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IgA vasculitis (HSP) Jonathan Barratt and John Feehally ESSENTIALS Immunoglobulin A nephropathy (IgAN) is the commonest pattern of glomerulonephritis identified in areas of the world where renal biopsy is widely practised. It is defined pathologically by IgA depos- ition in the glomerular mesangium accompanied by a mesangial proliferative glomerulonephritis which may vary greatly in severity. Aetiology is uncertain, but abnormalities of IgA1 hinge-region O-glycosylation are consistently found. Clinical features—IgAN can present with (1) visible haematuria, typically in children and young adults, developing within a day or two of upper respiratory tract infection (‘synpharyngitic’); (2) asymptom- atic nonvisible haematuria/proteinuria; (3) nephrotic syndrome (<5% of cases); (4) acute kidney injury (uncommon); and (5) chronic renal failure with up to 25% of patients reaching endstage renal failure within 20 years of diagnosis. IgA vasculitis (HSP) is a small vessel systemic vasculitis characterized by small blood vessel deposition of IgA that predominantly affects the skin, joints, gut, and kidney, with nephritis that may be histologically indistinguishable from IgA nephropathy. Management—there is no treatment known to modify mesangial deposition

of IgA. Treatment options are mostly directed at con- trolling blood pressure and limiting proteinuria through blockade of the renin–angiotensin–aldosterone axis. In the rare patient pre- senting with acute kidney injury in whom biopsy shows crescentic IgA nephropathy, a regimen such as those used for renal vascu- litis and other forms of crescentic glomerulonephritis should be considered, for example, oral prednisolone in combination with cyclophosphamide. Introduction Immunoglobulin A nephropathy (IgAN) was first described by Berger in 1968 and at one time was known as Berger's disease. It is defined by IgA deposition in the glomerular mesangium accom- panied by a mesangial proliferative glomerulonephritis which may vary greatly in severity. Although recurrent visible haematuria is the hallmark of the disease, the old term 'benign recurrent haematuria' is a discredited misnomer since it is now clear that IgAN is associ- ated with a significant risk of progression to endstage renal failure. IgA vasculitis (HSP) is a somewhat misleading historical term: the purpuric rash is in fact a cutaneous vasculitis, and the renal lesion (HSP nephritis) is a mesangial proliferative glomerulonephritis usu- ally indistinguishable from IgAN. Aetiology In most cases the aetiology of IgAN remains unclear. The provo- cation of visible haematuria by mucosal infection in IgAN and the 21.8 Glomerular diseases

section 21 Disorders of the kidney and urinary tract 4910 presumption that the mesangial IgA represented deposited immune complexes led to the view that IgAN was a complication of infection. Cytomegalovirus and Haemophilus parainfluenzae have been most studied, but neither these nor any other viral or bacterial antigens have been consistently associated with development of the disease or identified in IgA immune complexes or mesangial deposits. Alternatively, it has been suggested that IgAN results from hyper- sensitivity to food antigens, in view of its association with gluten- sensitive enteropathy. There is some evidence that withdrawal of gluten from the diet of these specific patients may improve the renal disease, but there is little evidence for widespread hypersensitivity to food antigens in IgAN. Genetics Despite many studies of potential immunogenetic associations, the genetic basis for susceptibility to IgAN has not yet been identified. IgAN is familial in less than 10% of cases, but the true frequency of familial IgAN remains uncertain because there are no reliable serological markers for the disease. Four kindreds have been de- scribed in which IgAN appears to show Mendelian inheritance, in each case autosomal dominance with incomplete penetrance. The genetic linkage differs in each of the four kindreds, arguing strongly against any generalizability of these findings to spor- adic IgAN. Furthermore, study of the three novel loci (designated IGAN1, IGAN2, IGAN3) has identified no likely candidate genes. Only the 2q36 locus identified in the Canadian pedigree is poten- tially informative since it contains COL4A3 and COL4A4 genes coding for basement membrane collagen, mutations of which are associated with thin membrane nephropathy (see Chapter 21.8.2). Three independent genome-wide association studies in different populations with IgAN have also been reported, and a fourth meta-analysis incorporating the populations from all three pre- vious genome-wide association studies and including additional populations from both Europe and Asia. All have shown an en- richment of single nucleotide polymorphisms implicated in auto- immune or inflammatory traits (multiple alleles within the HLA region at chromosome 6p21 and chromosome 1q32 suggesting a role for complement regulatory proteins), and furthermore most loci associated with IgAN encode proteins implicated in mainten- ance of the intestinal barrier and regulation of mucosal immune response to pathogens. Pathogenesis Mechanism of mesangial IgA deposition Mesangial proliferative glomerulonephritis such as is seen in IgAN and HSP nephritis may be the consequence of immune complex deposition, either due to trapping of circulating IgA immune com- plexes or the formation of complexes in situ by reaction of IgA with antigen which has already been deposited.

