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EDITORIAL COMMENTARY

Glomerular B7-1 staining: toward precision medicine for treatment of recurrent focal segmental glomerulosclerosis

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Focal segmental glomerulosclerosis (FSGS) is a major contributor to kidney failure in adults and children [1, 2]. The risk for disease recurrence is high and results in a devastating fivefold increase in the incidence of graft loss. This increased risk is primarily due to unremitting FSGS that is resistant to treatment, reported to occur in 43% of patients with recurrent FSGS [3]. A significant issue in the treatment of recurrent FSGS is the lack of established clinical indicators or biomarkers that are able to predict treatment response or guide therapy selection. The current mainstays of treatment are plasmapheresis and low-density lipoprotein apheresis, which are untargeted therapies that presumably remove pathogenic circulating factors. Additional agents that may be effective in recurrent FSGS treatment include anti-CD20 monoclonal antibodies and high-dose cyclosporine, though again, clinicians use these treatments blindly without the benefit of any predictors of response for guidance [4].

Burke et al. [5] report in *Pediatric Nephrology* the use of abatacept in twelve patients with treatment-resistant post-transplant de novo or recurrent FSGS. The response to abatacept, an anti-CTLA-4 antibody that modulates T-cell costimulation by binding B7-1 and B7-2, was examined in relation to the presence or absence of B7-1 staining on graft biopsies of ten of the twelve patients. Only two patients had negative B7-1 staining on biopsy, and both failed to respond to abatacept and experienced graft loss. Conversely, seven out of eight patients with positive B7-1 staining responded to abatacept treatment with either complete remission (5 patients; 62%) or > 50% proteinuria reduction (2 patients; 25%). Two additional pediatric patients with recurrent FSGS, in whom B7-1 staining was not performed, also responded to abatacept with complete remission after failing plasmapheresis and rituximab. These findings provide hope for an additional therapeutic option in this devastating condition. Importantly, the report offers the exciting suggestion that a biologically plausible histologic marker could predict treatment response and help guide therapy.

Evidence for recurrent FSGS treatment has thus far been limited to retrospective reports and case series such as this current report [4, 6]. These studies address urgent needs in managing this rare and challenging condition and generate new hypotheses. The report by Burke et al. [5] may bring some hope for patients with post-transplant FSGS, but interpretation of these results still requires careful consideration.

As discussed by the authors, the role of anti-CTLA-4 antibodies in recurrent FSGS treatment has been questioned due to the inability of other groups to replicate B7-1 staining and demonstrate treatment efficacy in either primary nephrotic syndrome or post-transplant recurrent FSGS [7, 8]. To address the concern of replicability of B7-1 staining, the authors point out an interesting observation that the current cohort consisted mainly of pediatric patients in contrast to studies showing negative B7-1 staining or lack of response to abatacept [9, 10]. Perhaps most notably, this study further provides a detailed immunohistochemistry protocol (including adequate controls) which appears to have good reproducibility under this group. External validation of B7-1 staining using this standardized protocol, particularly with respect to the proposed difference between adult and pediatric patients, could be important, as it could imply differences in pathogenesis despite the same glomerular injury pattern, and could also provide a rationale for this targeted therapy in post-transplant FSGS. Further studies, including children and adults, are needed to validate data from this

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report, and to establish the prevalence and clinical impact of positive B7-1 staining (using a standardized reproducible protocol) among patients with post-transplant FSGS.

Next, the cellular source of B7-1 in the glomerulus remains unclear. Burke et al. [5] assumed that B7-1 is expressed by podocytes, but colocalization studies were lacking in this report. This is important because B7-1 has been recently found on glomerular endothelial cells in adults with nephrotic syndrome [11]. This observation aligns with emerging data suggesting a role for glomerular endothelial cells in the pathogenesis of nephrotic syndrome and FSGS [12]. Likewise, quantification of B7-1 in urine, proposed as a surrogate marker of glomerular B7-1 expression [13], was only available in 1 patient (case 2) [14]. Notably, this patient had high urinary B7-1 levels, and his proteinuria resolved within days after receiving a single dose of abatacept, in addition to other immunosuppressive therapies and plasmapheresis [14]. Determining the glomerular source(s) of B7-1 and the correlation between urinary levels and disease activity could shed light on the pathogenesis of the disease and provide a rapid and non-invasive tool that could potentially enable clinicians to tailor abatacept according to urinary B7-1 levels.

Additionally, another concern that puts the clinical impact of B7-1 staining into question is that the clinical effectiveness of abatacept treatment in recurrent FSGS has yet to be clearly established. Though the authors reported promising responses to abatacept in nine out of twelve treatment-resistant post-transplant FSGS patients, the retrospective study design as presented limited the ability to attribute the favorable clinical responses directly to abatacept therapy. All patients received different treatments for post-transplant FSGS, including different numbers of plasmapheresis sessions and doses of rituximab, in addition to other agents (IVIG, bortezomib, thymoglobulin, corticosteroids). Abatacept was also given at different time points following FSGS diagnosis, and the numbers of doses and routes of administration were not standardized. Critically, treatment-related adverse events and potential long-term side effects were also not reported in the current study, nor would the small sample size allow conclusions to be made about the safety profile of abatacept in post-transplant FSGS. Notably, both abatacept and belatacept have been associated with an increased risk of EBV-associated post-transplant lymphoproliferative disorder and cytomegalovirus infection in the transplant population [15, 16]. In this context, the decision to use abatacept must be made with careful balancing of risks and potential benefits and patients and caregivers need to be counselled on the unproven benefits of this therapy.

Mechanistically, the authors presumed that abatacept acts only or primarily directly on B7-1-positive podocytes [17]. However, abatacept has also been shown to mitigate proteinuria in experimental models of kidney disease by preventing T cell activation or modulating T regulatory cells [18]. Therefore, further experimental studies are needed to determine whether abatacept may also exert a direct protective role on B7-1-positive glomerular cells.

The central conclusion of this report is that B7-1 staining can be used to identify a subset of post-transplant FSGS patients who may benefit from abatacept. The authors reason that prior reports demonstrating a lack of response to abatacept support this claim because B7-1 staining was negative in those studies. Only one patient with B7-1 staining failed to respond to abatacept, and the authors suggest this may be due to prior treatment with belatacept, an anti-CTLA-4 antibody with weaker B7-1 binding compared to abatacept.

The implications of this report for glomerular disease research are substantial: they offer a basis for designing a biomarker-driven clinical trial that would optimize the limited patient numbers with this rare condition, and thus could be another step toward matching treatments to mechanistic pathways in glomerular disease. Data from a randomized trial to evaluate abatacept for children and adults with resistant nephrotic syndrome are not yet published, but careful interpretation of this trial is required, as the presence of B7-1 in either the kidney tissue or urine was not investigated nor required as an inclusion criterion [19]. In contrast, this report suggests the potential usefulness of B7-1 staining as a predictive biomarker for future trials. The current glomerular disease research landscape is also ready to support exploration of biomarkers of pathogenesis and treatment response and development of clinical trials. Multicenter, international research networks including the National Institute of Health-sponsored Nephrotic Syndrome Study Network (NEPTUNE) and Cure Glomerulonephropathy (CureGN) have rich biobanking and experienced centers that have worked together for years on both observational and controlled studies. A newly established FSGS Recurrence Collaboration sponsored by the University of Michigan also aims to bring together researchers to jointly address urgent clinical questions in recurrent FSGS. We commend the authors for this important report and are excited for follow-up clinical and experimental studies that will improve our ability to offer our patients with recurrent FSGS targeted therapies that are safer and more effective.

Declarations

Competing interests The authors declare no competing interests.

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