Randomized Clinical Trial Design to Assess Abatacept in Resistant Nephrotic Syndrome

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation
Trachtman, H., D. S. Gipson, M. Somers, C. Spino, S. Adler, L. Holzman, J. B. Kopp, et al. 2017. “Randomized Clinical Trial Design to Assess Abatacept in Resistant Nephrotic Syndrome.” Kidney International Reports 3 (1): 115-121. doi:10.1016/j.ekir.2017.08.013. http://dx.doi.org/10.1016/j.ekir.2017.08.013.

Published Version
doi:10.1016/j.ekir.2017.08.013

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:34868825

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Randomized Clinical Trial Design to Assess Abatacept in Resistant Nephrotic Syndrome

Howard Trachtman, Debbie S. Gipson, Michael Somers, Cathie Spino, Sharon Adler, Lawrence Holzman, Jeffrey B. Kopp, John Sedor, Sandra Overfield, Ayanbola Elegbe, Michael Maldonado, and Anna Greka

1Division of Nephrology, Department of Pediatrics, New York University Langone Medical Center, New York, New York, USA; 2Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA; 3Division of Nephrology, Boston Children’s Hospital, Boston, Massachusetts, USA; 4Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA; 5Division of Nephrology and Hypertension, Harbor-University of California Los Angeles Medical Center, Los Angeles, California, USA; 6Department of Medicine, University of Pennsylvania Medical School, Philadelphia, Pennsylvania, USA; 7Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA; 8Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA; 9Bristol-Myers Squibb, Princeton, New Jersey, USA; and 10Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, and Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge, Massachusetts, USA

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 ≥ 50% and to a level < 3. The projected sample size is 90 patients, which has 80% power to detect a treatment difference of 28%.

Conclusion: 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.

Kidney Int Rep (2018) 3, 115–121; http://dx.doi.org/10.1016/j.ekir.2017.08.013
KEYWORDS: albuminuria; chronic kidney disease; glomerular disease; podocyte; proteinuria
© 2017 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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.
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 neprhon 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 immune effector 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.

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.6 Yu et al.5 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...
defined by current immunohistochemical staining methods. It is anticipated that ongoing work using novel antibodies, specific staining protocols, and advanced imaging techniques will enable more accurate delineation of the proportion of proteinuric kidney disease patients who are “CD80 positive.” A retrospective study in the pathology archives of a single center found that “CD80-positive” proteinuric kidney disease patients represent approximately 30% of all kidney biopsies with treatment-resistant proteinuria.9

Recent efforts at urinary detection of CD80 are also encouraging,13–15 suggesting that this approach, once the procedure is optimized, may be complementary or superior to the detection of CD80 in kidney biopsy material.

In the absence of a clinically validated biomarker, we have decided to proceed with testing the clinical efficacy of abatacept in a clinically well-defined population of individuals with treatment-resistant nephrotic syndrome, in the hopes of detecting a sufficient signal to merit further study in a future, targeted, biomarker-driven trial. These assumptions and the importance of collecting appropriate samples for CD80 biomarker derivation and validation studies in responders versus nonresponders in this trial informed the study design.

**CLINICAL TRIAL DESIGN**

**Study Objectives**

**Primary Objective**

The main aim is to compare whether abatacept, relative to placebo, improves proteinuria (from nephrotic range to subnephrotic range) while maintaining renal function in patients with TRNS presenting as native disease (in contrast to recurrent disease after transplantation). This will be assessed by the difference in the percentage of participants who achieve a renal response (a composite renal index at day 113). The renal index is defined as achieving all of the following components: (i) a ≥ 50% reduction from baseline to day 113 in urine protein:creatinine ratio (UPCR); (ii) day 113 UPCR < 3 g/g; and (iii) estimated glomerular filtration rate (eGFR) at day 113 remaining normal (defined as > 90 ml/min per 1.73 m²) or if below normal at baseline, remaining ≥ 75% of baseline.