No exogenous antigen has been consistently identified in the mesangial deposits in IgAN, which may indicate that the IgA complexes are a common re- sponse to different antigens, or that the initiating antigen has dis- appeared by the time of the renal biopsy. Alternatively, the IgA may be deposited by some mechanism independent of classic antigen– antibody interactions, such as a physicochemical abnormality of the IgA. The frequent recurrence of both IgAN and HSP nephritis after renal transplantation strongly suggests that the abnormality resides in the host IgA immune system. The mesangial IgA deposits are polymeric IgA1 (pIgA1). Most pIgA is synthesized in the mucosa and the clinical association of visible haematuria with mucosal in- fection originally led to the assumption that an exaggerated mucosal IgA response resulted in mesangial IgA deposition. But IgA produc- tion is in fact down-regulated in the mucosal immune system and up-regulated in the bone marrow, and exaggerated IgA1 responses to immunization in these patients are marrow rather than mucosally derived. There is increasing evidence of under-galactosylation of both serum and mesangial IgA1 in patients with IgAN and HSP neph- ritis. Changes in the O-glycan composition of circulating IgA1 may favour the development of immune complexes or may directly pro- voke mesangial deposition. Data suggest that poorly galactosylated IgA1 O-glycoforms might in fact act either as autoantigens driving the formation of glycan-specific autoantibodies, or antigens for cross-reactive antimicrobial antibodies. The resultant formation of IgA:IgG immune complexes appears pivotal to the pathogenesis of IgAN and there is strong in vitro data to support their role in activa- tion of mesangial cells, induction of podocyte injury, and activation of proximal tubular epithelial cells. Progression of IgA nephropathy IgA deposition may occur in many patients with mild disease with little mesangial injury. What decides the prognosis in any individual is the extent to which the IgA deposition is followed by mesangial proliferation, inflammation, and scarring. There is nothing to suggest that these subsequent mechanisms of damage and scar- ring are unique to IgAN, rather they are generic to many forms of glomerulonephritis. Relationship of IgAN and HSP There is much indirect evidence to suggest a close relationship be- tween IgAN and HSP. Monozygotic twins have been described, one who developed IgAN and the other HSP at the same time. HSP developing on a background of proven IgAN has been described in both adults and children. Many abnormalities of the IgA im- mune system, including abnormal IgA1 glycosylation, have been described in both IgAN and HSP. IgAN is increasingly thought of as ‘HSP without the rash’. Why some individuals get a renal-limited disease (IgAN) and others a systemic disease (HSP) is not known. Pathology Immune deposits IgAN and HSP nephritis are defined by the presence of mesangial IgA detected by immunofluorescence or immunoperoxidase (Fig. 21.8.1.1). Complement C3 frequently accompanies IgA in the same mesangial distribution; IgG and IgM are less common. Electron microscopy identifies mesangial electron-dense deposits corresponding to the mesangial IgA (Fig. 21.8.1.2).

21.8.1 Immunoglobulin A nephropathy and IgA vasculitis (HSP) 4911 Light microscopy Mesangial proliferative glomerulonephritis is the characteristic ap- pearance, although when haematuria is the only clinical finding abnormalities on light microscopy may be minimal despite florid IgA deposition. Mesangial hypercellularity and matrix expansion are usually global (Fig. 21.8.1.3a) but may be focal and segmental (Figs. 21.8.1.3b and 21.8.1.3c). The hypercellularity is followed by increasing mesangial matrix deposition and eventual sclerosis (Fig. 21.8.1.3b). In acute kidney injury there may be severe glom- erular inflammation with crescent formation. In advanced cases there is glomerulosclerosis and corresponding tubular atrophy and interstitial fibrosis; these are entirely nonspecific changes of ‘endstage kidney’. A number of histological scoring systems have been devised to evaluate the renal biopsy appearances of IgAN. Of these the most extensively

evaluated is the Oxford Classification of IgAN. In the recently updated classification, five variables—(1) the mesangial hypercellularity score, (2) segmental glomerulosclerosis, (3) endocapillary hypercellularity, (4) tubular atrophy/interstitial fibrosis, and (5) presence of crescents—were shown to have inde- pendent value in predicting renal outcome. Epidemiology IgAN is the commonest glomerulonephritis in countries where renal biopsy is widely used. It is typically found in 30% of biopsies Fig. 21.8.1.1 Immunofluorescence of a glomerulus in IgAN. Bright fluorescent staining is seen within the mesangium with labelled antibodies to IgA. In some cases similar staining is also seen along capillary walls. A similar distribution of staining for C3 is commonly present. Antihuman IgA, magnification ×375. Fig. 21.8.1.2 Electron micrograph of glomerular capillary loop in IgAN. Numerous electron-dense deposits representing deposits of IgA (large arrows) are seen within the expanded mesangium. BM, basement membrane; BS, Bowman's space; C, capillary lumen; En, fenestrated endothelium; Ep, visceral epithelium; MC, mesangial cell nucleus. Magnification ×5200. (a) (b) (c) Fig. 21.8.1.3 Light microscopic appearances of IgA nephropathy. (a) Glomerulus showing global increase in mesangial matrix and cellularity. Alcian blue/PAS stain, magnification ×375. (b) Glomerulus showing segmental increase in mesangial matrix and hypercellularity with fibrinoid necrosis (solid arrow) and synechia formation (open arrow) between the segmental lesion and parietal epithelium of Bowman's capsule. Alcian blue/PAS stain, magnification ×375. (c) Glomerulus showing segmental increase in mesangial matrix and segmental sclerosis with synechia formation (open arrows) overlying Bowman's capsule. Masson's trichrome stain, magnification ×375.

