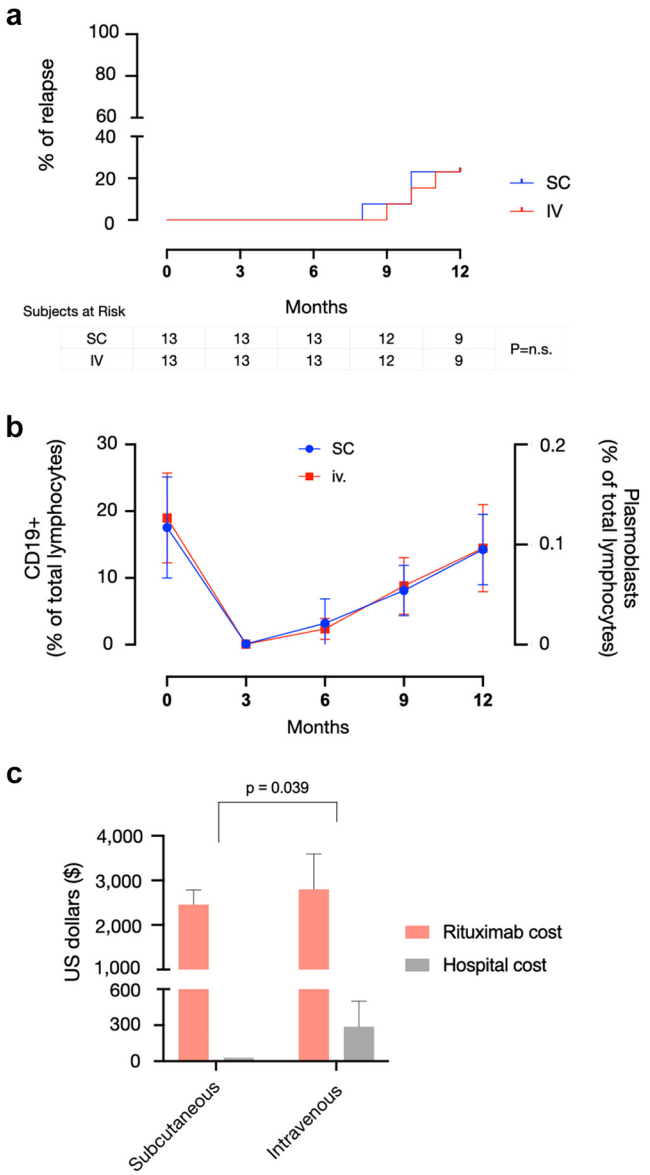

Figure 1. (a) Relapse-free survival at 12 months of follow-up after single s.c. and i.v. treatment; (b) CD20 B cell and plasmablasts count at baseline (month 0) and at different time points up to 12 months of follow-up after s.c. and i.v. rituximab treatment; (c) cost analysis comparing s.c. and i.v. administration of rituximab (red) in the cohort of 13 subjects, considering daily out-patient and a 2-night hospitalization costs (grey). All resource use was valued at 2024 Euro prices. s.c., subcutaneous.

administered as out-patient in 5 cases and 8 cases required hospitalization. Considering a daily outpatient cost of €27.00 ($29.31) and a 2-night hospitalization cost of €450.00 ($488.54), we compared the median costs for SC and i.v. rituximab for the 13 enrolled patients, corresponding to the median cost of €2486.42 ($2713.34) for SC and €3086.58 ($3368.28) for i.v. administration (Figure 1c). Overall, the SC treatment saved €7802.1 ($8424.5) compared with i.v. rituximab treatment. Giving the median of 50 non-naive rituximab treatments per year in our unit, we estimate

a yearly saving of €30,000 ($32,546.8), corresponding to the 19% of overall treatment costs.

We did not measure serum levels of rituximab after the 2 treatment modalities. However, similar trends in B cells and efficacy in preventing disease relapse suggest similar kinetics. Consistently, a multicentric randomized clinical trial including 410 patients with B-cell non-Hodgkin lymphoma documented similar maximal concentration of rituximab in participants who received SC versus i.v. formulation.[S1,S2]

CONCLUSION

In conclusion, our small cohort study shows that SC rituximab administration has a similar safety or efficacy profile to a prior i.v. administration in patients with SDNS. Given the reduced cost and time of administration, our data support the wider use of SC rituximab administration for patients with idiopathic nephrotic syndrome and, potentially, other nephrological conditions in which rituximab is indicated, especially in resource limited settings.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

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

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

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