**Secondary Objectives**

Abatacept and placebo will be compared for the following secondary outcomes: (i) change in proteinuria, defined as the difference in mean change in UPCR from baseline to day 113; (ii) change in serum albumin levels, defined as the difference in mean change in serum albumin from baseline to day 113; (iii) occurrence of complete remission while maintaining renal function, defined as the difference in percentage of participants achieving complete remission (UPCR < 0.3 g/g) with preservation of eGFR (as defined above) at day 113; (iv) change in age-appropriate patient-reported outcomes related to nephrotic syndrome assessed by the Patient Reported Outcomes Measurement Information System (PROMIS) items for physical function, fatigue, and pain interference; (v) percentage of participants with adverse events and serious adverse events; (vi) immunogenicity testing parameters (only for abatacept-treated participants); and (vii) pharmacokinetics of abatacept.

**Study Population**

Participants will be recruited from more than 20 participating centers in the United States. Participants who enroll will meet the inclusion and exclusion criteria described below.

**Key Inclusion Criteria**

Key inclusion criteria are as follows: (i) male and female participants, aged ≥ 6 years; (ii) participants diagnosed with TRNS (FSGS/MCD), excluding collapsing FSGS confirmed by central pathology review; (iii) preserved renal function as defined by eGFR ≥ 45 ml/min per 1.73 m² for both adults and children, calculated based on the CKD-EPI formula for adults and the bedside Schwartz equation for children;16 (iv) nephrotic syndrome defined as UPCR ≥ 3 (g/g) at screening; (v) treatment-resistant nephrotic syndrome (TRNS) defined as persistence of UPCR ≥ 3 despite therapy with any 1 of the following agents: glucocorticoids, CNI (cyclosporine and tacrolimus), sirolimus, mycophenolate mofetil, mycophenolic acid, or cyclophosphamide. In this study, the term “resistance” applies to participants with both primary and secondary resistance to glucocorticoids and to responders who have unacceptable treatment-related toxicities. The duration of glucocorticoid therapy required to determine treatment resistance will be a minimum of 6 weeks in participants < 18 years of age and 12 weeks for participants ≥ 18 years. For all other agents, the minimum duration of therapy will be 16 weeks, regardless of age or intolerance to any 2 of these agents, regardless of duration of treatment or age. (vi) Stable dose of currently prescribed MCD/FSGS therapy for at least 4 weeks.

**Key Exclusion Criteria**

Key exclusion criteria are as follows: (i) participants with causes of TRNS other than FSGS or MCD (e.g., IgA nephropathy or membranous nephropathy, lupus nephritis); (ii) participants with diabetes mellitus, both type 1 and type 2; (iii) participants with clinically significant congestive heart failure (CHF; New York
Heart Association Class III or Class IV); (iv) body mass index (BMI) > 40 for adults or > 99th percentile for pediatric participants that is not related to fluid retention; (v) recent active infection, tuberculosis, HIV, or hepatitis B or C infection; (vi) any test results that, in the opinion of the investigator, might place the participant at unacceptable risk for participation in this study.

Study Design

This study represents collaboration between the industry sponsor and a network of academic centers with experience in the performance of randomized clinical trials for patients with glomerular disease and specifically TRNS, MCD/FSGS. The team includes clinical trialists, translational scientists, clinicians in nephrology and rheumatology, pathologists, and biostatisticians. The partners jointly designed the study protocol and will participate as members of the Steering Committee to oversee the conduct of the trial, in addition to a data-monitoring committee.

This pilot study will enroll approximately 90 participants who will be randomized 1:1 to receive i.v. abatacept or placebo in a double-blind fashion into 2 parallel arms with a switchover study design. Study drug will be administered following labeled-dosing previously established age and weight-based guidelines for rheumatoid arthritis and juvenile idiopathic arthritis. The trial will consist of 4 phases: (i) a 28-day screening period (can be extended an additional 14 days to complete testing by repeating screening laboratory tests); (ii) a 16-week treatment period 1 (parallel arms: i.v. abatacept given on days 1, 14, 28 of period 1, and every 28 days thereafter vs. placebo at same time points); a switchover in treatment in a second 16-week treatment period 2 (same administration schedule as period 1); a 169-day abatacept open-label extension (OLE) period; and a 6-month follow-up period.