section 21 Disorders of the kidney and urinary tract 4912 with primary glomerular disease, but the apparent prevalence varies markedly around the world. It is commoner in the Pacific rim and Mediterranean countries, and less so in North America and northern Europe. At least part of this apparent difference is ex- plained by the varying use of urine testing in health screening and varying attitudes to the value of renal biopsy in individuals with isolated haematuria or other minor clinical evidence of renal dis- ease. For example, in Japan there is routine urine testing of school-children and employed adults, the threshold for renal biopsy is low, and the reported prevalence of IgAN is high. There are also important racial differences in susceptibility. IgAN is uncommon in Afro-Caribbean people and also less common in Polynesian people than white people in Australasia, a particularly striking finding given the exaggerated susceptibility of Polynesian people to most forms of renal disease. Clinical features IgAN IgAN can occur at any age, but the peak age of onset is in the second and third decades of life (Fig. 21.8.1.4). In western Europe, IgAN is three times more common in males than females, but this sex differ- ence disappears in the Pacific Rim.
Visible haematuria The characteristic clinical picture of recurrent visible haema- turia occurs in about 40 to 50% of cases. A child or young adult develops episodes of painless visible haematuria occurring within a day or so of the onset of an upper respiratory tract infection, or occasionally infections of other mucosal or IgA-se- creting surfaces such as gastrointestinal tract, bladder, or breast. The urine may be frankly bloody, but more often is brown (like Coca- Cola or tea without milk), there are no clots passed, and it is usually painless although there may be dull loin ache. The episodes settle spontaneously after 1 to 5 days and may be recurrent, but rarely for more than a year or two. Serum IgA is moderately elevated in 30% of cases, but serum complement C3 and C4 are normal. Between episodes there will be persistent nonvisible haematuria. This pres- entation does not occur beyond the age of 40 years (Fig. 21.8.1.4). Asymptomatic haematuria/proteinuria About 30 to 40% of cases of IgAN are identified by urine testing, when nonvisible haematuria may be combined with proteinuria (usually <2 g/24 h). Since this is glomerular haematuria, dysmorphic

red cells may be seen on phase contrast microscopy, but red cell casts are frequently absent in mild disease. Nephrotic syndrome Nephrotic syndrome is the presentation in only 5% of IgAN. Very occasionally in children or young adults this appears to be the con- sequence of coincidental minimal-change nephrotic disease; the proteinuria resolves completely with corticosteroid therapy, but haematuria and IgA deposits persist. More commonly nephrotic syndrome may develop in IgAN with overt mesangial proliferative glomerulonephritis, or may be a consequence of glomerular scar- ring in advanced IgAN. Acute kidney injury Acute kidney injury occurs for two reasons in IgAN. Episodes of macroscopic haematuria may produce acute tubular occlusion by red cells in the face of minor glomerular injury. Alternatively, there can be acute severe necrotizing glomerulonephritis with crescent formation, ‘crescentic IgA nephropathy’, which may be the presenting feature or occur on a background of known milder disease. Chronic kidney disease IgAN may also present with hypertension and established renal impairment, often in older patients (Fig. 21.8.1.4). Too little is yet known about the pathogenesis of IgAN to understand whether this is a distinct disease entity or the same disease presenting much later because there was never an episode of visible haematuria or a urine test to bring it to medical attention earlier. Clinical associations with IgAN The commonest secondary cause of IgAN is chronic liver disease, typically alcoholic liver disease, in which it is probable that IgA deposition is a consequence of impaired IgA clearance from the circulation via the liver. Most hepatic IgAN is asymptomatic, and progression to endstage renal failure is unusual. The other best established associations are with coeliac disease and dermatitis 10 20 30 Age (years) Number of cases 40 50 60 70 80 IgA vasculitis (HSP) Asymptomatic urine abnormality Nephrotic syndrome Chronic kidney disease Visible haematuria Fig. 21.8.1.4 Clinical presentations of IgAN and HSP in relation to age at diagnosis. HSP is most common in childhood but may occur at any age. Visible haematuria is very rare over the age of 40 years. The importance of asymptomatic urine abnormality as the presentation of IgAN will depend on attitudes to routine urine testing and renal biopsy. It is uncertain whether those presenting with chronic kidney disease have a disease distinct from that of those presenting younger with visible haematuria.

