Nephrol Dial Transplant (2015) 30: 360–366
doi: 10.1093/ndt/gfu343
Advance Access publication 11 November 2014

ndt
Nephrology Dialysis Transplantation

Full Reviews

The intestine–renal connection in IgA nephropathy

Rosanna Coppo

Nephrology, Dialysis and Transplantation Unit, University and Hospital Health Agency "Città della Salute e della Scienza di Torino", Regina Margherita Children's Hospital, Turin, Italy

Correspondence and offprint requests to: Rosanna Coppo; E-mail: rosanna.coppo@unito.it

ABSTRACT

It is commonly stated that mucosal immunity plays a role in the pathogenesis of IgA nephropathy (IgAN); however, the search for specific eliciting factors has been largely inconclusive. A dysregulated mucosal immune system with defective immune tolerance to commonly encountered pathogens or alimentary components is likely to be the key factor in triggering IgAN. Most of the interest, particularly in Asia, was being focussed on the possibility of modulating the mucosal immune system by tonsillectomy, a simple way of eradicating a source of pathogens, meanwhile reducing mucosal-associated immune system (mucosal-associated lymphoid tissue, MALT), but results are still inconclusive. Over the last years, a resurgence of interest has addressed the role of intestinal immunity facing dietary components, like gluten or the complex intestinal flora, the microbiota. The latter is focussing particular interest in recent reports, because it can vary according to diet and environmental factors, is modulated by the host genes and influences, in return, the MALT activity. Some data suggest a tempting new hypothesis for a strong intestine–kidney connection in IgAN. A defective immune tolerance might favour an abnormal response to microbiota with alterations of the intestinal barrier, including increased alimentary antigens and bacterial toxins absorption, triggering MALT activation and subclinical intestinal inflammation. This can produce abnormal response to alimentary antigens or commensal microbes with synthesis of aberrantly glycosylated polymeric IgA1 which eventually enter the circulation with renal deposits formation. The hypothesis is tempting also because it offers new treatment options, targeted to subclinical intestinal inflammation or microbiota modifications.

Keywords: IgA nephropathy, microbiota, mucosal immunity, pathogenesis

THE ROLE OF MUCOSAL IMMUNITY IN IgA NEPHROPATHY

IgA nephropathy (IgAN) was identified almost 50 years ago by Berger *et al.* [1]; but in spite of a large number of investigation, its pathogenesis is only partially defined and the triggering event is still to be identified. The mucosal immunity has been considered to play a role in this renal disease since the first clinical reports, as gross hematuria frequently follows mucosal infections, mostly involving the upper-respiratory tract, less frequently the gastro-intestinal and urinary tracts [2]. The hallmark of the renal damage in these patients, often young and in good general health, was identified by Berger to be mesangial deposits of a selected class of immunoglobulins, the IgA. Since IgA molecules are the most represented immunoglobulins in mucosal secretions, the first hypothesis for the pathogenesis of IgAN was of a hyperactive mucosal system response to germ presented at mucosal surface [3].

The mucosal surfaces of respiratory and gastrointestinal tracts represent a 400 m^2 interface with the environment constituted by commensal bacteria and pathogens, alimentary components and potentially noxious substances introduced by water, aliments and air. The mucosal-associated lymphoid tissue (MALT) enters in contact with antigens present in the lumen and develops antigen-sensitized lymphocytes which through the blood stream migrate to submucosal areas forming the MALT, which is rich in plasma cells derived from B cells [4]. MALT represents 50% of total body immunity and accounts for 70% of total antibody production, mostly in the form of secretory IgA (SIgA), providing specific immunologic protection against both resident flora and infectious pathogens, in cooperation with innate defence mechanisms [5]. SIgA is composed of two IgA molecules connected by a join chain (J) covalently bound to a secretory component (Sc).

This receptor mediates the epithelial transport of dimeric and larger polymers of IgA (collectively called pIgA) to the mucosal lumen and external secretions [6]. The polymeric nature of IgA renders the molecule more effective in binding to pathogens and Sc protects IgA from protease. Elevated serum IgA is found in 35–50% of patients with IgAN being polymeric IgA in 25% instead of 10% of total IgA, as found in controls [7].