Figure 1. Schematic representation of the study design. The trial will consist of 5 periods: the screening period will be 28 days (can be extended an additional 14 days to complete testing by repeating screening laboratory tests); a 16-week treatment period 1 (parallel arms: i.v. abatacept given on days 1, 14, 28 of period 1, and every 28 days thereafter vs. placebo at same time points); a switchover in treatment in a second 16-week treatment period 2 (same administration schedule as period 1); a 169-day abatacept open-label extension (OLE) period; and a 6-month follow-up period.

Concomitant Therapy

Patients with TRNS are usually treated with a variety of drugs that are designed to reduce proteinuria, including specific immunosuppressive agents and nonspecific antihypertensive and lipid-lowering agents. During the study, participants will be allowed to continue the background concomitant therapy for TRNS with low-dose glucocorticoids (prednisone or
on expert opinion and the observed rate of renal response in the Novel Therapies for Resistant FSGS (FONT II) study, which enrolled a population similar to the participants who will be entered into the abatacept trial.

**Analysis**

An intention-to-treat (ITT) approach will be used for analyses of the primary endpoint in period 1. It will include all randomized and treated participants. For participants who drop out or have missing data, we will consider the participant to be a nonresponder. The primary analysis of renal response will be performed using a logistic regression model that includes treatment arm, randomization stratification factor (APOL1 genotype and age) and baseline UPCR as a continuous variable. The treatment effect will be estimated by the adjusted OR for treatment, with corresponding 95% confidence interval (CI) and P value. Sensitivity analyses (e.g., using a per protocol analysis set, alternative imputation methods) will be performed to confirm the robustness of conclusions regarding the primary endpoint.

Differences in the proportion of participants achieving complete remission at day 113 will be the main secondary efficacy analysis. The same analytic approach as for the primary endpoint will be used. Other secondary endpoints that are measured at the end of period 1 that are continuous (e.g., differences in mean change from baseline in UPCR, serum albumin, cholesterol, and triglycerides) will be analyzed using a longitudinal (repeated-measure) mixed model, including treatment group, baseline value of variable and randomization stratification factors, time, and time-by-treatment interaction as fixed effects and participant as a random effect. The test of treatment group—by-time interaction will provide the test of whether treatment affects mean outcomes over the course of study treatment.

For outcomes assessed in period 2 and the OLE periods, including safety outcomes, descriptive statistics will be provided. Other efficacy analyses will include analysis of proportions of participants in each cohort who are in phase II and in relapse. A point estimate of response rate, 95% confidence interval, point estimates, and 95% confidence interval of treatment difference adjusted for the 2 randomization stratification factors (based on minimum risk weights) will be calculated.

**DISCUSSION**

In this report, we describe the design of a multicenter, prospective, randomized clinical trial to test the efficacy of abatacept in the treatment of children and...
adults with treatment-resistant nephrotic syndrome presumably caused by FSGS or MCD. Treatment-resistant identifies those patients who are either unresponsive to or intolerant to existing therapies due to unacceptably severe side effects. This group of patients is at high risk for loss of kidney function and progression to ESKD. In the absence of a proven therapy, this condition represents a pressing unmet need in the clinical care of patients with glomerular disease. The selection of the test agent is based on a body of preclinical and translational research demonstrating that the target protein, CD80, is expressed in podocytes and interacts with β1 integrin on the podocyte cell surface, leading to disruption of the actin cytoskeleton, foot process effacement, and proteinuria. A small case series detailed the course in patients with recurrent FSGS in a kidney transplant (n = 4) or disease in the native kidneys (n = 1) who responded to abatacept. In contrast, Delville et al.19 detailed a series of 9 patients with recurrent FSGS based on the development of nephrotic-range proteinuria post transplantation who failed to improve after abatacept treatment. Other case reports have also described both response and failure of response to abatacept in participants with native kidneys. There are case reports of patients with FSGS or MCD who responded or failed to respond to abatacept.20–22 These conflicting data underscore the importance of this randomized clinical trial to determine the efficacy of abatacept in the management of TRNS and of separating the treatment of native kidney disease from the treatment of posttransplantation recurrence.

