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Combined Rituximab and Daratumumab Treatment in Difficult-to-Treat Nephrotic Syndrome Cases

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Idiopathic nephrotic syndrome (NS) is characterized by severe proteinuria, hypoalbuminemia, and/or edema and affects about 1 to 3 per 100,000 children and young adults.[1] Corticosteroids represent the first line therapy for primary NS, leading to disease remission in 70% to 80% of cases.[2] However, 70% to 80% may relapse after steroid withdrawal, and approximately 10% to 30% of patients have steroid-resistant NS. Treatment of steroid-resistant NS includes calcineurin inhibitors, mycophenolate mofetil, and anti-CD20 monoclonal antibodies (rituximab or obinutuzumab) used alone or in combination.[3] With these approaches, remission can be achieved in about 40% to 60% of steroid-resistant cases; however, relapses may occur despite chronic immunosuppressive therapies (multidrug-dependent NS).[4] The remaining patients are defined as multidrug-resistant NS and the lack of effective treatment response often leads to end-stage kidney disease.[5] The main histopathological entities in steroid-resistant NS cases are focal segmental glomerulosclerosis, minimal change disease, and diffuse mesangial sclerosis. The glomerular deposition of IgM and C3 represents a negative prognostic factor.[6]

Considering that mechanistic studies suggest that autoreactive IgM play a pathogenic role through complement activation,[7] we tested the hypothesis that combined B cell and plasma cell depletion (both cells are responsible for IgM production) safely promotes remission in subjects affected by multidrug dependent or steroid resistant NS.

Treatment with rituximab or cyclophosphamide in the 6 months before enrolment represented an exclusion criterion. Rituximab and daratumumab were administered as single doses at 375 mg/m^2 and 16 mg/kg, respectively. After combined treatment, oral immunosuppressive drugs were progressively tapered and withdrawn in all subjects over 4 to 6 weeks.

In multidrug-resistant NS, the primary end point was the achievement of partial or complete remission of proteinuria, defined according to KDIGO guidelines.[S1]

In multidrug-dependent NS, the end point was the time on remission without immunosuppressive drugs. Full methods are provided in the supplemental file

RESULTS

Between September 2021 and March 2023, we enrolled a total of 23 consecutive patients, 7 with multidrug resistant and 16 with multidrug dependent NS. The mean follow-up time was 14 (9–18) months and 12 (9–28) months in multidrug-resistant and multidrug-dependent NS, respectively. Supplementary Table S1 reports the main baseline characteristics of the subjects at enrolment.

Multidrug-Resistant NS

Combined rituximab and daratumumab reduced proteinuria in all the patients with multidrug-resistant NS and promoted complete or partial proteinuria remission in 4 and 2 patients, respectively. Five patients experienced proteinuria relapse, which was effectively treated