 herpetiformis; with rheumatoid arthritis, ankylosing spondylitis, and Reiter’s disease; and with HIV infection. Many other condi- tions have been reported occasionally with IgAN, but since IgAN is so common it is difficult to know if these are more than chance associations. HSP nephritis HSP can occur at any age but is commonest in the first decade of life (Fig. 21.8.1.4). There is a slight male preponderance. A palp- able purpuric rash caused by cutaneous vasculitis is the presenting feature. It has a characteristic extensor surface distribution with sparing of the trunk and face (Fig. 21.8.1.5). Crops of rash, often provoked by intercurrent infection, may continue for some time, but rarely beyond a year from first presentation. Polyarthralgia is common. Abdominal pain, due to gut vasculitis, is usually mild and transient, but severe pain and bloody diarrhoea may develop due to intussusception. Apart from intussusception, the major sequelae of HSP come from renal involvement. Much of the renal disease in HSP is tran- sient, with asymptomatic haematuria or proteinuria disappearing in a few weeks. Of those with persistent evidence of renal disease, asymptomatic haematuria/proteinuria is the commonest clinical state, but 20% will have nephrotic syndrome. Serum IgA is raised in 50%, but complement C3 and C4 are normal. Acute kidney in- jury due to crescentic HSP nephritis usually occurs early and is com- moner than crescentic IgAN. Differential diagnosis Visible haematuria Nonglomerular causes of haematuria, including renal stones and neoplasia, must always be considered and excluded where appro- priate by urological investigation. While episodic visible haema- turia coinciding with upper respiratory tract infection in

children and young adults is the hallmark of IgAN, it is not pathognomonic. Similar episodes can occur with other glomerular diseases, most commonly hereditary nephropathies such as Alport's syndrome and thin membrane nephropathy. The distinction of IgAN from postinfectious (usually poststreptococcal) glomerulonephritis is also important. In poststreptococcal glomerulonephritis there is a 10- to 14-day latency from the onset of infection and the devel- opment of symptomatic renal disease, contrasting with the imme- diacy of haematuria in IgAN, for which the term 'synpharyngitic haematuria' has been coined. The haematuria is usually less heavy in poststreptococcal glomerulonephritis so that the urine is typ- ically smoky rather than frankly bloody; hypertension, oedema, and other features of the acute nephritic syndrome are usually present. Serological evidence of recent streptococcal infection (such as antibodies to endostreptosin) and low C3 are not found in IgAN. Nephrotic syndrome The differential diagnosis when IgAN presents with nephrotic syn- drome includes the usual range of glomerular disease known to cause nephrotic syndrome given the age of the patient. Chronic kidney disease Advanced IgAN presenting with hypertension, proteinuria, and renal impairment is clinically indistinguishable from many other causes of chronic progressive renal disease. Renal biopsy can estab- lish the diagnosis since mesangial IgA can often still be identified even when light microscopy shows 'endstage kidney', but should only be performed if there is a reasonable expectation that the result might benefit the particular patient. HSP In children, HSP is the commonest form of vasculitis, and a clinical diagnosis is often made from the characteristic rash and abdom- inal pain. In adults, the differential diagnosis is wider, including many other forms of small vessel vasculitis which must be distin- guished on the basis of clinical, serological, and histopathological findings.
Clinical investigation No accumulation of clinical and laboratory evidence has suffi- cient specificity and sensitivity to avoid the need for diagnostic biopsy in IgAN or HSP. IgA deposits are seen in blood vessels in affected skin, but this is not a universal feature. Raised serum IgA1 levels are found in 30 to 50% of all patients, but are less common in children and do not correlate with disease activity or severity. A high proportion of λ light chain, rather than the normal predominance of the κ isotype, is also a distinctive fea- ture of serum IgA in IgAN, although the significance of this is unknown. Complement components C3 and C4, and CH50 in the serum, are usually normal, but there is some evidence of systemic complement activation with more specific testing. Circulating autoantibodies to the IgA1 hinge region glycans, IgA rheumatoid factors, and IgA-containing circulating immune complexes have been reported by many different assay methods, but they are not currently diagnostically useful, nor can they be reliably correlated with disease activity. Fig. 21.8.1.5 Characteristic purpuric rash affecting the lower limbs in HSP.

