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Why Target the Gut to Treat IgA Nephropathy?

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Kidney Int Rep (2020) **5,** 1620–1624; https://doi.org/10.1016/j.ekir.2020.08.009

It is more than 50 years since the first description of IgA nephropathy (IgAN) by the Parisian pathologist, Jean Berger.[1] Over this time, IgAN became recognized as the most common pattern of glomerular disease worldwide.[2] Despite the significant global burden of chronic and end-stage kidney disease associated with IgAN, there are currently no approved treatments.[3] Standard of care continues to be supportive therapy, which focuses on optimal blood pressure control, a low-sodium diet, and maximum tolerated blockade of the renin-angiotensin-aldosterone system (Kidney Disease Improving Global Outcomes Glomerulonephritis Work Group. KDIGO clinical practice guideline on glomerular diseases - public review draft, June 2020, personal communication).[4] There is no evidence for the efficacy of traditional immunosuppressive agents, such as cyclophosphamide, azathioprine, mycophenolate mofetil, and rituximab.[4,5] The safety and efficacy of systemic corticosteroids in IgAN have recently been challenged by the publication of the TESTING and the STOP-IgAN studies.[6,7] There is a clear unmet need for safe and effective disease-modifying therapies in IgAN. This need may be met in the near future because a number of novel therapies are now being evaluated in phase 2 and phase 3 clinical trials.[8] Of these, the most advanced is the NefIgArd trial, which is evaluating the safety and efficacy of a targeted-release formulation of the corticosteroid, budesonide (NEFECON).[S1] NEFECON is designed to release budesonide in the terminal ileum, a region of the gastrointestinal tract with a high density of lymphoid-rich Peyer's patches.[S2,S3] But why is one of the largest ever clinical trials for IgAN testing a drug that targets the gut?

It was soon recognized after the first description of IgAN that there was a close association between mucosal inflammation, and episodes of nephritis in patients with IgAN.[S4] The archetypal presentation is a young adult, commonly male, presenting with an episode of painless visible hematuria 24 to 48 hours after developing a mucosal infection, usually affecting the upper respiratory or gastrointestinal tract.[S5,S6] We still do not completely understand the connection between mucosal inflammation and the kidney, but a number of important observations have led to the concept of a "gut–kidney" axis in IgAN.[S7]

The mucosal-associated lymphoid tissue is responsible for the synthesis of the bulk of IgA in the body, with more IgA produced at mucosal surfaces per day than all other types of antibody combined.[S8,S9] The gut-associated lymphoid tissue (GALT) alone secretes between 3 and 5 g of IgA into the intestinal lumen every day, 15% of the body's total Ig production.[S10,S11] Furthermore, in the normal gut there are approximately 1×10^{10} IgA-producing lymphocytes per meter, which equates to at least 80% of all immunoglobulin-producing cells in the body.[S8] Secreted IgA is an important first line of defense against microbial invasion. Secretory IgA attaches to the mucus layer covering epithelial surfaces, where it is available to bind to microbial pathogens and both prevent their attachment to epithelial cells by steric hinderance and crosslink the pathogens, trapping them in the mucus layer for excretion in the feces.[S12–S14] The GALT is highly organized and covers a surface area of 260 to 300