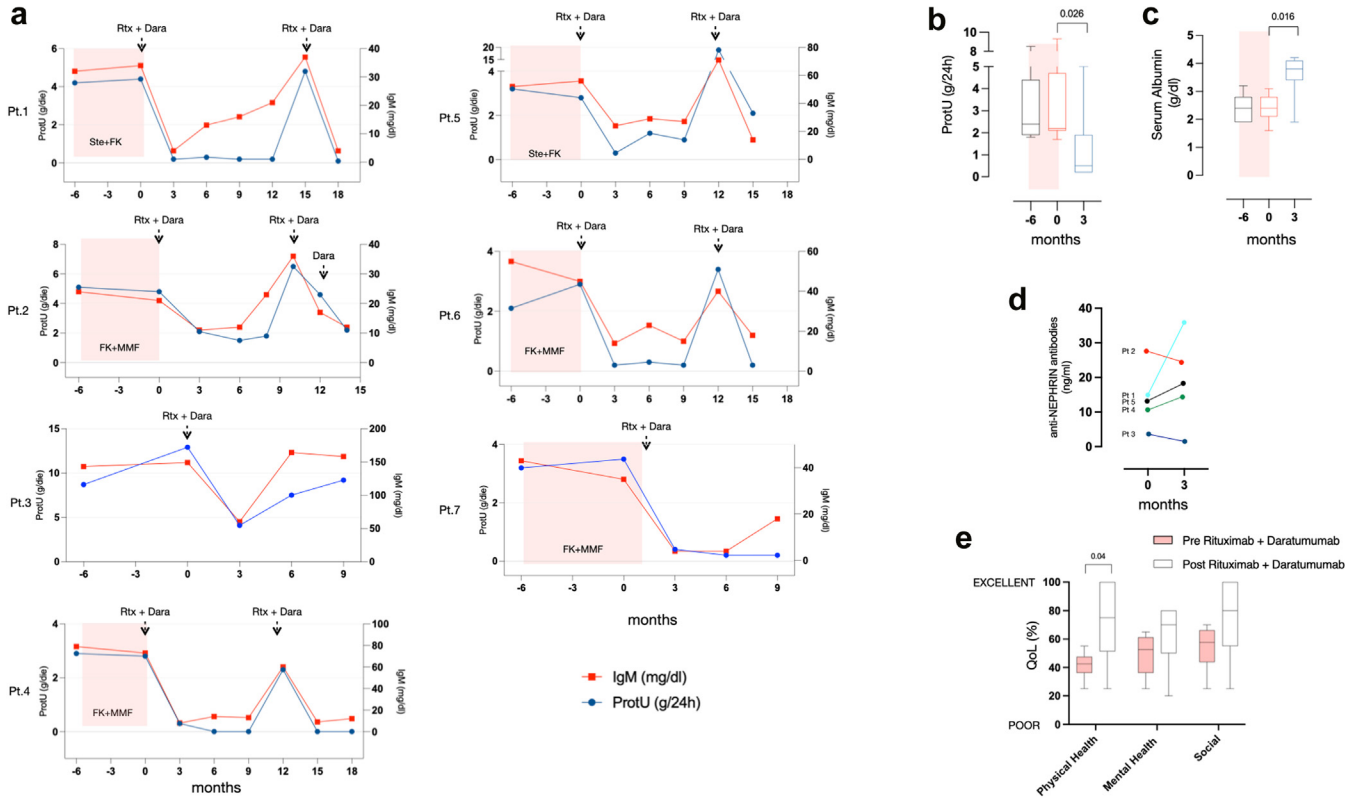

Figure 1. Response to treatment with combined rituximab and daratumumab in multidrug-resistant nephrotic syndrome. (a) Proteinuria and IgM levels before and after combined rituximab + daratumumab in steroid-resistant nephrotic syndrome for each patients. (Patient 3 is a multidrug-resistant nephrotic syndrome, not in therapy at enrolment because, in the 2 years before enrolment, she declined any treatments due to the lack of efficacy. After rituximab and daratumumab treatment, she did not respond and refused further treatments; patient 7 had only 9 months of follow-up). (b) Overall proteinuria and serum albumin. (c) Levels before and after combined rituximab + daratumumab in steroid resistant-nephrotic syndrome. (d) Levels of circulating anti-NEPHRIN antibodies before and 3 months after combined rituximab + daratumumab in 5 patients. (e) QoL index (expressed as percentage, 100 for excellent and 0 for poor) based on questionnaire adapted by Cure GN[S2–S4] (for subjects < 12 years, QoL index was based on parents' responses). Dara, daratumumab; NS, nephrotic syndrome; ProtU, proteinuria; QoL, quality of life; Rtx, rituximab.

with a second course of combined treatment (Figure 1a). Patient 3 did not achieve remission and declined consent to further treatments (Figure 1a). Overall, combined rituximab and daratumumab induced a significant reduction of proteinuria (Figure 1b) and increased serum albumin (Figure 1c), allowing to reduce oral immunosuppression (Supplementary Figure S1). IgM and proteinuria followed similar trends (Figure 1a), whereas IgG and circulating anti-NEPHRIN antibodies did not significantly change (Figure 1d, Supplementary Figure S1A). Of note, in the 4 subjects receiving prior rituximab infusion, lower serum levels of IgM after prior single rituximab infusion was 30 mg/dl. Circulating B cells significantly decreased in all the patients and CD38+ plasma cells significantly decreased in patients 5 and 6 who achieved complete remission, whereas they did not decrease in patient 3, who did not reach the primary end point (Supplementary Figure S1B and Table S2). T cell subsets did not significantly change (Supplementary Table S3).