 Secondary causes of IgAN must be identified. A thorough history and physical examination, along with laboratory checks for liver function and hepatitis B status are sufficient to exclude the common secondary associations with IgAN. Criteria for diagnosis IgAN By definition, the diagnosis of IgAN requires a renal biopsy; no sero- logical or other laboratory indices provide diagnostic information reliable enough to avoid the need for biopsy. HSP While the distribution of the vasculitic rash may be highly suggestive in HSP, ultimate confirmation requires identification of tissue IgA deposition which can be found in the vessels of affected skin as well as the kidney. Treatment IgAN The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) treatment guidelines for IgAN are summarized in Table 21.8.1.1. Only in very few patients with IgAN is there any evidence that drug therapy alters the natural history of the disease. Despite being so common among renal diseases, there is still a dearth of well- conducted

prospective randomized controlled trials in IgAN on which to base therapeutic decisions. Specific treatment for IgAN would either restrict the forma- tion of relevant pathogenic IgA molecules or prevent their depos- ition in the mesangium. However, so little is understood about the pathogenesis of the disease that the prospect for such treatment is still remote. Haematuria There is no specific treatment for the great majority of patients with IgAN who have isolated haematuria with or without low-grade proteinuria (<1 g/24 h). Nonvisible haematuria should merely be observed. Recurrent visible haematuria settles without treatment; there is no role for prophylactic antibiotics as most precipitating in- fections are viral. Tonsillectomy will reduce the number of episodes of visible haematuria, but there is no evidence that it reduces the risk of progressive renal failure. Proteinuria Those with proteinuria above 1 g/24 h as well as haematuria have a worse prognosis. Immunosuppressive therapies have been tried, although the frequent recurrence of IgAN in transplanted kidneys when patients are receiving immunosuppressive therapy argues against their value. Short-term randomized controlled trials of cor- ticosteroids have shown no benefit. A controlled trial of 6 months of treatment with corticosteroids (prednisolone 0.5 mg/kg per day) showed a significant reduction in proteinuria and reduced risk of developing renal impairment at 10 years' follow-up. This requires further confirmation, and corticosteroid treatment is not presently recommended except in the rare circumstance where the biopsy suggests coincidental minimal-change nephrotic syndrome which may be fully steroid responsive. Other immune modulating drugs have been tried in IgAN, including cyclophosphamide, mycophenolate mofetil, azathioprine, ciclosporin, and pooled human intravenous im- munoglobulin, but there are few properly controlled studies and for none is there consistent evidence of benefit or an acceptable risk–benefit ratio in most patients who have indolent slowly pro- gressive disease. There are a number of well-designed, placebo-controlled, double- blinded randomized controlled trials examining the efficacy of a variety of novel therapies in IgAN underway or nearing formal re- porting (Table 21.8.1.2). Table 21.8.1.1 Current recommendations for the treatment of IgAN Clinical feature Recommendation Visible haematuria No treatment Nonvisible haematuria No treatment—no indication for prophylactic antibiotics or tonsillectomy Acute kidney injury Biopsy Tubular occlusion Supportive treatment only Crescentic IgAN Prednisolone 0.5 mg/kg per day, reducing to 5–10 mg daily by 3 months Cyclophosphamide 2–3 mg/kg per day for 3 months, followed by azathioprine 2–3 mg/kg per day Proteinuria <1 g/24 h No treatment Nephrotic syndrome with minimal change on biopsy Prednisolone 0.5 mg/kg per day for 8–12 weeks All other proteinuria >1 g/24 h ACE inhibitor and ARB Hypertension Target BP 125/75 mmHg if proteinuria >1 g/24 h, otherwise target BP 130/80 mmHg, using regimen including ACE inhibitor and ARB Proteinuria >1 g/24h and GFR >50 ml/min per 1.73 m2 despite maximal ACE inhibitor/ARB and BP control Consider immunosuppression or enrolment in a randomized controlled trial (see Table 21.8.1.2) ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; GFR, glomerular filtration rate.

 Acute kidney injury Renal biopsy is mandatory when acute kidney injury develops in IgAN. If this shows mild glomerular disease but tubular occlusion with erythrocytes and accompanying acute tubular necrosis, sup- portive treatment only is required while recovery is awaited. If there is crescentic IgAN, a regimen such as those used for renal vascu- litis and other forms of crescentic glomerulonephritis should be considered unless the histological appearances are thought to be advanced and irreversible, for example, oral prednisolone 0.5 mg/ kg per day (reducing to a maintenance dose of 5–10 mg daily by Table 21.8.1.2 Clinical trials of novel/repurposed drugs in IgAN underway or nearing formal