The accumulation of IgA containing immune material together with complement fractions in mesangial area of patients with IgAN was initially ascribed to deposition of IgA immune complexes (IgAIC), found in 50–70% of patients and due to an abnormally great mucosal immune response with predominant synthesis of polymeric IgA [2]. Notably, polymeric IgA and also the Sc component are present in renal deposits [8]. This hypothesis offered a unifying explanation of the relationship between mucosal infections and gross haematuria. However, IgA in renal deposits of IgAN are mostly constituted by IgA1 subclass, which is more typical of bone marrow than MALT plasma cells [6], hence lymphocytes sensitized at mucosal level were supposed to migrate to bone marrow to differentiate into IgA1 producing plasma cells [9]. Moreover, IgA1 in IgAN patients has a defective galactosylation of the short O-linked oligosaccharide chains present in the hinge region. The *N*-acetylgalactosamine (GalNAc) core can be extended with β1,3-linked Gal by the activity of a β1,3-galactosyltransferase (which needs a specific chaperone called Cosmc) and covered with sialic acid in α 2,3 and/or α 2,6 linkage. In patients with IgAN, there is a prevalence of IgA1 O-glycoforms consisting of GalNAc alone or with premature sialylation of GalNac due to hyperactive sialyltransferase [10]. This aberrantly glycosylated IgA1 can form macromolecular self-aggregates and elicit IgG autoimmune response. IgG antibodies recognize GalNAc-containing epitopes on the galactose-deficient hinge region of IgA1, forming IgG/IgA1IC, and can cross react with bacterial or viral cell-surface GalNAc-containing glycoproteins present on pathogens [11]. Serum levels of IgG/IgA1IC were found to be increased and in correlation with proteinuria, and progression of IgAN and IgG reacting to IgA1 was recently found to be the most sensible biomarker of IgAN [12].

Despite the progress made on the characterization of macromolecular IgA in sera and in renal deposits, the search for specific antigens eliciting IgA synthesis has been largely inconclusive.

SEARCH FOR SPECIFIC MUCOSAL PATHOGENS TRIGGERING IgAN

IgA reacting with environmental pathogens have been detected in sera and in glomeruli of patients with IgAN, including *Haemophilus parainfluenzae*, parvovirus, cytomegalovirus, Epstein–Barr virus and *Helicobacter Pylori* [7]. The interest has been focussed mostly on pathogens from upper-respiratory tract and particularly from tonsils, due to the clinical association with gross haematuria. A cross-reactivity of IgA eluted from tonsils and mesangial deposits of these patients was demonstrated, in support of the clue role of tonsillar infections [13]. However, no particular germ resulted to be associated with development of IgAN. More recently, *Staphylococcus aureus* cell envelope antigens have been detected in renal biopsies of patients with IgAN [14], and IgA deposits were reported in patients with methicillin-resistant *S. aureus* infection, indicating a possible a role for microbial superantigens in IgAN [15]. Furthermore, periodontitis and caries-related bacteria have been suggested to be possible triggers of IgAN [16].

Several of these pathogens can reproduce in experimental animals temporary IgA renal deposits although without urinary signs of nephritis. It was of interest to note that persistent IgA deposits and microhaematuria, mimicking more strictly human IgAN, were induced in mice by intranasal administration followed by systemic challenge of the common respiratory Sendai virus only after induction of a defective mucosal tolerance [17]. A disrupted tolerance was essential for development of IgAN also in models of oral immunization [18], or in transgenic animals carrying a dysregulation of lymphotoxin-like inducible protein (LIGHT), which develop intestinal inflammation and high levels of pIgA [19].

No particular pathogen was found to be responsible for experimental models of IgAN, and indeed the same conclusion was reached for pathogens triggering human IgAN.

