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Why, when and how should immunosuppressive therapy considered in patients with immunoglobulin A nephropathy?

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Summary

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Lifelong mesangial deposition of IgA1 complexes subsist inflammation and nephron loss, but the complex pathogenesis in detail remains unclear. In regard to the heterogeneous course, classical immunosuppressive and specific therapeutic regimens adapted to the loss of renal function will here be discussed in addition to the essential common renal supportive therapy. Renal supportive therapy alleviates secondary, surrogate effects or sequelae on renal function and proteinuria of high intraglomerular pressure and subsequent nephrosclerosis by inhibition of the renin angiotensin system (RAASB). In patients with physiological (ΔGFR $<$ 1·5 ml/min/year) or mild (ΔGFR 1·5–5 ml/min/year) decrease of renal function and proteinuric forms ($>$ 1 g/day after RAASB), corticosteroids have shown a reduction of proteinuria and might protect further loss of renal function. In patients with progressive loss of renal function (ΔGFR $>$ 3 ml/min within 3 months) or a rapidly progressive course with or without crescents in renal biopsy, cyclophosphamide with high-dose corticosteroids as induction therapy and azathioprine maintenance has proved effective in one randomized controlled study of a homogeneous cohort in loss of renal function (ΔGFR). Mycophenolic acid provided further maintenance in non-randomized trials. Differentiated, precise, larger, randomized, placebo-controlled studies focused on the loss of renal function in the heterogeneous forms of IgAN are still lacking. Prospectively, fewer toxic agents will be necessary in the treatment of IgAN.

Keywords: IgA nephropathy, cyclophosphamide, mycophenolic acid, corticosteroids, high dose intravenous immunoglobulines

Introduction

Pathogenesis of the primary, idiopathic mesangioproliferative Immunoglobulin a nephropathy – Morbus Berger

In the early 1960s, Berger and Hinglais first described the entity of mesangial immunoglobulin (Ig)A deposits by immunofluorescence, frequently in concordance with IgG and complement factor 3 (C3) [1]. They established the technique of immunofluorescence microscopy as a standard in renal histopathology. Primary or idiopathic IgA nephropathy (IgAN) – Morbus Berger – is the most common form of primary glomerulonephritis worldwide with heterogeneous outcome, and at least 30% of affected patients have a progressive clinical course with loss of renal function after 10–20 years [2].

During the last 50 years there has been an extensive, unresolved discussion concerning the origin and the formation of the polymeric IgA1 immune complexes, in particular, and the mechanism of mesangial deposition on a cellular and humoral basis (pIgA; IgA-IC) (Fig. 1, Table 1). Aberrant glycosylation is the main characteristic of these mesangial IgA-immune complexes with poor galactosylated pIgA1 [15]. Disease progression might be associated with the amount of aberrant IgA1 [16] and circulating autoantibodies [17–20]. A mucosal origin was proposed by the polymeric structure, presence of IgA1 and the J secretory component in the pathogenic inflammatory mesangial IgA-IC. Hence, systemic IgA is monomeric and mainly