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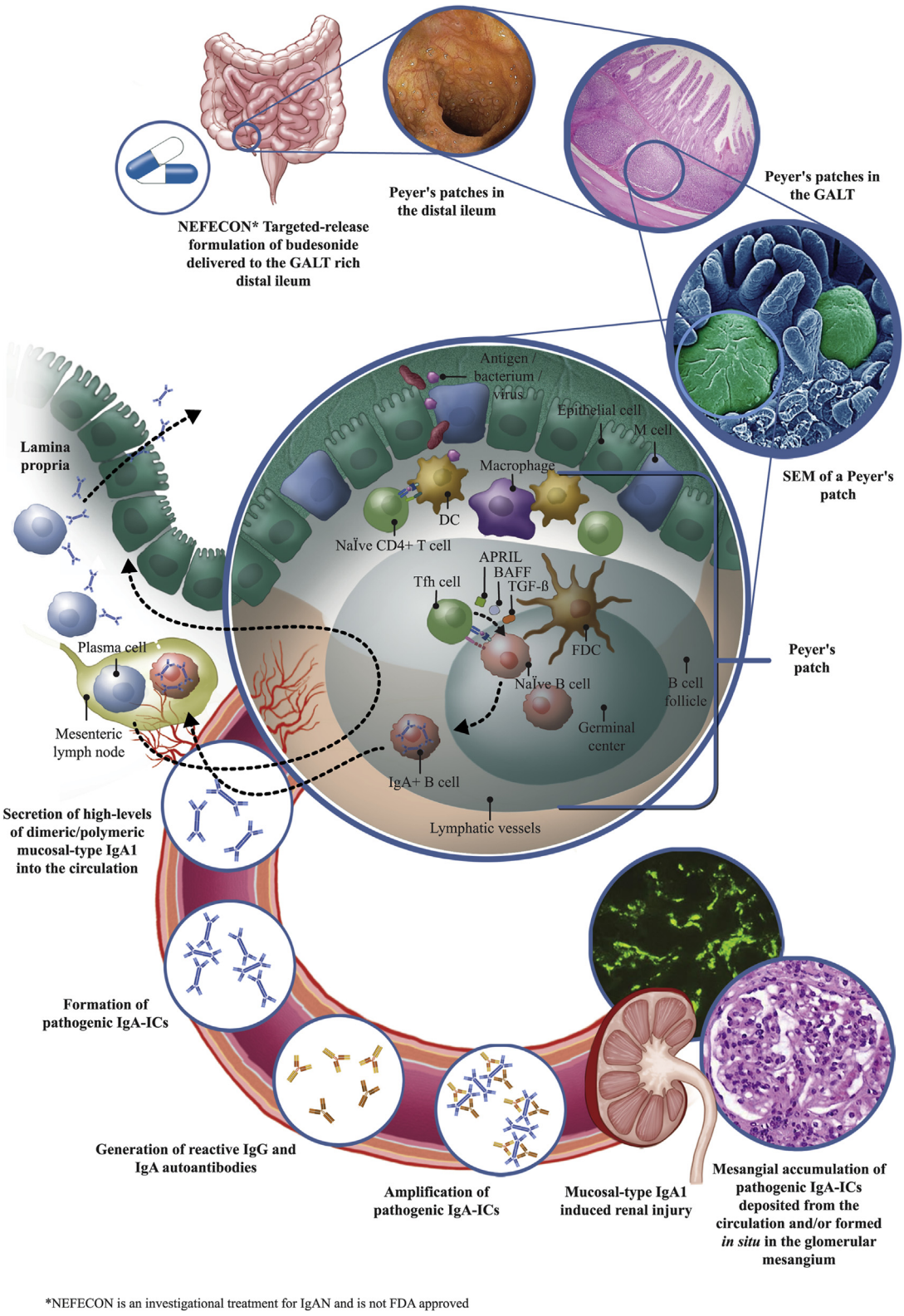
m^2.[S15] The most immunologically significant components of the GALT are the Peyer's patches, which consist of at least 5 (but can contain up to 200) aggregated lymphoid follicles.[S13,S16] Peyer's patches are located in the mucosal layer of the intestine and extend into the submucosal layer, and they serve as the major antigen sampling and inductive sites of the GALT.[S3,S17,S18] In humans, there are approximately 100 Peyer's patches at birth, 225 in the mid-teens and approximately 100 in later years (≥70 years), at least 46% of these are concentrated in the distal 25 cm of the ileum.[S3,S16] Human intestinal IgA is mostly dimeric and comprises both IgA1 and IgA2 subclasses. The ratio of plasma cells secreting the 2 subclasses of IgA is not the same throughout the gastrointestinal tract. Whereas most plasma cells in the small intestine secrete IgA1, the proportion secreting IgA2 increases from the duodenum through to the terminal ileum, and the subclasses are present in approximately equal proportions in the colon. In general, IgA2 is more resistant to bacterial proteases than IgA1 and may, therefore, have a longer half-life in the lumen of the distal intestinal tract.[S19] Peyer's patches are thought to be the main source of conventional surface IgA1-expressing primed mucosal B cells.[S20] By contrast, the adjacent lamina propria is principally an effector site where surface IgA-expressing primed mucosal B cells terminally differentiate to plasma cells that produce IgA, which is then transported across the mucosal epithelium as secretory IgA (Figure 1).[S21,S22]