SEARCH FOR SPECIFIC DIETARY COMPONENTS TRIGGERING AND MAINTAINING IgAN

The first approach to the role of intestinal immunity and dietary constituents followed the reports of association between coeliac disease or dermatitis herpetiformis and IgAN [20]. Both coeliac disease and dermatitis herpetiformis are associated with HLA-DQ2 and/ or HLA-DQ8 [21] and present with high levels of IgA and IgAIC in one-third of the cases. In patients with coeliac disease, after binding of gluten peptides —particularly gliadin—to HLA-DQ2 and DQ8 molecules and optimal antigen presentation to antigen-presenting cells, specific CD4 + T cells are elicited, inducing intestinal epithelium cytotoxicity and inflammation. This increases the intestinal permeability to all antigens present in the intestinal lumen, hence favouring their contact with MALT and a broad mucosal immune response [22]. The enzyme tissue transglutaminase 2 enhances the gluten toxicity in patients with coeliac disease by producing gluten peptides which have more affinity for HLA-DQ2 and HLA-DQ8. This haplotype has no statistically significant increased frequency in IgAN in comparison with controls [23]; however, patients with primary IgAN and IgAN secondary to Henoch–Schonlein purpura were found to have more healthy control and similar to coeliac subjects, high intestinal permeability [24, 25] and high levels of IgA against gliadin as well as other alimentary antigens, including bovine serum albumin and lactoglobulin, were found in 20–30% of the cases [26, 27].

Steven Emancipator was the first to reproduce IgAN in mice after oral immunization with alimentary components, including ovalbumin, bovine gamma globulin and horse spleen ferritin [28]. Among the alimentary components, based on the

reported association between gluten intolerance and IgAN [20] and the high frequency of IgAN in dietary gluten-rich Mediterranean people, our group in the 1980s focussed on the possible role of gluten in IgAN by performing a series of investigations, rather being pilot studies exploring this hypothesis [27, 29–33].

We investigated the effects of gluten-free, meat-free and egg-free diets in a small group of patients with IgAN with persistent heavy microscopic haematuria, proteinuria and high levels of IgAIC, with skin biopsy and intestinal permeability test negative for subclinical coeliac disease, and we observed that only gluten-free diet over two periods of 1 month and 6 months was associated with a significant reduction in IgAIC, followed by a significant rebound after intervals of 1 and 3 months of gluten-free diet [29, 30]. These fluctuations of IgAIC were not observed during diets avoiding other alimentary components, such as meat or eggs. After 6 months on gluten-free diet, all patients had normal IgAIC levels and selectively greater decrease in IgA2IC subclasses, suggesting a mucosal origin of IgA. We detected a parallel decrease in baseline high levels of IgA as well of other antibodies directed to various alimentary components (β-lactoblobulin, casein and ovalbumin), suggesting that gluten-free diet may have interrupted a gluten-dependent abnormal intestinal permeability [30].

In an experimental model [31], we investigated the effect of alimentary gluten and of its lectin-like fraction gliadin in inducing IgA mesangial deposits in BALB/c mice. In a pilot experiment, we reported that mice fed with standard gluten-containing fodder had mesangial IgA deposits, which were prevented in mice on gluten-free diet since birth. Then, we considered groups of BALB/c mice fed with gluten-free diet, gliadin, ovalbumin or standard gluten-containing diet, respectively. IgA deposits were found to be significantly greater in mice on standard gluten-containing diet or even more in diet enriched in gliadin in comparison with those on gluten-free diet. Anti-gliadin IgA in circulation as well as in renal deposit eluates were significantly increased in gluten-eating mice as compared with the gluten-free control group. These observations indicated that gliadin was responsible for induction of IgA immune deposits in BALB/c mice.

Some further studies from our group reported a lectin-binding activity of IgA in sera of patients with IgAN [26, 32], which was expression of altered sugar residue content in circulating IgA, and indeed the test for the detection of degalactosylated IgA1 is based on the binding to lectins (*Helix aspersa*, HA or *Vicia villosa*, VV), which express free GalNAc residues [10]. We reported also that gliadin interacted with mesangial cells via lectinic (sugar dependent) interactions, which were likely to occur also between degalactosylated IgA1 and gliadin and that this binding activated cultured mesangial cells to a similar extent as macromolecular IgA did [33].