Multidrug-Dependent NS

In patients with multidrug dependent NS, combined rituximab and daratumumab administration resulted in longer relapse-free time compared to the 12 months immediately before combined treatment (Figure 2a), despite withdrawal of oral immunosuppressive drugs in all subjects after combined treatment (Supplementary Figure S2). Combined treatment induced significant reduction of CD19+ B cells and CD38+ plasma cells (Figure 2c, Supplementary Table S5) and IgM, but not IgG (Supplementary Figure S2A and B) and circulating anti-NEPHRIN antibodies (Figure 2b). Moreover, disease relapse was invariably anticipated by a recovery of circulating IgM; patients with IgM levels below median values measured at 3 months posttreatment had a significantly lower rate of relapse at 9 months than patients with higher IgM levels at 3 months (Figure 2d). T cell subsets did not significantly change (Supplementary Table S5).

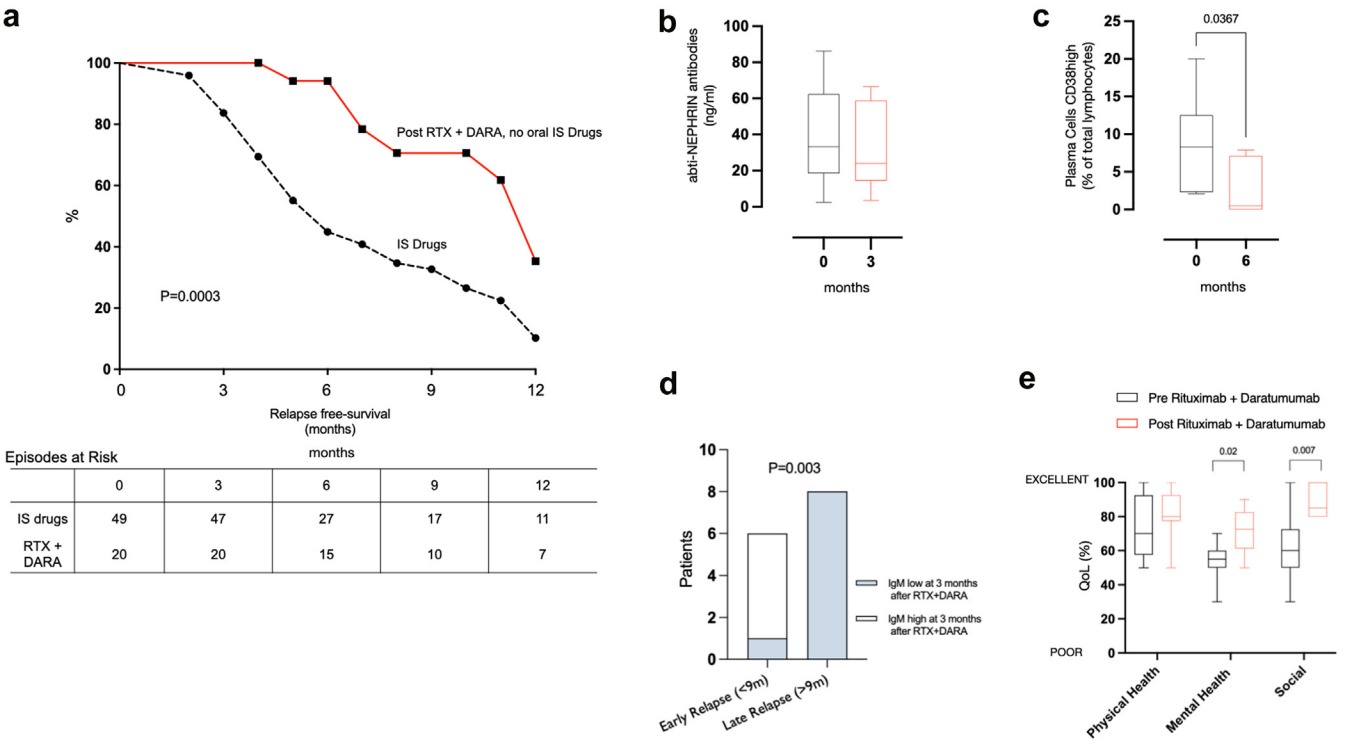

Figure 2. Response to treatment with combined rituximab and daratumumab in multidrug-dependent nephrotic syndrome. (a) Relapse-free survival during combined immunosuppressive drugs (MMF, CNI and/or rituximab and/or steroids) (black dot line) versus after combined treatment with rituximab + daratumumab (red line). Immunosuppressive oral drugs were removed after combined treatment. (b) Overall levels of circulating anti-NEPHRIN antibodies before and 3 months after combined rituximab + daratumumab in multidrug-dependent nephrotic syndrome. (c) Changes in CD38+ plasma cells before and after combined rituximab + daratumumab in multidrug-dependent nephrotic syndrome. (d) We performed a contingency analysis between early and late nephrotic syndrome recurrence (< or > 9 months after rituximab + daratumumab treatment, respectively), based on IgM values at 3 months after treatment in 14 of the 20 patients with available data. Low and high IgM values were defined based on IgM value at 3 months after combined infusions (above or below average value of 32 mg/dl). IgM values > 32 mg/dl at 3 months associated with significantly increased risk of early relapse. (e) QoL index (expressed as percentage, 100 for excellent and 0 for poor) based on questionnaire adapted by Cure GN[S2–S4] (for subjects < 12 years, QoL index was based on parents' responses). CNI, calcineurin; Dara, daratumumab; IS, immunosuppressive; MMF, mycophenolate mofetil ;QoL, quality of life; Rtx, rituximab.