reporting Trial Intervention Inclusion criteria Exclusion criteria Trial design Primary end point Follow-up duration Atacicept NCT02808429 Atacicept at varying doses vs placebo Proteinuria 1–6 g/day Stabilized on RASi for 8 weeks Prior cyclophosphamide treatment Use of other immuno-suppressants within 4 months Randomized, double-blind, placebo-controlled Phase II trial Incidence of adverse events 180 weeks BRIGHT-SC NCT02062684 Blisibimod vs placebo Proteinuria 1–6 g/day Stabilized on RASi for 8 weeks Immunosuppressant use over last 6 months or corticosteroid use over last 3 months. Malignancy over last 5 years Randomized, double-blind, placebo-controlled Phase II/III trial Reduction of proteinuria at 24 weeks 104 weeks SIGN NCT02112838 Fostamatinib at varying doses vs placebo Stabilized on RASi for 90 days. BP < 130/80 Proteinuria > 1 g/day at diagnosis and > 0.5 g/day at second screening visit Recent use of corticosteroids, cyclophosphamide, mycophenolate mofetil, azathioprine or rituximab Randomized, multicentre, double-blind, placebo- controlled, Phase II trial Reduction of proteinuria at 24 weeks 24 weeks VELCADE NCT01103778 Bortezomib Proteinuria > 1 g/day Stabilized on RASi for 4 weeks Peripheral neuropathy, history of cardiac problems, malignancy within last 3 years Open-label, Phase IV trial Reduction of proteinuria at 1 year 1 year ACTHAR NCT02282930 Acthar gel Proteinuria > 1 g/day Stabilized on RASi for 3 months BP > 130/80 HSP patients included Crohn’s disease or celiac sprue Glucocorticoid treat- ment in last 3 months Immunosuppressive therapy in last 6 months Previous ACTH treatment History of malignancy History of cardiac or pulmonary disease Open-label, Phase III trial Reduction in proteinuria at 1 year, stabilization of eGFR at 1 year 1 year OMS721 NCT02682407 OMS721 vs placebo Patients on immuno- suppressive patients in- cluded, if on stable dose for 2 months Optimized RASi, BP < 150/90, Urine ACR > 600 mg/g Renal transplant History of malignancy Use of belimumab, rituximab, or eculizumab within last 6 months HSP within 2 years Randomized, double-blind, placebo- controlled, Phase II trial Incidence of adverse events 18 weeks LNP023 NCT03373461 LNP023 vs placebo Stabilized on RASi for 90 days eGFR ≥ 30, pro- teinuria ≥ 0.75 g/ day Recent use of immunosuppression, history of drug/alcohol abuse, malignancy Randomized, double-blind, placebo-controlled Phase IIa/IIb trial Reduction of proteinuria at 90 days 180 Days Cemdisiran NCT03841448 Cemdisiran vs placebo Stabilized on RASi for 90 days eGFR ≥ 30, proteinuria ≥ 1 g/day Recent use of immunosuppression, history of drug/alcohol abuse, malignancy Randomized, double-blind, placebo-controlled Phase IIa/IIb trial Reduction of proteinuria at week 32 952 Days Sparsentan NCT03762850 Sparsentan vs Irebsartan Stabilized on RASi for 12 weeks eGFR ≥ 30, proteinuria ≥ 1 g/day Recent use of immunosuppression, history of drug/alcohol abuse, malignancy Randomized, double-blind, controlled Phase III trial Reduction of proteinuria at week 36 798 Days Nefecon NCT03643965 Nefecon vs placebo Stabilized on RASi for 90 days eGFR ≥ 45, proteinuria ≥ 1 g/day Recent use of immunosuppression, history of drug/alcohol abuse, malignancy Randomized, double-blind, placebo-controlled Phase III trial Reduction of proteinuria at 9 months 2190 Days

 3 months) in combination with oral cyclophosphamide 2 to 3 mg/kg per day (replaced by azathioprine 2–3 mg/kg per day after 3 months). Plasma exchange has also been used. There are no randomized con- trolled trials of these treatments in crescentic IgAN. Although the initial response to treatment is excellent, the medium-term outlook is much less good; 50% will be on long-term dialysis after 12 months. Progressive renal impairment Slowly progressive renal impairment due to IgAN requires a management approach common to any form of chronic renal failure. Rigorous control of blood pressure is the one established method of delaying progressive renal failure. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are widely used as first-line

