Treatment of focal segmental glomerulosclerosis with immunophilin modulation: when did we stop thinking about pathogenesis?

Alain Y. Meyrier[1]

[1]Department of Nephrology, University Paris-Descartes, Hôpital Georges Pompidou and Broussais, Paris, France

Nephrotic focal segmental glomerulosclerosis (FSGS) represents a difficult therapeutic challenge. FSGS has long been considered a subset of idiopathic nephrotic syndrome, lumping together FSGS and minimal change disease (MCD). The time-honored 'Shalhoub hypothesis' has led to treating FSGS as a T-cell-driven condition in which a lymphokine, considered without proof as being the 'glomerular permeability factor,' induces proteinuria and podocyte functional and structural derangement. This has led to trying, in addition to steroids, every new drug marketed in the field of organ transplantation, first cyclosporine (CsA) and then other immunophilin modulators. The fact that alkylating agents and mycophenolate mofetil have obtained a poor and inconstant favorable effect, and that rituximab may obtain remissions, although inconstantly, has not led to reconsidering the T-cell hypothesis. This wrong thinking has fostered innumerable, mostly uncontrolled, treatment trials with various immunosuppressive agents. In fact, clinicians have not considered the fact that some but not all immunophilin modulators may be effective as nonspecific antiproteinuric agents, rather than as immunosuppressive drugs, and that treatment success does not exclude a non-immunologic pathophysiology. Recent findings on the mode of action of CsA and FK-506 have lent support to this concept. This review should be considered as a plea to reconsider the pathogenesis of nephrotic FSGS, applying all efforts to the identification of the factor, or factors, responsible for nephrotic FSGS, and to fund treatment to counteract the 'factor,' rather than pursuing costly and non-evidence-based immunosuppressive therapeutic trials.

Kidney International (2009) **76,** 487–491; doi:10.1038/ki.2009.204; published online 3 June 2009

KEYWORDS: clinical trials; focal segmental glomerulosclerosis; immunophilin modulation; minimal change disease; pathophysiology

Correspondence: *Alain Y. Meyrier, Department of Nephrology, University Paris-Descartes, Hôpital Georges Pompidou and Broussais, 20 rue Leblanc, Paris F-75015, France. E-mail: alain.meyrier@gmail.com*

Received 19 March 2009; revised 30 March 2009; accepted 5 May 2009; published online 3 June 2009

Focal segmental glomerulosclerosis (FSGS) is the convenient term used to define five histopathological subsets of glomerular changes, categorized by the 'Columbia classification.'[1] This clinico-pathological spectrum ranges from the glomerular tip lesion, a relatively benign entity, to the most severe cellular lesion, collapsing glomerulopathy. Most are profusely proteinuric and often stubbornly resist therapy. This review suggests that the response of nephrotic syndrome to treatment, especially to treatment with immunophilin modulators, does not yet provide answers, but rather opens up a new line of thought with respect to the elusive pathophysiology of FSGS.

There is no evidence that FSGS and minimal glomerular changes are the same disease

The debate between defenders and detractors of the unity or the diversity of FSGS versus minimal glomerular disease (MCD) is still open,[2] despite laboratory evidence pointing to a different pathogenesis. Shankland *et al.*[3] showed that cyclin-dependent kinase inhibitor markers, p57 and p27, which inhibit podocyte proliferation, are expressed in controls and in MCD but not in FSGS, whereas cyclin-dependent kinase inhibitors, p21 and KI-67, which elicit podocyte proliferation, are not expressed in MCD but are expressed in FSGS.[3] Garin *et al.*[4] demonstrated that urinary-soluble CD80 excretion increases in nephrotic MCD but not in similarly proteinuric FSGS.

The concept of a podocytopathy that can be structural in FSGS and functional in minimal glomerular changes[5] may reconcile nephrologists caring for patients suffering from 'idiopathic nephrotic syndrome,' the new denomination for what was classically known as 'nephrosis.' In fact, a concept can be more or less reassuring to the clinician, who may wonder how a case of nephrotic syndrome, with no other lesion than foot-process flattening detected by electron microscopy and fast remission with steroids, can be the same disease as the worst form of highly cellular FSGS leading to end-stage renal insufficiency within months, despite high-dose steroids and various immunosuppressive drugs. It has long been established that the response to corticosteroids is the best prognostic factor of idiopathic nephrotic syndrome, irrespective of histopathology,[5–9] and