Gluten-free diet was of benefit in some patients, with a reduction of proteinuria in our pilot study; however, in progressive cases this diet was not effective in halting the worsening of the disease [30]. The difficultly of proving the benefits of gluten-free diet in early cases of IgAN frustrated the development of long-term randomized controlled trials, even more because in the early 1990s the benefits of steroids raised much interest and hope on one hand, while the detection of aberrantly glycosylated IgA1, apparently unrelated to antigen stimulation, seemed to offer a new and interesting pathogenetical hypothesis for IgAN.

INTESTINAL IMMUNITY AND IgAN

Apart from the search of the eliciting antigen(s), an interesting area of research was devoted to investigating the intestinal immunity and the permeability of the intestinal barrier in experimental models and in patients with IgAN.

In a spontaneous murine strain with high levels of IgA and IgA renal deposits, the number of intestinal IgA-producing plasma cells was similar to control mice till the 10th week of age, then showed a 3-fold increase with down-regulation of sIgA excretion into the intestinal lumen, favouring high IgA levels in circulation and nephritis. This study suggests that the contact with alimentary components and intestinal flora triggers the development of IgA response and deposits in genetically predisposed animals [34].

An increased intestinal permeability was reported, as mentioned above, in patients with primary and secondary IgAN [24, 25]. In a study that investigated the intestinal permeability tests in the same patients with IgAN 5 years apart, high levels of IgA against gliadin, soy, salt extracted antigens of oat flour and ovalbumin were constantly detected and intestinal permeability was persistently abnormal [35]. A strong correlation was observed between the intestinal permeability and the IgA antibody against soy, suggesting an intestinal functional abnormality leading to production of IgA against food antigens at least in a proportion of patients with IgAN, with IgAIC formation and mesangial deposition.

In several gastrointestinal diseases—besides coeliac disease—including Crohn's disease, ulcerative colitis and liver diseases, high frequency of IgAN has been reported [36]. On the other hand in patients with IgAN aberrant duodenal histopathological findings were observed [37], in association with high levels of IgA directed against alimentary components. In these subjects, intestinal inflammation of varying degree was detected as an increase in inflammatory CD3(+) cells and cyclooxygenase 2 positive cells in the small bowel mucosa [38]. The degree of inflammation significantly correlated with serum IgA and levels of proteinuria and haematuria. Increased number of small intestine intraepithelial T lymphocytes together with IgA1 and IgA2 mucosal plasma cells were found also in other primary glomerulonephritides, suggesting a possible role of oral tolerance breakdown in various immune-mediated glomerular diseases [39]. In another study, gastroscopy specimens of patients with IgAN showed small bowel T cells, HLA class II antigen DR, and GroEL a stress protein. The mucosal architecture was normal, and gamma-delta T cells and the total CD3+ T cells were increased in comparison with controls. These data suggested that ongoing small bowel inflammation with signs of stress is present in IgAN, despite normal morphology, suggesting its involvement in the pathogenesis of this renal disease [40].

RECENT RESURGENCE OF INTEREST IN GUT IMMUNITY AND IgAN

Although there are frequent case reports of association between IgAN and inflammatory bowel disease [41], the high frequency of subclinical IgAN left open the possibility of chance association. A recent large survey was performed on renal biopsies in cases of renal complications during inflammatory bowel disease, including Crohn's disease and ulcerative colitis, to better define spectrum and frequencies of renal abnormalities during these intestinal pathological conditions [42]. IgAN resulted to be more frequent than other glomerular diseases, suggesting a causal link between the two diseases. Similarly, in a large study, IgAN was found to occur more frequently in patients with coeliac disease than in reference controls [43] and some reports indicate an increase in frequency of biopsy-proven coeliac disease in patients with IgAN [23]. Not all reports are however consonant, as for example a recent paper did not confirm increased levels of anti-gliadin and anti-TG2 antibodies in a group of patients—which included transplanted IgAN under immunosuppressive therapy—hence the authors claimed a lack of serologic evidence to link IgAN with coeliac disease [44]. However, 49% of patients were receiving immunosuppressive drugs at the time of sampling and this could have affected the immune response against alimentary components.