therapy for their special role in lessening proteinuria for the same degree of blood pres- sure control. Fish oil therapy (which provides a supplement of ω-3 fatty acids) has effects likely to impact favourably on mech- anisms of progressive renal damage and has been used in ran- domized controlled trials in IgAN, but there is no reason to expect its effects are specific for IgAN rather than other pro- gressive diseases. One randomized controlled trial has shown a substantial reduction in the risk of progression to endstage renal failure, but other studies have not shown comparable benefit and at present the use of fish oil is not recommended until confirma- tory studies are available. HSP nephritis There is very little information to guide treatment of HSP neph- ritis. There are no published randomized controlled trials and most therapeutic studies in IgAN exclude those with HSP, hence it is un- clear whether their conclusions can be extrapolated to HSP. Transient early nephritis requires no specific treatment. There is no evidence that corticosteroids or other immunosuppressive re- gimens alter the natural history of nephrotic syndrome or slowly progressive glomerular damage in HSP. Crescentic HSP nephritis is more common than crescentic IgAN. Regimens used for renal vas- culitis have also been applied to crescentic HSP nephritis with ap- parent benefit, although there are no controlled trials. Prognosis Thirty per cent of children will have a spontaneous clinical remis- sion with complete disappearance of haematuria within 10 years of diagnosis. But IgAN, despite the apparently benign presentation in many cases, is an important cause of endstage renal failure, with up to 25% of patients reaching this within 20 years of diagnosis. Where a lower risk of endstage renal failure is reported, the series will con- tain larger numbers of patients with mild disease, such as those with isolated nonvisible haematuria. Perhaps unexpectedly, a history of episodic visible haematuria is a favourable prognostic feature. The prognosis for patients who present with microscopic haematuria and minimal proteinuria (<1 g/24 h) is very good, but not perfect; even in this group up to 5% of patients will develop worsening proteinuria and hypertension during follow- up and are at eventual risk of endstage renal failure. Consequently, the long-term follow-up of any patient with biopsy-proven IgAN is mandatory. The risk of progressive renal failure can be predicted by clinical and pathological features at diagnosis (Table 21.8.1.3). Both IgAN and HSP nephritis recur after renal transplantation. Mesangial IgA deposits appear within a few months in 60% of pa- tients with IgAN. Initially this is benign, accompanied by little mesangial injury, but in the long term, recurrent disease will con- tribute to progressive graft loss in a number of patients. However, overall transplant success and graft longevity do not differ in IgAN or HSP from other primary renal diseases. The changes in im- munosuppressive regimens used to prevent rejection over the last two decades have not altered the recurrence rate or its prognosis. FURTHER READING Clinical Barbour SJ, et al. (2019). Evaluating a New International Risk- Prediction Tool in IgA Nephropathy. JAMA Intern Med, doi: 10.1001/jamainternmed.2019.0600. D’Amico G (2004). Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol, 24, 179–96. Davin JC, Ten Berge IJ, Weening JJ (2001). What is the difference be- tween IgA nephropathy and Henoch–Schönlein purpura nephritis? Kidney Int, 59, 823–34. Floege J (2004). Recurrent IgA nephropathy after renal transplant- ation. Semin Nephrol, 24, 287–91. Pouria S, Feehally J (1999). Glomerular IgA deposition in liver disease. Nephrol Dial Transplant, 14, 2279–82. Table 21.8.1.3 Variables included in the IgA nephropathy risk prediction score eGFR at biopsy MAP at biopsy Proteinuria at biopsy Histology: ● M1 ● E1 ● S1 ● T1 ● T2 ● Crescents Age Race: ● Chinese ● Japanese ● Caucasian RASB at biopsy (Immunosuppression use after biopsy) Source data from Barbour SJ, Coppo R, Zhang H, et al. Evaluating a New International Risk-Prediction Tool in IgA Nephropathy, JAMA Intern Med. 2019 Apr 13. doi: 10.1001/ jamainternmed.2019.0600. [Epub ahead of print] PMID: 30980653.