Safety

Overall, the combined treatment was well-tolerated. No serious side effects occurred during drug infusions. Adverse events of minor or moderate severity occurred during 31% of daratumumab infusions, that required slowdown and/or temporary suspension of infusions. However, all infusions have been completed. Significant hypogammaglobulinemia (<200 mg/dl) was limited to 1 patient, and we did not detect infective complications (Supplementary Table S6 and Figure S2).

Quality of Life

Disease remission and immunosuppression withdrawal led to a significant increase in the quality of life in both groups of patients (Figures 1e and 2e).

DISCUSSION

Multidrug-resistant NS is burdened by high risk of progression to end-stage kidney disease, whereas patients affected by multidrug-dependent NS have a high risk of infections and a poor quality of life due to chronic immunosuppression. To the best of our knowledge, this is the first report of the successful use of combined rituximab and daratumumab treatment in patients with complicated NS. Of note, the removal of oral immunosuppression promoted a considerable improvement in the quality of life of enrolled subjects. Therefore, our findings respond to a major unmet clinical need and provide a new therapeutic option for affected patients.

The pathogenic role of B cells in NS is supported by the evidence that B cell depletion reduces disease severity in many cases. However, in complicated forms of NS, the efficacy of rituximab alone is limited.[8] Autoantibodies and plasma cells have been recently implicated in focal segmental glomerulosclerosis pathogenesis.[S5–S7] Unlike short-lived plasmablasts, long-lived plasma cells, a major source of antibodies, including IgM, are unresponsive to anti-CD20 treatments and highly express CD38. This formed the basis for our combined treatment with rituximab plus daratubumab.[4]

In a recent clinical study, the humanized anti-CD20 antibody obinutuzumab was combined with daratumumab to treat 14 subjects with steroid-dependent or frequently relapsing NS,[9] inducing longer remission than prior administration of rituximab alone. However, similar to our experience, this study does not allow to distinguish the roles of anti-CD20 and anti-CD38 in promoting disease remission.