Twenty years after the reports, which suggested some roles for gluten and alimentary antigens in IgAN, gluten sensitivity was resurged to scientific interest by Smerud *et al.*, from Sweden, who reported in IgAN patients with high immune response to gluten or soy of intestinal mucosa [45, 46]. Gluten reactivity was defined as increase in myeloperoxidase and/or nitric oxide after gluten exposure and was observed in one-third of IgAN patients. The prevalence of HLA-DQ2 and DQ8 was not increased among gluten-sensitive patients. Anti-gliadin antibody level further increased after the test in 30% of the cases. The authors concluded that a subclinical inflammation to gluten might be involved in the pathogenesis of a subset of patients with IgAN.

Based on these observations and supposing that this intestinal inflammatory condition could represent the origin of IgA which eventually deposits in the mesangium, the Swedish group performed a pilot study [47] investigating in patients with IgAN the effect on proteinuria levels of a new enteric formulation of the locally acting glucocorticoid budesonide (Nefecon®), designed to release the drug in the ileocecal region. Budesonide given for 6 months reduced proteinuria by 40% in proteinuric patients with IgAN, indicating the interest for a larger study, which is ongoing (NEFIGAN trial).

The role of gliadin has been recently supported also from some interesting results from experimental IgAN. Monteiro's group has recently reported an interaction between degalactosylated IgA1 and the myeloid receptor FcαR1 (CD89) [48], which has been detected in renal deposits of patients with IgAN. In an experimental mouse strain expressing human CD89 and human IgA1, they demonstrated that the development of IgAN needs the interaction of IgA1-sCD89 with the receptor for transferrin (TfR1/CD71) and with the cross-linking enzyme transglutaminase (TGase) 2. TGase 2 is an autoantigen for coeliac disease patients and the reaction with the corresponding antibody results in the inflammation of the small intestine and subsequent villous atrophy.

THE MICROBIOTA AND IgAN

Apart from gluten and other alimentary components, a particular interest has been recently raised for the extraordinary high number of microbes, which are present in the gut, collectively called microbiota, which can vary according to diet and environmental factors, and are likely to be modulated by the host genes and influencing, in return, the MALT activity [49]. In particular, the gut microbiota controls the organization and maturation of lymphoid tissues and acts both locally and systemically coordinating recruitment, differentiation and function of innate and adaptive immune cells. The microbiota contributes to immune function of MALT, e.g. by controlling the T-helper (TH1/TH2) balance [50] and it was found to play an unsuspected role not only in inflammatory bowel disease [51] but also in autoimmune diseases [52].

A correlation with diet has been inferred from some recent studies, as dietary changes are known to affect both the composition and function of the gut microbiota, which in turn can modulate the innate and adaptive immune system [53, 54].

From an experimental point of view, microbiota could be involved in IgAN, as suggested by the observation that B-cell activation factor (BAFF) transgenic mice have high levels of aberrantly glycosylated serum polymeric IgA leading to IgAN mesangial deposition. The presence of commensal flora and the circulation of corresponding specific IgA antibodies have recently been shown to be essential for the development of IgA deposits [55]. These authors reported also that a subgroup of patients with IgAN had elevated serum levels of a proliferation-inducing ligand (APRIL), a cytokine related to BAFF.

The intestinal epithelium functions as a barrier for antigens and pathogens, and commensal gut microbes maintain functional integrity of gut, by favouring the tight junction efficacy, by secreting antimicrobial products or by upregulating mucin genes. Thus, microbiota plays a role in suppressing intestinal inflammation possibly elicited by gut pathogens. An example of microbiota immunomodulation activity is the effect of polysaccharide A from *Bacteroides fragilis*, which acts on the T-helper balance [50]. Bacterial lypopolysaccharide, endotoxin (LPS), is a phospholipid that constitutes the outer membrane of most Gram-negative bacteria. Toll-like receptors (TLRs), highly expressed on mucosal epithelial cells, recognize molecular patterns of microbes, e.g. LPS (TLR4) and lipoteichoic acid (TLR2). The microbiota signalling via TLRs plays a key role for intestinal repair and new injury. Altered intestinal barriers facilitate LPS increased absorption and circulation.

