A
utoantibodies are a hallmark of essentially all systemic autoimmune disease. Although autoantibodies are not necessarily of direct pathogenic importance, they apparently do have a detrimental role in systemic autoimmune diseases. For some examples, there is evidence for a direct pathophysiological role of antibodies to double-stranded DNA (dsDNA), of anti-neutrophil cytoplasm antibodies (ANCA), and for anti–glomerular basement membrane (GBM) antibodies. The permanent exposure of the kidney’s vascular structures, and of the glomeruli in particular, to blood-borne pathogens, including autoantibodies, partly may explain the frequency of renal involvement in systemic autoimmune disease, even if the binding characteristics of some of these antibodies and/or their cognate autoantigens may be even more important. Thus, both immune complex nephritides and the pauci-immune glomerulonephritis of ANCA-associated vasculitides (AAV) quite obviously are caused by antibodies.

With respect to therapy, cyclophosphamide has been used successfully for decades to treat the severe organ manifestations of systemic lupus erythematosus (SLE), ANCA-associated vasculitides, and anti-GBM disease. It reduces B-cell numbers and targets plasmablasts and short-lived plasma, which usually leads to decreases in anti-dsDNA, ANCA, or anti-basal membrane antibodies (ABMA) levels. Moreover, new therapies targeting B cells have been approved in SLE and ANCA-associated vasculitis and also are used in other systemic autoimmune diseases.

It is therefore a logical step to attempt directly reducing circulating autoantibodies. In fact, as early as the 1970s, different extracorporeal therapies have been used and reported in the management of autoimmune diseases, especially if an (auto-)antibody-mediated pathogenesis was known, or at least assumed. In most of the reported cases, extracorporeal therapies have been used as a last option in refractory or life-threatening conditions or whenever standard-of-care (SOC) therapy was contraindicated.

Initially, plasma exchange (or plasmapheresis) was the only extracorporeal modality available. Although plasma exchange is successful clinically in critical situations such as pulmonary hemorrhage, this may be more related to removing other pathogenic substances or to adding proteins than to actual immunoglobulin removal. In fact, the humoral immune system is able to produce huge quantities of autoantibodies, and therefore, can overcome the effects of plasma exchange. Accordingly, trials on longer-term plasmapheresis in SLE failed to show benefit, whereas attempts to increase efficacy by combining plasmapheresis with synchronized pulse cyclophosphamide were associated with severe infections.

Immunoadsorption in Autoimmune Diseases Affecting the Kidney
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Summary: Autoantibodies play an important role in the pathophysiology of renal involvement in systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), systemic vasculitis, and anti–glomerular basement membrane disease (or Goodpasture syndrome). Direct removal of autoantibodies therefore has been tried in various ways, first by plasma exchange. Today, immunoadsorption is the extracorporeal method that most effectively removes (pathogenic) immune complexes and antibodies. Although past data have shown efficacy and biocompatibility of immunoadsorption in (renal) SLE, it is still an experimental and expensive procedure, and evidence from randomized controlled trials is needed. Nevertheless, immunoadsorption is being used as a rescue therapy in life-threatening situations of SLE patients because of its fast mode of action and its acceptable safety profile. In granulomatosis with polyangiitis (GPA) (or Wegener’s granulomatosis), microscopic polyangiitis (MPA), and anti–glomerular basement membrane disease, the current standard is plasma exchange. Immunoadsorption, which probably would reduce the autoantibody burden more effectively, might be an even better more effective option, but sufficient evidence is lacking.

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More recently, immunoadsorption added a more effective approach that emerged as an attractive alternative in many indications. In contrast to plasma exchange, immunoadsorption allows for the specific and nearly complete clearance of circulating Ig and immune complexes (ICs) while neither removing other plasma proteins nor necessitating substitution with fresh-frozen plasma, albumin, or immunoglobulins.\textsuperscript{22–24} Moreover, the plasma volume processed is not restricted, even if patients are maintained on daily immunoadsorption\textsuperscript{22,24} (Fig. 1).

Extracorporeal procedures have been used in a variety of autoimmune disorders (Table 1). With regard to autoimmune diseases affecting the kidney, most experience and (case) reports are available for SLE, but AAV and anti-GBM disease also have been treated by means of both plasma exchange and immunoadsorption, which will be detailed later.\textsuperscript{16,17}

In SLE patients, immunoadsorption has appeared relatively safe in highly active patients with a similar frequency of infectious adverse events to a matched group, and immunoadsorption also was safe during long-term observation in moderately active SLE.\textsuperscript{23,26} Therefore, immunoadsorption is feasible in severe SLE, and in complicated situations with limited therapeutic options, such as in pregnancy,\textsuperscript{27} active tuberculosis under triple therapy,\textsuperscript{24} or patients with (catastrophic) antiphospholipid syndrome.\textsuperscript{28}

Although in general the results of immunoadsorption in autoimmune-mediated renal diseases are encouraging given the fact that most patients have been refractory to SOC therapy, there is a big demand for more and better evidence. Still, the total number of patients treated by immunoadsorption is low, different types of adsorbers have been used, different protocols have been followed, and different outcomes have been reported.\textsuperscript{21,29} Nevertheless, immunoadsorption provides a valuable rescue option in refractory cases or when SOC immunosuppressive therapy cannot be applied.

**POTENTIAL INDICATIONS FOR IMMUNOADSORPTION IN KIDNEY DISEASE**

In kidney disease, there are two classic situations in which the removal of autoantibodies may be of benefit. On one hand is systemic autoimmune diseases with renal involvement, in which these autoantibodies are an essential element in the pathophysiology of nephritis.\textsuperscript{1–4}

On the other hand, there are situations in which the immune response is appropriate per se, but unwanted in a specific situation of the patient, namely in the context of solid-organ transplantation. In renal transplant recipients, immunoadsorption is applied successfully in ABO-incompatible recipients or in humoral rejection after renal transplantation.\textsuperscript{30–36} The latter, however, is not the focus of this review.