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Randomized Clinical Trial Design to Assess Abatacept in Resistant Nephrotic Syndrome

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Introduction: Treatment-resistant nephrotic syndrome is a rare form of glomerular disease that occurs in children and adults. No Food and Drug Administration–approved treatments consistently achieve remission of proteinuria and preservation of kidney function. CD80 (B7-1) can be expressed on injured podocytes, and administration of abatacept (modified CTLA4-Ig based on a natural ligand to CD80) has been associated with sustained normalization of urinary protein excretion and maintenance of glomerular filtration rate in experimental and clinical settings.

Methods: In this report, we describe the rationale for and design of a randomized, placebo-controlled, clinical trial of abatacept in patients with treatment-resistant nephrotic syndrome caused by focal segmental glomerulosclerosis or minimal change disease. The design is a hybrid of a parallel-group and crossover design (switchover) with the primary objectives assessed in the first period of the study and the secondary objectives assessed using data from both periods. All participants will receive the active agent in 1 of the periods. The duration of treatment will be 4 months per period.

Results: The primary outcome will be improvement in nephrotic-range proteinuria to subnephrotic range, that is, reduction from baseline to 4 months in urine protein:creatinine ratio $\geq$ 50% and to a level $<$ 3. The projected sample size is 90 patients, which has 80% power to detect a treatment difference of 28%.

Discussion: This study advances efforts to validate CD80 as a therapeutic target for treatment-resistant nephrotic syndrome, and implements a precision medicine-based approach to this serious kidney condition in which the selection of a therapeutic agent is guided by the underlying disease mechanism operating in individual patients.

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CLINICAL ASPECTS

Focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) are clusters of syndromes that can present with asymptomatic proteinuria, in either the subnephrotic or the nephrotic range, or with nephrotic syndrome in children and adults. The terms MCD and FSGS are histopathologically defined and are descriptive of processes that, at least in the early stages, cause either no scarring (MCD) or segmental scarring in some glomeruli (FSGS). Over time, more glomeruli are involved, and some manifest global scars. MCD is the most common diagnosis in children, and a subset of these children fully respond to glucocorticoid treatment with no further complications or sequelae (''treatment-sensitive'' disease). Our study focuses on the significant proportion of children or adults with an MCD or FSGS biopsy diagnosis who do not respond to glucocorticoids

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and/or other treatments, and therefore have "treatment-resistant" nephrotic syndrome (TRNS). These patients are at the greatest risk for progression to end-stage kidney disease (ESKD).[1]

The terms MCD or FSGS do not provide any mechanistic insight into the cellular or molecular mechanisms leading to disease. There is ongoing debate as to whether MCD and FSGS are entities along a spectrum of disease from minimal injury to extensive sclerosis. Recent studies have implicated kidney podocyte injury or death as the initial step in the development of focal and segmental scarring of glomeruli.[2] Understanding that there may be other unidentified pathways, there are currently 3 potential mechanisms of disease in patients with MCD/FSGS that can cause proteinuria and progressive glomerular injury: (i) a genetic mutation in a podocyte protein leading to an alteration in cell structure and function; (ii) a circulating factor(s) that increases glomerular permeability to protein; and (iii) adaptive changes in the podocyte in response to a variety of insults including nephron loss and metabolic disorders.[2,3] Other causes include viral infection, including HIV and certain medications.

First-line treatment in patients with MCD/FSGS is an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.[4] In patients with overt nephrotic syndrome, glucocorticoids are also a common component of first line therapy. Calcineurin inhibitors (CNIs) are recommended for patients who fail to respond to glucocorticoids, for those who relapse, and for those with a contraindication to corticosteroids.[5] The prognosis in patients who are unresponsive to glucocorticoids and/or CNIs is poor, with an estimated 50% progressing to ESKD over 5 to 10 years of follow-up. In regional and national registries of kidney disease, MCD/FSGS accounts for 10% to 15% of ESKD cases in pediatric and adult patients. Finally, nearly 25% of patients undergoing a kidney transplantation for FSGS induced-ESKD will develop recurrent FSGS in the allograft.[5] Thus, treatment-resistant MCD/FSGS represents a rare but significant cause of morbidity and mortality, and remains a largely untreatable disease. Developing proven therapies that retard progression of this glomerular disease represents a large unmet need in clinical nephrology.

BIOLOGY, TARGET AND AGENT RATIONALE

Glomerular podocytes, with their foot processes and interposed slit diaphragms, serve as the final barrier to urinary protein loss. Disrupted podocyte function damages the kidney filter, leading to proteinuria and nephrotic syndrome.[6] Clinically, proteinuria is the common denominator of a heterogeneous group of diseases, termed podocytopathies, which includes MCD, FSGS, and membranous nephropathy.[6]

Cluster of differentiation 80 (CD80 and B7-1) is a protein found on the surface of a variety of immunoeffector cells including dendritic cells, activated B cells, and monocytes. It provides a costimulatory signal necessary for T-cell activation and survival. It is the ligand for 2 different proteins on the T-cell surface: CD28 (for autoregulation and intercellular association) and CTLA-4 (for attenuation of regulation and cellular disassociation). CD80 works in tandem with CD86 to prime T cells.[7]

Podocyte CD80 induction is associated with development of proteinuria in human lupus nephritis, murine lupus nephritis, β3-integrin knockout mice, nephrin knockout mice, and murine lipopolysaccharide (LPS)—induced proteinuria.[8] Yu *et al.*[9] reported induction of podocyte CD80 in biopsy samples of patients with nephrotic syndrome, including primary and recurrent FSGS. Thus, they introduced the idea that CD80 staining may serve as a biomarker to facilitate the diagnosis and targeted treatment of proteinuric kidney diseases. Treatment with abatacept (modified CTLA4-Ig), a specific CD80 antagonist currently approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis,[10] induced a durable remission of proteinuria in 4 patients with rituximab-resistant recurrent FSGS in renal allografts and achieved on-drug complete remission in 1 patient with primary treatment-resistant nephrotic syndrome in the native kidneys.[9]

Is podocyte CD80 induction a characteristic of other proteinuric kidney diseases such as diabetic nephropathy,[11,12] and does it represent a final common pattern of injury? Unfortunately, our ability to answer these questions has been limited by the lack of specificity and sensitivity of CD80 staining in human kidney biopsy samples, a procedure that has been found to be technically difficult and prone to misinterpretation. First, antibodies to CD80 have been notoriously difficult to work with since the early days of its discovery. Second, the abundance of CD80 in podocytes, even after injury and stress, is modest, and so there is a limited dynamic range for immune-detection methods. Third, the CD80 epitope(s), detectable only in fresh-frozen tissue, appears to readily degrade over time even under storage conditions that preserve other antigens, leading to false-negative results (S. Hewitt, personal communication). These technical considerations suggest that the contribution of CD80 to glomerular disease may be underestimated. Thus, the number of patients with treatment-resistant proteinuria in whom podocyte CD80 positivity renders them candidates for abatacept treatment may exceed the number