Supporting the importance of mucosal-derived IgA as a major source of pathogenic IgA, a number of studies have reported elevated serum levels of secretory IgA in IgAN, which increase after mucosal immunization, and perhaps more importantly suggests that secretory IgA contributes to the mesangial IgA deposits characteristic of IgAN.[S23–S25] In parallel, a number of investigators have reported elevated levels of IgA antibodies specific for food antigens, mucosal vaccines, and gut-associated bacteria in the serum, suggesting a dysregulation of the mucosal-associated lymphoid tissue, and in particular the GALT.[S26–S28] The most consistent finding is an increase in serum levels of poorly *O*-galactosylated IgA1 glycoforms (Gd-IgA1) and there is now convincing evidence that this IgA is derived from the mucosal-associated lymphoid tissue, predominantly the Peyer's patches of the GALT.[S13,S26,S29,S30] Indeed, multiple studies have reported that mucosally derived IgA has the same physicochemical properties as the IgA that forms circulating immune complexes and deposits in the mesangium.[S31–S34] Mucosal IgA is polymeric, low affinity, poorly *O*-galactosylated, and found at increased concentrations in the serum in IgAN.[S35] Two recent studies demonstrated that IgA1 *O*-galactosylation is in part determined by single nucleotide polymorphisms in the promoter region of the gene encoding core 1 ß1,3-galactosyltransferase (*C1GALT1*).[S36,S37] This is consistent with earlier observations reporting that IgA1 *O*-galactosylation is modulated following class switch recombination and by the tissue microenvironment, in particular by cytokines and growth factors that are enriched in the Peyer's patches.[S38,S39] There are also intriguing data suggesting that gut bacteria may themselves be capable of modulating IgA class switching, the amount of mucosal IgA production, and IgA1 *O*-galactosylation in the GALT through activation of lymphoid Toll-like receptors.[S40,S41] Moreover, there is early evidence that the composition of the gut microbiome may be different in patients with IgAN.[S42] In addition, genome-wide association studies have identified a number of risk alleles, which are both strongly associated with age at disease onset and whose frequency increase sharply with eastward and northward distance from Africa, paralleling the known east–west gradient in disease risk.[S43] Pathway analysis based on a large meta-analysis of genome-wide association studies identified the intestinal immune network for IgA production as the most enriched Kyoto Encyclopedia of Genes and Genomes pathway in IgAN.[S44] Also, most of the identified risk alleles are either directly associated with risk of inflammatory bowel disease or maintenance of the intestinal epithelial barrier, as well as response to mucosal pathogens. The geospatial distribution of risk alleles is highly suggestive of multilocus adaptation, and genetic risk correlates strongly with variation in the local gut pathogens, suggesting a possible role for host-intestinal pathogen interactions in shaping the genetic landscape of IgAN.[S44] These genetic observations are also entirely consistent with known secondary causes of IgAN, which include a range of gastrointestinal disorders, including inflammatory bowel disease and celiac disease.[S45]

Due to the increasing recognition of the role of the GALT, in particular the Peyer's patches, in the generation of pathogenic IgA, a novel, oral, targeted-release formulation of the glucocorticoid, budesonide was developed to release the drug in the Peyer's patch–rich distal ileum. An initial exploratory phase 2a trial of NEFECON in 16 patients with IgAN was performed and showed a statistically significant reduction



*NEFECON is an investigational treatment for IgAN and is not FDA approved

Figure 1. The Peyer's patch, mucosal IgA synthesis, IgA nephropathy (IgAN), and a role for NEFECON in the treatment of IgAN. The Peyer's patches are concentrated in the terminal ileum and are the major antigen sampling and inductive sites of the gut-associated lymphoid tissue (GALT). Antigens are taken up by specialized M cells in the follicle-associated epithelium overlaying the Peyer's patches. Subepithelial dome-resident dendritic cells (DCs) then take up and process these antigens, and after priming, naïve CD4+ T cells differentiate into helper T cells. T follicular helper (Tfh) cells interact with cognate B cells at the B cell follicular border. Next, Tfh cells colocalize with B cells in the B-cell follicle in close proximity to the follicular dendritic cell (FDC) network, and this allows the formation of a germinal center. In the germinal center, the antigen-specific B cells undergo class switching to IgA1 and somatic hypermutation to generate high-affinity antibodies. B-cell class switching to IgA1 is stimulated through T-cell CD40L binding to B-cell CD40, together with the action of transforming growth factor (TGF)-β. In parallel, T-independent IgA class switching may also occur, which involves dendritic cell activation of naïve B cells. Toll-like receptor (TLR) (continued)

in proteinuria.[S46] NEFECON was also well tolerated.[S46] A second phase 2b trial, the NEFIGAN trial, assessed the safety and efficacy of 2 different doses of NEFECON in patients who were at risk of progression to end-stage kidney disease due to persistent proteinuria despite optimized renin-angiotensin-aldosterone system blockade therapy.[S2] After 9 months of treatment, the urine protein-to-creatinine ratio was reduced by approximately 30% in the 16 mg NEFECON treatment group compared with placebo. In addition, the estimated glomerular filtration rate showed no deterioration in the 16 mg NEFECON group compared with a drop of 4.7 ml/min per 1.73 m^2 in the placebo group. The incidence of patients reporting adverse events was similar in all groups. These data led to the design of the ongoing phase 3 NefIgArd study (Supplementary Introduction).