Quantitative and qualitative alterations of microbiota have been recently found to be associated with chronic kidney disease (CKD) [56]. Endotoxin from gut bacteria enhances a strong inflammatory response. Disruption of gut barrier in

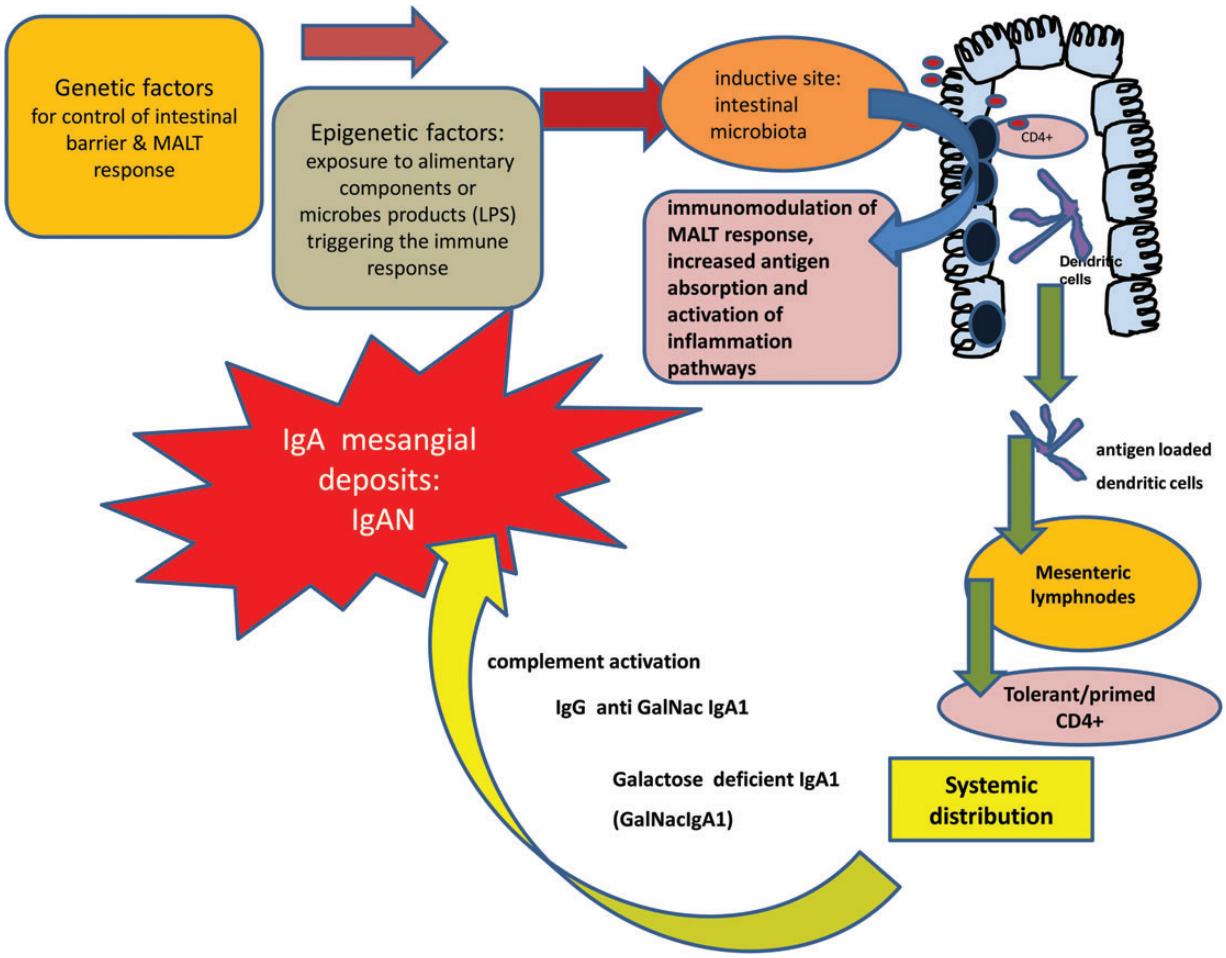

FIGURE 1: Hypothesis of a possible role of genetic and epigenetic factors, intestinal microbiota and MALT in the pathogenesis of IgAN.

CKD facilitates the abnormal entry of endotoxin in circulation, contributing to uraemic toxicity and systemic inflammation.

