LINK TO ORIGINAL ARTICLE

Continuing the paradigm shift in the treatment of idiopathic membranous nephropathy

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I read with interest the recent Review by P. Ruggenenti *et al.* (Treatment of membranous nephropathy: time for a paradigm shift. *Nat. Rev. Nephrol.* **13**, 563–579; 2017)[1]. The observed inconsistency in therapeutic responses with conventional therapies directed at T cells and B cells[2], as well as the superior complete remission rates (53%) achieved with rituximab in patients with recurrent membranous nephropathy post-transplantation[3] compared to rates in those with native kidneys (13.6–19%)[4,5], highlight the important role of T cells in autoimmune kidney diseases[6] and the likely added value of T cell-targeted therapies in addition to anti-CD20 monoclonal antibody therapy in increasing remission rates. These observations imply the existence of different immunopathogenic signatures — primarily B cell-mediated pathways with a component of T cell help[6,7] — in addition to distinct mechanisms of autoantibody and alloantibody secretion by different B cell lineages, for example, by $CD20^+$ activated B cells in spleen and lymph nodes, $CD19^+CD20^-$ plasmablasts and short-lived plasma cells in blood, and $CD19^-CD20^-CD38^+CD138^+$ long-lived memory plasma cells located in the bone marrow and ectopically in the inflamed kidney[8]. These non-proliferating long-lived memory plasma cells produce considerable amounts of IgG autoantibodies and alloantibodies, and provide the basis for humoral memory and refractory autoimmune diseases[7–10].

As pointed out by Ruggenenti *et al.*, the lack of CD19 and CD20 expression by long-lived memory plasma cells renders these cells resistant to depletion by anti-CD20 monoclonal antibodies[1,5,9]. This resistance might explain the limited rate of sustained complete remission and recovery achieved by rituximab in patients with idiopathic membranous nephropathy, despite successful depletion of circulating B cells[4,5,10–12]. I agree that use of plasma-cell-depleting therapies, such as the newly introduced anti-CD38 monoclonal antibodies and the less specific proteasome inhibitors with anti-B cell and anti-T cell activities[13], might offer novel therapeutic alternatives for patients with idiopathic membranous nephropathy, at least in those who are refractory or only partially respond to combined conservative treatment plus rituximab therapy[12]. Whether new second and third generation anti-CD20 monoclonal antibodies can achieve higher rates of sustained complete remission than rituximab[1] remains to be determined, but such agents do not target long-lived memory plasma cells[8,14]. Surprisingly, another anti-CD20 monoclonal antibody, ofatumumab, failed to demonstrate superiority over rituximab as salvage chemotherapy in patients with relapsed or refractory diffuse large B cell lymphoma[15]. New immunologic biomarkers are needed to help to identify patients who are likely to respond to T cell[3], B cell[7,8], or combination therapy[12,14]. In addition to measuring CD19 and CD20 (REFS 1,4,5,9,11), assessment of patients with membranous nephropathy should include measurement of the long-lived memory plasma cell markers, CD38 and CD138, particularly in patients with relapsing or rituximab-resistant disease[7–10,12,14].

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Competing interests statement
The author declares no competing interests.