MCD and FSGS represent heterogeneous conditions, and it is unlikely that 1 intervention will be effective in all patients. Similar to the approach that is being applied in oncology, there is an increasing attempt to categorize glomerular diseases by the underlying biology to enable selection of patients who are most likely to benefit from a novel therapy. To make this method practical, a biomarker profile based on testing of the kidney tissue or noninvasive assays of blood or urine samples should be available that indicates abnormal activity of the disease pathway. Unfortunately, this is not yet available for the CD80 pathway, and therefore this clinical trial does not incorporate testing to identify patients who are more likely to respond favorably to abatacept treatment as an eligibility criterion.23 As a consequence, the sample size is relatively large for a rare condition such as TRNS, and we may fail to document benefit with abatacept therapy. Future research is needed to identify a validated biomarker signature that will enable preselection of patients for whom abatacept is an appropriate choice for the treatment of resistant nephrotic syndrome.

Urine, serum, mRNA, and DNA samples will be collected and stored in a study biorepository to facilitate the performance of ancillary studies with the goal of identifying biomarkers that correlate with response to abatacept.

Recruitment into trials of rare diseases is always a challenge. Nephrology ranks near the bottom of medical subspecialties in the implementation and completion of clinical trials.24 The nephrology community is organizing to overcome this obstacle by establishing consortia of nephrology practices that have strong clinical experience in studies of patients with primary glomerular disease. In addition, the switchover design, escape option with first relapse following the switchover, and OLE assures all patients that they will have access to the test drug in a timely manner in both randomized and extension periods. It is anticipated that this will enhance patient acceptance of the protocol and promote steady enrollment into the trial. To prevent period effects and potential bias based on the escape with initial relapse for patients on randomized therapy following the switchover, primary outcome analysis will be restricted to the treatment response in the first phase of randomized treatment prior to switchover.

Abatacept is already approved for use in patients with rheumatoid arthritis and juvenile idiopathic arthritis. It has been in use for more than a decade, and it has a well-characterized safety profile. We are proposing to repurpose the drug and to expand its therapeutic profile to include glomerular disease. This is consistent with current efforts to study this drug for lupus nephritis, another rheumatologic condition associated with proteinuric kidney disease, for which abatacept is currently under evaluation in a randomized controlled phase III trial (NCT01714817). Because our study of TRNS does not represent a first-use-in-humans trial, we anticipate that this will foster greater enrollment by potential participants. Because TRNS may alter the handling of drugs including monoclonal antibodies with increased renal clearance,25 we have taken this into account in the selection of the test dose. In addition, we will perform pharmacokinetic studies to assess the relationship between exposure to abatacept and the clinical response.

In conclusion, we describe the design of a pilot randomized clinical trial to test the efficacy of abatacept in patients with TRNS. We have adopted a trial design that should promote enrollment, and we will conduct the study using a network of experienced academic nephrology centers. We specifically intend for this pilot study to guide the execution of subsequent studies of abatacept, based on biomarkers derived from analysis of biosamples from responders versus
nonresponders in this pilot study. Future studies may therefore use these specific biomarkers for patient enrollment, thus greatly increasing the potential for a substantial treatment effect. It is hoped that this trial will spur the identification of biomarkers of CD80 involvement in TRNS, and will initiate a precision medicine–based approach to this serious kidney disease in which the selection of a therapeutic agent is guided by the underlying disease mechanism operating in each individual patient.

DISCLOSURE

The authors of this protocol declare consulting relationships with Bristol-Myers Squibb, SO, AE, and MM are employees of Bristol-Myers Squibb.

ACKNOWLEDGMENTS

We are thankful to the many colleagues around the country who have supported this study in their respective participating centers. This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases Intramural Research Program, National Institutes of Health, Bethesda, MD (JBK).

REFERENCES

1. Trautmann A, Schnaidt S, Lipska-Żiętkiewicz BS, et al., PodoNet Consortium. Long-term outcome of steroid-resistant nephrotic syndrome in children [e-pub ahead of print]. J Am Soc Nephrol. http://dx.doi.org/10.1681/ASN.2016101121.

2. Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2017;12:502–517.

3. D’Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365:2389–2411.

4. Beck L, Bombback AS, Choi MJ, et al. KDIGO US commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis. Am J Kidney Dis. 2013;62:403–441.

5. Trachtman R, Sran SS, Trachtman H. Recurrent focal segmental glomerulosclerosis after kidney transplantation. Pediatr Nephrol. 2015;30:1793–1802.

6. Greka A, Mundel P. Cell biology and pathology of podocytes. Annu Rev Physiol. 2012;74:299–323.

7. Esensten JH, Helou YA, Chopra G, et al. CD28 Costimulation: from mechanism to therapy. Immunity. 2016;44:973–988.

8. Reiser J, von Gersdorff G, Loos M, et al. Induction of B7-1 in podocytes is associated with nephrotic syndrome. J Clin Invest. 2004;113:1390–1397.

9. Yu CC, Fornoni A, Weins A, et al. Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med. 2013;369:2416–2423.

10. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353:1114–1123.

11. Bassi R, Fornoni A, Doria A, Fiorina P, CTLA4-Ig in B7-1-positive diabetic and non-diabetic kidney disease. Diabetologia. 2016;59:21–28.

12. Fiorina P, Vergani A, Bassi R, et al. Role of podocyte B7-1 in diabetic nephropathy. J Am Soc Nephrol. 2014;25:1415–1429.

13. Garin EH, Diaz LN, Mu W, et al. Urinary CD80 excretion increases in idiopathic minimal-change disease. J Am Soc Nephrol. 2009;20:260–266.

14. Garin EH, Mu W, Arthur JM, et al. Urinary CD80 is elevated in minimal change disease but not in focal segmental glomerulosclerosis. Kidney Int. 2010;78:296–302.

15. Mishra OP, Kumar R, Narayan G, et al. Toll-like receptor 3 (TLR-3), TLR-4 and CD80 expression in peripheral blood mononuclear cells and urinary CD80 levels in children with idiopathic nephrotic syndrome. Pediatr Nephrol. 2017;32:1355–1361.

16. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20:629–637.

17. Trachtman H, Vento S, Herreshoff E, et al. Efficacy of galactose and adalimumab in patients with resistant focal segmental glomerulosclerosis: report of the FONT clinical trial group. BMC Nephrol. 2015;16:111.

18. Mundel P, Greka A. Developing therapeutic ‘arrows’ with the precision of William Tell: the time has come for targeted therapies in kidney disease. Curr Opin Nephrol Hypertens. 2015;24:388–392.

19. Delville M, Baye E, Durrbach A, et al. B7-1 blockade does not improve post-transplant nephrotic syndrome caused by recurrent FSGS. J Am Soc Nephrol. 2016;27:2520–2527.

20. Jayaraman VK, Thomas M. Abatacept experience in steroid and rituximab-resistant focal segmental glomerulosclerosis. BMJ Case Rep. 2016. http://dx.doi.org/10.1136/bcr-2016-214396.

21. Sprenger-Mähr H, Zitt E, Soleiman A, Lhotta K. Successful treatment of focal segmental glomerulosclerosis after kidney transplantation with plasma exchange and abatacept in a patient with juvenile rheumatoid arthritis. Case Rep Transplant. 2016;7137584.

22. Garin EH, Reiser J, Cara-Fuentes G, Wei C, et al. CTLA4-IgG1 therapy in minimal change disease and focal segmental glomerulosclerosis. Pediatr Nephrol. 2015;30:469–477.

23. Novelli R, Gagliardini E, Ruggiero B, et al. Any value of urinary CD80 as a biomarker in human MCD and FSGS? Am J Physiol Renal Physiol. 2016;310:F335–F341.

24. Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. J Am Soc Nephrol. 2004;15:411–419.

25. Roberts BV, Susano I, Gipson DS, et al. Contribution of renal and non-renal clearance on increased total clearance of adalimumab in glucerulor nephritis. J Clin Pharmacol. 2013;53:919–924.