NefIgArd is a randomized, double-blind, placebo-controlled phase 3 trial, composed of 2 parts (Supplementary Methods). Part A of the trial comprises a 15- to 35-day screening period, 9-month treatment, and a 3-month follow-up period. Part B contains a 12-month no-treatment follow-up period (see Supplemental Methods for full protocol). The study is recruiting 360 patients across 150 nephrology clinics in 20 countries (Supplementary Results). Patients must be at least 18 years old with biopsy-confirmed primary IgAN and persistent proteinuria >1 g/24 hours, and an estimated glomerular filtration rate of ≥35 and ≤90 ml/min per 1.73 m^2 despite optimized renin-angiotensin-aldosterone system blockade. Patients are randomized in a 1:1 ratio to 16 mg/day NEFECON or placebo, stratified by baseline 24-hour urine protein-to-creatinine ratio. The primary outcome of Part A is to assess the effect of NEFECON 16 mg treatment on 24-hour urine protein-to-creatinine ratio over 9 months compared with placebo. This is consistent with a recent article indicating that proteinuria reduction can be used as a surrogate endpoint in trials of IgAN.[3] The Part B primary outcome is based on data presented at the National Kidney Foundation/Food and Drug Administration/European Medicines Agency workshop in March 2018 that supported estimated glomerular filtration rate slope as an endpoint for full approval, and is to assess the effect of NEFECON 16 mg treatment on a 2-year estimated glomerular filtration rate–based endpoint compared with placebo.[S47] In comparison with other currently recruiting studies, it is expected that the relatively short period required to provide validation of the surrogacy of proteinuria reduction will significantly reduce the risks of non-protocol treatments and loss of patients from the study that could dilute the true treatment effect of the drug. In contrast to the earlier studies of NEFECON,[S2] NefIgArd is including Asian patients to expand the generalizability of the trial.

The NefIgArd study will be the largest commercially sponsored study ever completed in IgAN, and could provide us with the first specific disease-modifying therapy that works by downregulating the production of pathogenic IgA in the Peyer's patches of the GALT (Supplementary Discussion).

DISCLOSURE

JB is Chair of the Study Steering Committee for the NeflgArd trial. BHR, DC, JF, RL, VT, HZ, and HT are members of the Study Steering Committee for the NeflgArd trial.

ACKNOWLEDGMENTS

Medical writing assistance was provided by Chameleon Communications International Ltd. This article was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating

Figure 1. (continued) ligand-activated DCs secrete factors that induce IgA1 class switch, including B-cell–activating factor (BAFF), A proliferation-inducing ligand (APRIL), and TGF-β. The resulting IgA1+ long-lived plasma cells and memory B cells generated within the germinal center leave the Peyer's patch and migrate to the mesenteric lymph nodes and then to the blood, from where plasma cells home to effector sites in the lamina propria of the small and large intestine. In the lamina propria IgA1+ B cells may sequentially switch to IgA2 expression in response to APRIL and interleukin (IL)-10 released by TLR-activated epithelial cells. In the lamina propria, additional IgM+ IgD+ B cells can undergo direct class switching from IgM to IgA1 or IgA2 in response to BAFF or APRIL and IL-10. IgAN is associated with an increase in circulating mucosal-type IgA1, which is believed to be due to an underlying dysregulation in mucosal IgA synthesis. This results in an increase in circulating poorly *O*-galactosylated dimeric and polymeric IgA1, which results in the formation of large IgA1 immune complexes with a propensity to accumulate in the kidney and cause nephritis. Most IgA1 in the glomeruli does not contain a secretory component and, therefore, has not been secreted across a mucosal surface, even though evidence suggests it is derived from the GALT. Potential mechanisms for GALT-derived IgA1 to directly enter the circulation rather than being secreted are either direct passage of mucosally synthesised (but not secreted) IgA1 into the circulation and/or displacement of GALT-derived B cells to systemic sites such as the bone marrow, where they secrete mucosal-type IgA1 directly into the circulation. Immune complex formation may be amplified further by the formation of IgA and IgG anti-IgA autoantibodies. These autoantibodies are directed against the poorly *O*-galactosylated hinge region of the IgA1 molecule. NEFECON is designed to deliver a targeted dose of budesonide to the Peyer's patches of the terminal ileum, where it is hypothesized to reduce the formation of the IgA molecules that ultimately drive immune complex formation in IgAN. CD, cluster of differentiation; FDA, Food and Drug Administration; IgA-IC, IgA immune complex; IL, interleukin; M, microfold; SEM, scanning electron microscope.

Company-Sponsored Medical Research: The GPP3 Guidelines."

Trial Registrations: EudraCT number: 2017-004902-16; ClinicalTrials.gov identifier: NCT03643965

AUTHOR CONTRIBUTIONS

All authors were involved in the preparation, critical revision, and final approval of this editorial. All authors were involved in the decision to submit this editorial and will take public responsibility for all aspects of the publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Introduction.
Supplementary Methods.
Supplementary Results.
Supplementary Discussion.
Supplementary References.
Figure S1. NeflgArd trial design.

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