21.8.1 Immunoglobulin A nephropathy and IgA vasculitis (HSP) 4917 Trimarchi H, et al. (2017). Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int, 91(5), 1014–21. doi: 10.1016/j.kint.2017.02.003. Wyatt RJ, Julian BA (2013). IgA nephropathy. N Engl J Med, 368, 2402–14. Yeo SC, Goh SM, Barratt J (2019). Is IgA Nephropathy Different in Different Ethnic Populations? Nephrology (Carlton). doi: 10.1111/nep.13592. Pathogenesis and genetics Barratt J, Feehally J (2011). Primary IgA nephropathy: new insights into pathogenesis. Semin Nephrol, 31, 349–60. Coppo R, Amore A (2004). Aberrant glycosylation in IgA nephropathy (IgAN). Kidney Int, 65, 1544–7. Gale DP, et al. (2017). Galactosylation of IgA1 Is Associated with Common Variation in C1GALT1. J Am Soc Nephrol, 28(7), 2158–66. doi: 10.1681/ASN.2016091043. Gharavi AG, et al. (2000). IgA nephropathy, the most common
cause of glomerulonephritis, is linked to 6q22–23. Nat Genet, 26, 354–7. Gharavi AG, et al. (2008). Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. J Am Soc Nephrol, 19, 1008–14. Hastings MC, et al. (2010). Galactose-deficient IgA1 in African Americans with IgA nephropathy: serum levels and heritability. Clin J Am Soc Nephrol, 5, 2069–74. Hsu SI, et al. (2000). Evidence for genetic factors in the devel- opment and progression of IgA nephropathy. Kidney Int, 57, 1818–35. Li M, Yu XQ (2018). Genetic Determinants of IgA Nephropathy: Eastern Perspective. Semin Nephrol, 38(5), 455–60. doi: 10.1016/j. semnephrol.2018.05.015. Lin X, et al. (2009). Aberrant galactosylation of IgA1 is involved in the genetic susceptibility of Chinese patients with IgA nephropathy. Nephrol Dial Transplant, 24, 3372–55. López-Mejías R, et al. (2018). Genetics of immunoglobulin-A vascu- litis (Henoch-Schönlein purpura): An updated review. Autoimmun Rev, 17(3), 301–15. doi: 10.1016/j.autrev.2017.11.024. Neugut YD, Kiryluk K (2018). Genetic Determinants of IgA Nephropathy: Western Perspective. Semin Nephrol, 38(5), 443–54. doi: 10.1016/j.semnephrol.2018.05.014. Novak J, Barratt J, Julian BA, Renfrow MB (2018). Aberrant Glycosylation of the IgA1 Molecule in IgA Nephropathy. Semin Nephrol, 38(5), 461–76. doi: 10.1016/j.semnephrol.2018.05.016. Suzuki H, et al. (2009). Aberrantly glycosylated IgA1 in IgA nephrop- athy patients is recognized by IgG antibodies with restricted hetero- geneity. J Clin Invest, 119, 1668–77. Yeo SC, Cheung CK, Barratt J (2018). New insights into the patho- genesis of IgA nephropathy. Pediatr Nephrol, 33(5), 763–77. doi: 10.1007/s00467-017-3699-z. Treatment Appel GB, Waldman M (2006). The IgA nephropathy treatment di- lemma. Kidney Int, 69, 1939–44. Audemard-Verger A, et al. (2017). Characteristics and Management of IgA Vasculitis (Henoch-Schönlein) in Adults: Data From 260 Patients Included in a French Multicenter Retrospective Survey. Arthritis Rheumatol, 69(9), 1862–70. doi: 10.1002/art.40178. Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B (2015). IgA vasculitis (Henoch-Shönlein purpura) in adults: Diagnostic and therapeutic aspects. Autoimmun Rev, 14(7), 579–85. doi: 10.1016/j.autrev.2015.02.003. Barratt J, Feehally J (2006). Treatment of IgA nephropathy. Kidney Int, 69, 1934–8. Cattran DC, et al. (2009). The Oxford classification of IgA nephrop- athy: rationale, clinicopathological correlations, and classification. Kidney Int, 76, 534–45. Donadio JV Jr, et al. (1999). The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. Mayo Nephrology Collaborative Group. J Am Soc Nephrol, 10, 1772–7. Floege J (2006). Is mycophenolate mofetil an effective treatment for persistent proteinuria in patients with IgA nephropathy? Nat Clin Pract Nephrol, 2, 16–17. Floege J, et al. (2019). Management and treatment of glomerular dis- eases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int, 95(2), 268–80. doi: 10.1016/j.kint.2018.10.018. Gharavi AG, et al. (2008). Aberrant IgA1 glycosylation is inherited in fa- milial and sporadic IgA nephropathy. J Am Soc Nephrol, 19, 1008–14. Hastings MC, et al. (2010). Galactose-deficient IgA1 in African Americans with IgA nephropathy: serum levels and heritability. Clin J Am Soc Nephrol, 5,

2069–74. Hou JH, et al. (2017). Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial. Am J Kidney Dis, 69(6), 788–95. doi: 10.1053/j.ajkd.2016.11.027. Lin X, et al. (2009). Aberrant galactosylation of IgA1 is involved in the genetic susceptibility of Chinese patients with IgA nephropathy. Nephrol Dial Transplant, 24, 3372–5. Lv J, et al. (2017). Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA, 318(5), 432–42. doi: 10.1001/ jama.2017.9362. Pozzi C, et al. (2004). Corticosteroid effectiveness in IgA nephrop- athy: long-term results of a randomized, controlled trial. J Am Soc Nephrol, 15, 157–63. Rauen T, et al. (2015). Intensive Supportive Care plus Immuno suppression in IgA Nephropathy. N Engl J Med, 373(23), 2225–36. doi: 10.1056/NEJMoa1415463. Rauen T, et al. (2018). Effects of Two Immunosuppressive Treatment Protocols for IgA Nephropathy. J Am Soc Nephrol, 29(1), 317–25. doi: 10.1681/ASN.2017060713. Samuels JA, et al. (2004). Immunosuppressive treatments for immuno- globulin A nephropathy: a meta-analysis of randomized controlled trials. Nephrology, 9, 177–85. Suzuki H, et al. (2009). Aberrantly glycosylated IgA1 in IgA nephrop- athy patients is recognized by IgG antibodies with restricted hetero- geneity. J Clin Invest, 119, 1668–77. Tumlin JA, Hennigar RA (2004). Clinical presentation, natural history, and treatment of crescentic proliferative IgA nephropathy. Semin Nephrol, 24, 256–68. Yeo SC, Liew A, Barratt J (2015). Emerging therapies in IgA nephrop- athy. Nephrology (Carlton), 20, 788–800.

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