that steroid resistance portends a poor prognosis in nephrotic FSGS. In fact, the response to corticosteroids has been nothing but a time-honored means of eschewing the nosology and the pathophysiology of FSGS and of MCD, which was more than poorly understood three decades ago. Moreover, the mode of action of steroids in suppressing proteinuria is still unclear. It is conceivable that their genomic and non-genomic effects[10] concur to exert a stabilizing effect on the podocyte cytoskeleton, as well as an immunosuppressive action on the lymphoid system. In fact, Peter Mathieson's group showed that dexamethasone exerts an effect on podocytes, including on their actin cytoskeleton.[11] Mathieson, discussing the relationship between proteinuria and autoimmunity,[12] stressed the fact that podocytes and lymphocytes might share the same pathways to respond to the action of glucocorticoids.

At any rate, reason tells us that the response of a disease to treatment is a rather elementary means of extrapolating its pathophysiology. The same applies to the 'Shalhoub hypothesis,' which still seems to be the rationale for treating MCD and FSGS.

The Shalhoub hypothesis, an apparently right source of wrong thinking

In 1974, a seminal paper appeared in the *Lancet*, at a time when no clear distinction was made between minimal change disease (MCD) and FSGS.[13] Shalhoub listed clinical and therapeutic reasons for the belief that 'nephrosis' is an immunological condition. Among these reasons stood clinical observations suggesting that which we now call the 'idiopathic nephrotic syndrome' is produced by an abnormality of the T-cell function, resulting in the secretion of a chemical mediator that is toxic to GBM. To support his hypothesis, Shalhoub stressed the lack of evidence of a humoral antibody response; of remission induced by measles, which modifies cell-mediated immunity; of the occurrence of this syndrome in Hodgkin's disease; and of the therapeutic benefits of steroids and cyclophosphamide, which abate cell-mediated responses. Taken together, the data suggested that idiopathic nephrotic syndrome (lumping MCD and FSGS) is the clinical expression of a self-limited primary immunological derangement. In fact, this reasoning, which applied rather well to MCD, led without further philosophical hesitation to the concept that primary FSGS is also a T-cell-driven condition, in which a cytokine (and Shalhoub did not necessarily assimilate the 'chemical mediator' to a cytokine) affects GBM permselectivity to serum albumin. In 1974, the notion that FSGS is a structural podocyte disease was unknown, and the slit diaphragm was a *terra incognita*. At any rate, in 1986, the nephrological community embarked on the Shalhoub hypothesis to treat FSGS with the first immunophilin modulator available for organ transplantation, that is, cyclosporine A (CsA).[6,14,15] This approach was as sophisticated as were the first attempts to treat childhood nephrosis in 1949 with febrile plasma, typhoid vaccine, and mechlorethamine (Figure 1). The latter, a nitrogen mustard inherited from World War 1 warfare, won the prize.[16] The rationale for using this alkylating agent was to induce 'reticuloendothelial suppression.' Thereafter, an adrenocorticotropic hormone (ACTH) was tried, and successfully so, before prednisone became available and ACTH obtained remissions, although mostly partial, of the FSGS-induced nephrotic syndrome. Interestingly, ACTH can still be used to suppress proteinuria in various glomerulopathies, not only in FSGS.[17]

Cyclosporine A substantially increased the rate of remission of nephrotic FSGS, which was considered to confirm the Shalhoub hypothesis, and prompted further trials using newer immunophilin modulators.[8,15] However, in the meantime, researchers who analyzed the available data regarding the cytokine presumably responsible for idiopathic MCD concluded that the pathogenic cytokine had not been identified, and that a Th2 predominance was questionable in MCD.[18] Furthermore, all attempts to identify the 'glomerular permeability factor' responsible for nephrotic FSGS led to conflicting results, possibly indicating that there could conceivably be several chemical substances inducing

Figure 1 | In 1949 the first attempts to treat glomerular disease, including 'nephrosis' were based on febrile plasma, typhoid vaccine, and mustard gas.[16] This bold endeavor calls for a comment that might apply to the present review: "One need not hope in order to undertake, nor succeed in order to persevere," a wise encouragement to every researcher formulated by William the Silent, Prince of Orange (1533–1584) whose portrait by Adriaen Thomasz Key (1544–1589) is represented here. Photo source: Erich Lessing/Art Resource, NY Mauritshius, The Hague, The Netherlands.