It is of interest that a possible correlation between LPS exposure and defective galactosylation of IgA was suggested by a study showing that bacterial LPS activates TLR4 in cultured peripheral B lymphocytes from patients with IgAN as well as from healthy controls inducing a methylation of the chaperone Cosmc, which is essential for the activity of galactosyltransferase, thus reducing its activity and hence the galactosylation of IgA1 [57].

Membrane CD14, the LPS binding receptor, and TLR4 are the major components for cellular LPS signalling in response to various microbes and it was supposed to affect the natural history of chronic inflammatory conditions. It has been hypothesized that variants in the promoter region of the CD14 gene might alter the expression of CD14, and this in turn could influence the progressive nature of inflammatory diseases including IgAN. The correlation found between CD14/-159 polymorphism and IgAN progressive cases [58] suggested that a genetic modification of the membrane receptor of LPS may modulate the level of the inflammatory response and be a marker for progression of IgAN.

We recently reported that patients with IgAN have increased expression of TLR4 mRNA in peripheral lymphomononuclear cells [59], which correlated with the immunoproteasome switch, a process which favours optimal antigen presentation and immune response. High TLR4 expression in peripheral mononuclear cells correlated with high levels of proteinuria and microscopic haematuria. Because TLR4 is specific for *Escherichia coli* LPS, these data further support the role of intestinal MALT as promoter of systemic microinflammation in IgAN.

A recent genome-wide association study (GWAS) of IgAN has shown interesting new association of IgAN and loci associated with risk of inflammatory bowel disease or maintenance of intestinal barrier and intestinal MALT response to pathogens [60]. All these recent data suggest a tempting new hypothesis for a strong intestine–kidney connection in IgAN (Figure 1). A defective immune tolerance might favour an abnormal response to microbiota with alterations of the intestinal barrier, increased antigen absorption, MALT activation and subclinical intestinal inflammation. This in turn can favour an abnormal handling of endotoxin by an intestinal barrier leading to increased production of aberrantly glycosylated polymeric IgA1 in the context of systemic microinflammation eventually producing IgA1 mesangial deposits and nephritis. It is a tempting speculation, which would support the attempt to treat IgAN by modulating intestinal immunity, a long lasting idea which might be proved after >30 years of investigations.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received for publication: 25.8.2014; Accepted in revised form: 1.10.2014

Nephrol Dial Transplant (2015) 30: 366–375
doi: 10.1093/ndt/gfu067
Advance Access publication 9 April 2014

FULL REVIEW

Management of atherosclerotic renovascular disease after Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL)

Sandra M.S. Herrmann, Ahmed Saad and Stephen C. Textor

Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Correspondence and offprint requests to: Stephen C. Textor; E-mail: stextor@mayo.edu

ABSTRACT

Many patients with occlusive atherosclerotic renovascular disease (ARVD) may be managed effectively with medical therapy for several years without endovascular stenting, as demonstrated by randomized, prospective trials including the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial and the Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) and ASTRAL. These trials share the limitation of excluding subsets of patients with high-risk clinical presentations, including episodic pulmonary edema and rapidly progressing renal failure and hypertension. Although hemodynamically significant, ARVD can reduce renal blood flow and glomerular filtration rate; adaptive mechanisms preserve both cortical and medullary oxygenation over a wide range of vascular occlusion. Progression of ARVD to severe vascular compromise eventually produces cortical hypoxia, however, associated with active inflammatory cytokine release and cellular infiltration of the renal parenchyma. In such cases ARVD produces a loss of glomerular filtration rate that no longer is reversible simply by restoring vessel patency with technically successful renal revascularization. Each of these trials reported adverse renal functional outcomes ranging between 16 and 22% over periods of 2–5 years of follow-up. Blood pressure control and medication adjustment may become more difficult with declining renal function and may prevent the use of angiotensin receptor blocker and angiotensin-converting enzyme inhibitors. The objective of this review is to evaluate the current management of ARVD for clinical nephrologists in the context of recent randomized clinical trials and experimental research.

Keywords: renal artery stenosis, atherosclerosis, angioplasty, stent, renovascular hypertension