Circulating anti-NEPHRIN antibodies have been recently proposed as responsible for the disarrangement of the slit diaphragm architecture in a subset of patients NS.[S5] However, available studies included limited cases and controls and different assays, preventing comparisons across studies.[S5,S8–S9] We here reported that circulating levels of anti-NEPHRIN antibodies are not affected by combined rituximab and daratumumab and do not correlate with response to treatment. However, the limited sample size do not allow any definitive conclusions on anti-NEPHRIN antibodies (Supplementary Figures S3 and S4).

Conversely, the association between circulating CD38+ plasma cells and IgM levels with disease activity implies a potential pathogenic role of these cells and antibodies.[S10] Further studies are needed to assess whether daratumumab alone, by depleting CD38+ plasma cells and reducing IgM, is sufficient in promoting disease remission. Total CD19+ B cells fully recovered at 9 to 12 months after treatment. Immune phenotyping did not reveal other major changes after treatment (Supplementary Tables S3 and S4).

Therefore, combined rituximab and daratumumab infusion reduced proteinuria both in multidrug-resistant and multidrug-dependent NS. Further daratumumab infusions may be considered in nonresponsive cases or after disease relapses.

Overall, combined treatment was well-tolerated. In line with previous papers describing single rituximab infusion per course,[S11] but differently to others reporting multiple rituximab infusions per course,[S12] hypogammaglobulinemia was limited.

Given the rarity of the disease, a major strength of our study is represented by the relatively large cohort of subjects, all negative for monogenic causes of NS. Unfortunately, renal biopsy at baseline was not available for all cases, preventing any speculations on the impact of IgM deposition in the glomeruli. We did not perform kidney biopsies after combined treatment.

CONCLUSION

Given the lack of viable treatments for multidrug-resistant and multidrug-dependent NS and the excellent short-term safety profile of combined rituximab and daratumumab treatment, the present data support the rationale for a pilot controlled trial testing the safety and efficacy profile of this strategy in complicated NS.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The authors declare that all data supporting the findings of this study are available within the article and its Supplementary Material.

AUTHOR CONTRIBUTIONS

AA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AA, SB, MB, PC, and MGG did acquisition, analysis, and interpretation of data. AA and PC drafted the manuscript. AA, PC, and MGG did critical review of the manuscript for important intellectual content. AA and MB did the statistical analysis. AA obtained funding. SB, XK, SS, GC, GC, EV, FL, AM and CB provided administrative, technical, or material support. AA, PC, and MGG provided supervision.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Changes in proteinuria, IgG, and plasma cells in patients with multidrug-resistant nephrotic syndrome treated with rituximab and daratumumab.

Figure S2. Changes in IgM and IgG in patients with multidrug-dependent nephrotic syndrome treated with rituximab and daratumumab.

Figure S3. Standard curve for ELISA for anti-NEPHRIN-A autoantibodies.

Figure S4. Competitive ELISA.

Table S1. Main baseline characteristics at the time of combined treatment.

Table S2. Changes in the percentages of circulating plasma cells in 3 patients with multidrug-resistant nephrotic

syndrome before and at 3 months after rituximab + daratumumab treatment.

Table S3. Changes in the percentages of circulating lymphocytes in 3 patients with multidrug-resistant nephrotic syndrome before and after rituximab + daratumumab treatment.

Table S4. Percentages of circulating plasma cells in 8 patients with multidrug-dependent nephrotic syndrome before and at 6 months after rituximab + daratumumab treatment.

Table S5. Percentages of circulating lymphocytes in 8 patients with multidrug-dependent nephrotic syndrome before and at 6 months after rituximab + daratumumab treatment.

Table S6. Adverse Events.

STROBE Statement.

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