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Review

Plasma exchange in kidney transplantation: Still a valuable option for nephrotic syndrome recurrence

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ABSTRACT

About 30% of the cases of steroid resistant nephrotic syndrome display a genetically determined disease and will not recur after kidney transplant; the other cases with fully or partially immunological pathogenesis display a high risk of post transplant recurrence.

Although lots of studies were carried out in the last 50 years the pathogenetic mechanism is still obscure and the therapeutic approach mostly empirical. The cornerstones principles of the therapies are based on removal of a still undefined "permeability factor" through plasma-exchange or other apheresis techniques and inhibition of its synthesis by the immunological system through different drugs.

The probability of successfully inducing persistant remission is nowadays around 30%through the different schemes experimented so far which mostly include plasmapheresis. Rituximab in the last years has significantly increased the efficacy of the treatments.

Non responders are rapidly evolving to graft loss and will most probably recur also in subsequent transplant.

Apart from genetics no other risk factors are predictive for recurrence.

Contents

1. Nephrotic syndrome resistant to steroids and other treatments

Nephrotic syndrome (NS) in a small percentage of children is still a difficult and challenging disease since in spite of a wider choice of new drugs in some cases it is resistant to multiple drugs and eventually progressive to end stage renal failure (ESRF).

Some children are steroid resistant (SRNS) since the onset of the disease and display a fully genetically determined form bearing monogenic causative mutations in one of the many genes nowadays fully recognized as responsible for nephrotic syndrome: these cases although steroid resistant and usually resistant also to most or even all the other treatments are considered at extremely low risk of recurrence after transplant.

Other cases instead, where no mutations or only minor polymorphisms of unknown pathogenetic role are identified, are nowadays

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considered at lower risk of recurrence (up to 20–40%). Some of these cases may initially be steroid sensitive and become secondary steroid resistant [1].

A third group of primary or secondary SRNS finally have a highly suspected or demonstrated immunological pathogenesis, mainly based on the empirical observation of response to therapies and are considered at highest risk of recurrence (up to 80%) [2,3].

These patients often have a variously troubled natural history of years of steroids, calcineurin inhibitors [4], mycophenolate [5,6], rituximab [7] in various association with Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptors blockers (ARB) and a huge supportive therapy [6]. A subgroup after different attempts may experience variable periods of proteinuria remission, leading to some expectations for a stable response to some compounds, followed by relapse and multi drug resistance until progression. In these cases the observation of some months or years of remission encourages kidney transplant, although the risk quantification for recurrence is still totally empirical due to lack of reliable markers. Neither the clinical course, including age at onset and time to ESRF nor histology are substantially predictive. Recently initial steroid sensitivity followed by secondary resistance was identified as strongly predictive for recurrence [8], but in other series age at onset and progression speed proofed predictive.

Focal segmental glomerular sclerosis (FSGS) accounts for the majority of the cases of SRNS both in children and in adults. The pathogenesis is complex and probably multifactorial, but with final events leading to diffuse podocyte damage, effacement on the basement membrane and glomerular filtration barrier derangement until massive proteinuria [9,10].

The therapeutic approach along the last 50 years took into account several temptative grossly immune-modulatory approaches [11] without however coming to a satisfactory and widely accepted scheme either in the native kidney or in recurrence on transplanted graft, where even less evidences of efficacy are available [12].

2. Nephrotic syndrome recurrence on the transplanted kidney: the hypothesis of permeability factors

After a troubled nephrotic syndrome history and the evolution to ESRF the immediate recurrence of massive nephrotic proteinuria after kidney transplant is one of the most frustrating events for the patient and the kidney transplantation team. Sometime proteinuria appears immediately after vascular declamp leading to the idea of a possible preformed circulating factor capable of inducing prompt podocyte damage and filtration barrier derangement through a sort of "toxic" mechanism. This obscure factor was nominated "permeability factor" [13,14] and along almost 50 years several candidates have been identified, without coming to a general consensus on one single molecule.

The first candidate was a substance secreted by T lymphocytes activated in vitro by Concanavalin A [15]; then Interleukin 13 and TNF-alpha were identified as transferrable factors able to induce proteinuria [16,17].

The serendipitous observation of positive effects of Rituximab on proteinuria reduction until remission either on native or in transplanted kidneys enforced the idea of a B cell released substance possibly interacting with T lymphocytes through an antibody independent mechanism, as alternative to an immunoglobulin secreted by plasmacells [18].

An alternative hypothesis identified as permeability factor a plasma fraction able to bind Galactose and named cardiotrophin-like cytokine factor 1 (CLC-1) encoded by the CLFC1 gene, member of the IL-6 superfamily. CLC-1 was able to induce proteinuria in experimental models, and to stimulate B cells [19,20]. These experimental data enforced the hypothesis of a pathogenic role for Galactose as a blocker of CLC1 function, so a therapeutic approach with high doses galactose has been proposed, with some encouraging results.

Podocyte damage and basement membrane derangement can also be induced by hemopexin, a heme scavenging and acute phase protein, provided with serine protease activity once activated [21].

In the last years the dabate has moved toward a new compound named soluble urokinase type plasminogen activator receptor (suPAR), the soluble form of a glycosylphospahatidylinositol (GPI) anchored membrane glycoprotein, expressed by podocytes and able to bind both vitronectin in the basement membrane and the integrin $\alpha V\beta 3$, and responsible for podocyte mobility. Several experimental in vivo and in vitro models demonstrated suPAR capacity to induce integrin activation, podocyte derangement, migration and proteinuria and that this activity could be transferred with serum. These results were not univocally confirmed by null mice models and also the human results were contradictory. suPAR was found not only in recurrent FSGS but also in other secondary glomerulonephritis and to be inversely correlated to the renal function and therefore its role might possibly be aspecific [13,14,22–24].

The failure to fulfill all the criteria to be considered responsible for SRNS in native kidneys and of recurrence in the kidney transplant however did not abolish the expectations that this factor may have some causative effect. A recent elegant model in mice was able to demonstrate that suPAR may originate from myeloid cells and that that its capacity to induce proteinuria may be transferred by bone marrow transplant, opening new fields for further search of a soluble pathogenic factor and some future alternative therapeutic approaches [25].

3. Permeability factors removal: plasma exchange is still the cornerstone

The empirical proofs of a beneficial effect of plasmapheresis on proteinuria reduction in recurrent nephrotic syndrome was first reported in the eighties [26] and so far hundreds of cases have been treated worldwide, in association with different other therapies. No controlled studies could be settled and most of the reports are single cases or small series in single centers. Although with these limitations the favourable results reported along the last 25 years allowed the inclusion of plasma-exchange for the treatment of post transplant recurrent FSGS in the KDIGO (Kidney Disease: improving Global Outcomes) guidelines released in 2009 [27].

Most cases were treated after observation of recurrence, most frequently within the first week post transplant and up to 70% remission in children and over 60% in adults was reported [28].

Other groups experimented a pre-emptive protocol in a prospective study enrolling high risk children and adults who were perioperatively treated with 8 sessions: seven out of the ten enrolled patients (4 with first grafts and 3 with prior recurrence) responded and were free of recurrence at follow-up [29].

The high impact of a post transplant recurrence encouraged pre-emptive treatment with plasma-exchange also in other more recent studies, in combination with the anti CD20 monoclonal antibody Rituximab, as in the case of a 7.9-yr-old girl treated with pre-transplantation prophylactic combined therapy consisting of four sessions of PE and one dose of rituximab before a second living-related kidney transplant after recurrence on the first graft [30].

Several drugs where associated to plasma-exchange: in a series of 10 patients intravenous Cyclosporin was given in association to