Steroids with local enteric action in IgA nephropathy and the association between kidney and bowel disease

Sir,

The interesting paper by Smerud et al. [1] showed a significant beneficial effect of a 6-month treatment with enteric budesonide targeted to the ileocaecal region on urine albumin excretion, along with a minor reduction of serum creatinine and a modest increase of Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR), in patients with IgA nephropathy (IgAN). The authors suggested that such targeted release of budesonide, specifically designed to act in the ileocaecal region, exerts a local effect by suppressing the mucosal immune response to gastrointestinal antigens supposedly involved in the pathogenesis of IgAN.

We have recently published a case report and review of the literature on the association between IgAN and inflammatory bowel disease [2], and we would like to add some comments on the therapeutic targeting of the intestinal mucosa by corticosteroids as an effective local immunosuppression. A pathophysiological link between inflammatory bowel disease and IgAN might offer an additional argument for such a local immunosuppressive effect. Immune complex glomerulonephritis, particularly IgAN, is a rarely described extraintestinal manifestation of inflammatory bowel disease, particularly Crohn’s disease, that occurs in the setting of active bowel inflammation [2]. In most cases, the relapse of bowel disease is associated with the onset or exacerbation of renal manifestations, mainly microscopic haematuria, mild proteinuria and renal impairment. Systemic steroid treatment of the bowel disease results in significant improvement in renal manifestations, although there is no clear evidence of concomitant renal histological remission [2, 3].

Although there is increasing literature reporting associations between IgAN and inflammatory bowel disease, whether these reports represent chance associations or pathophysiological related conditions still remains a matter of debate [2, 4]. We always have to take into consideration the relatively high frequency of subclinical IgAN in supposedly healthy populations and the issue of a chance association between IgAN and other frequent, pathophysiological unrelated conditions. Furthermore, at present, there is no evidence supporting a link between immune mechanisms operating in inflammatory bowel disease and IgAN. However, a potential common mechanism in these conditions can be speculated through the possible association of a bowel disease exacerbation, at least in part, with the loss of mucosal antigen exclusion, due to impaired integrity of mucosal barriers. This results in increased systemic antigenaemia and subsequent increased immune activation which drives the synthesis of pathogenic IgA, a path that, as acknowledged by Smerud et al. [1], is implicated in the pathogenesis of IgAN as well. Immunosuppressive treatment of the bowel disease re-establishes mucosal integrity with antigen exclusion and subsequent reduction of pathogenic IgA synthesis leading to a clinical remission of IgAN [2, 4]. These observations are in favour of a common pathogenetic mechanism involving an IgA immune response to a mucosal challenge in the intestine. However, the possibility of primary unrelated IgAN that deteriorates by coexistent inflammatory bowel disease or becomes clinically evident during a relapse of the bowel disease cannot be excluded [4]. Furthermore, active intestinal inflammation of varying degree has been described in patients with IgAN and manifested itself as an increased COX-2 expression in small bowel mucosa, while the degree of inflammation significantly correlates with serum IgA and the amount of proteinuria and haematuria [5].

In our case report [2], mild proteinuria (0.5 g/24 h) and renal impairment (serum creatinine 1.8 mg/dL and creatinine clearance 53 mL/min/1.73m²) were present at the time of diagnosis of IgAN in the setting of an exacerbation of Crohn’s disease. Systemic steroid treatment of the bowel disease resulted in complete remission of Crohn’s disease and an improvement in renal function (serum creatinine 1.3 mg/dL and creatinine clearance 60 mL/min/1.73m²), while proteinuria remained constant at 0.5 g/24 h, 20 months after initial presentation. Treatment with budesonide, a steroid with mainly local action but with possible systemic effects, in the study by Smerud et al. [1] had a favourable, but sporadic and temporary, effect on albuminuria and a modest improvement in renal function assessed by serum creatinine and MDRD eGFR, while Cockcroft–Gault eGFR and cystatin C remained unchanged. It is of note, however, that in most cases, pre-treatment renal function was not impaired. Furthermore, gastrointestinal disease history was not reported in the study by Smerud et al. [1], and thus, the observed effect of local steroids indicates a potential pathophysiological link between IgAN and a mucosal defect without a gastrointestinal clinical syndrome.

Further investigation is needed to clearly elucidate the pathogenesis of this association between inflammatory bowel disease and IgAN. Consequently, local enteric immunosuppressive treatment with targeted release of budesonide could be further supported as a new therapeutic approach to IgAN.

Conflicts of interest statement. None declared.

Editorial Note: Smerud et al. had no further comments on this letter.


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