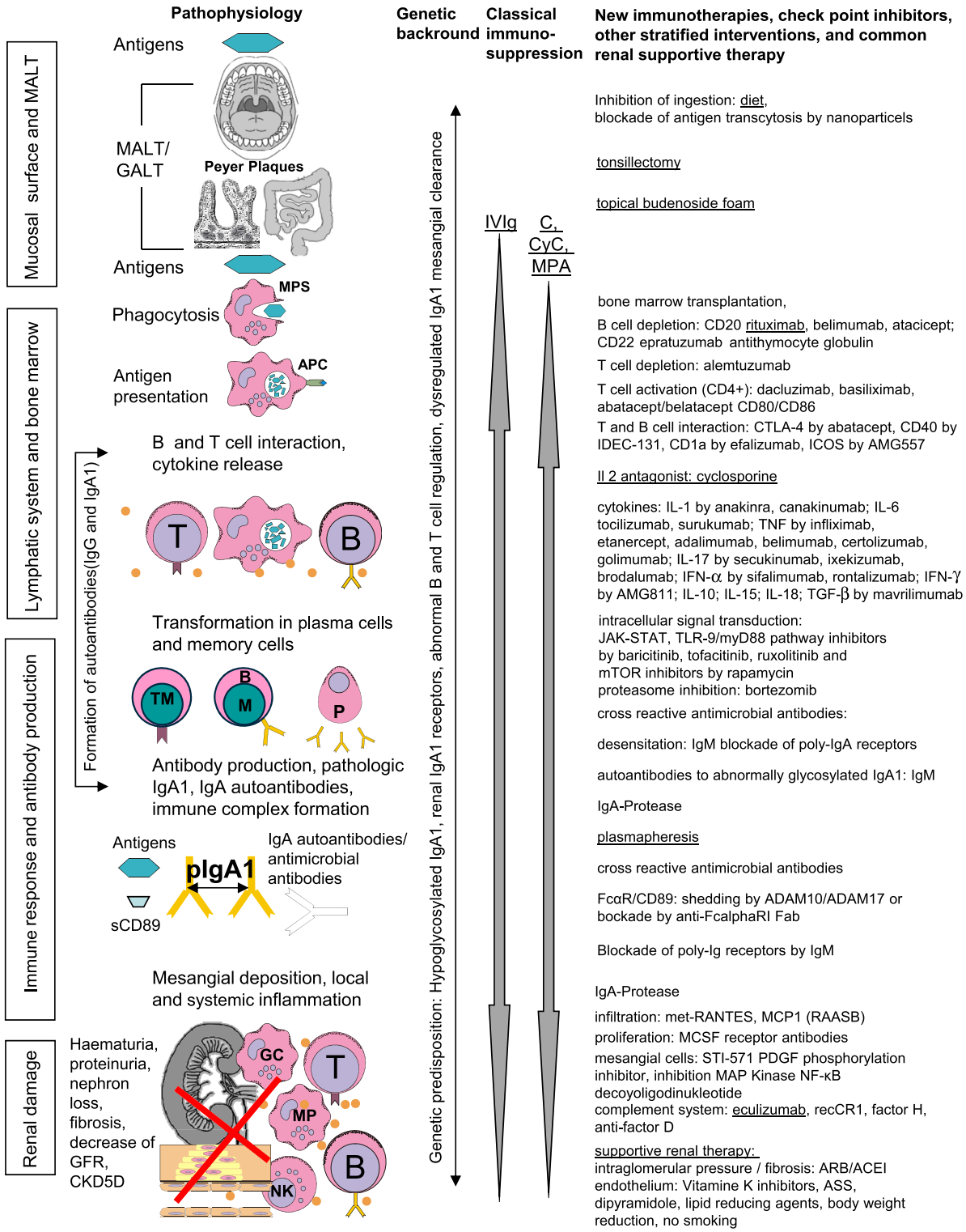

Fig. 1. Pathophysiology, proven immunosuppressive drugs and new immunotherapies, check-point inhibitors and other stratified interventions with their modes of action in immunoglobulin A nephropathy (IgAN). The pleiotropic effects of the classical immunosuppressive drugs are depicted in Table 1 and their clinical use in Table 2. Underlined interventions were used in therapy of primary IgAN. References are given in Table 1 and in the text. ACEI = angiotensin converting enzyme inhibitor = ADAM A disintegrin and metalloproteinase; AMG = anti-interferon (IFN)-γ IgG1 monoclonal antibody; APC = antigen-presenting cells; ARB = angiotensin receptor blocker; ASS = acetylsalicylic acid; C = corticosteroids; CD = cluster of differentiation; CKD = chronic kidney disease; CTLA = cytotoxic T lymphocyte-associated protein; CyC = cyclophosphamide; Fab = fragment antigen-binding; GALT = gut-associated lymphoid tissue; GFR = glomerular filtration rate; ICOS = inducible T cell co-stimulator; IDEC = epidermal cell-like dendritic cells; IL = interleukine IVIg = intravenous immunoglobulin; JAK-STAT = Janus kinase–signal transducers and activators of transcription; MALT = mucosa-associated lymphoid tissue; MAP = mitogen-activated protein; MCSF = macrophage colony-stimulating factor, MMF = mycophenolate mofetil = MPA mycophenolic acid; MPS = mononuclear phagocyte system; mTOR = mechanistic target of rapamycin; nuclear factor (NF) kappaB nuclear factor k-light-chain-enhancer of activated B cells; NK = natural killer cell; p = pathological; PDGF = platelet-derived growth factor; RAASB = renin angiotensin system blocker; RANTES = regulated on activation, normal T cell expressed and secreted; s = soluble; STI-571 = Imatinib mesylate; TNF = tumour necrosis factor; TLR = Toll-like receptor.

IgA1. After stem cell bone marrow transplantation, a decrease of IgA and remission of IgAN was described in murine models [21–23]. Mesangial deposition of IgA could be mediated be IgG anti-mesangial cell autoantibodies (IgG-MESCA) in the sera of patients with IgA nephropathy, specific by F(ab′)(2) binding to 48- and 55-kD autoantigen(s) [17–19]. Soluble FcαRI (CD89) receptor was identified in the formation of IgA-IC [24–28]. Mesangial binding might be mediated by membrane-bound Fc alpha receptors that could be expressed on autochthonous mesangial cells or immigrating myeloid cells. Asialoglycoprotein receptor (ASGP)-R, CD 89 and the transferrin receptor (TfR1 or CD71) were involved and induce mesangial cell activation [29–32]. Mesangial deposition induces infiltration of granulocytes and macrophages and activation of the alternative complement pathway by complement factor 3 (C3). Functional nephron loss by the inflammatory response discharges into in a downstream cascade of fibrosis, high glomerular pressure and hypertension, which appears as sequelae or surrogate parameters, e. g. proteinuria. Therefore, proteinuria consists of two fractions: (i) mesangial damage by inflammation due to IgAN and (ii) conversely, high glomerular pressure by altered glomerular microdynamics due to nephron loss [33–36]. Therefore, the individual linear regression analysis of the time-dependent course of estimated glomerular filtration rate (GFR) (eGFR; ΔGFR) or inverse serum creatinine is the only validated direct method in the assessment disease activity.

The unanswered burning question is the pathological explanation of the heterogeneous courses of IgAN: (i) the structure of the IgA1, (ii) the secondary, surrogate effects and comorbidity and (iii) the complement system. Clinically, mesangial inflammation and subsequent renal injury appears in haematuria, mixed tubular casts, proteinuria, reflecting intraglomerular pressure and damage of the glomerular filtration barrier and progredient nephron loss, with increase of serum creatinine, arterial hypertension and secondary nephrosclerosis. These findings, called nephritic syndrome [37,38], require renal biopsy.

IgAN, a polygenetic disease with different incidences worldwide

Genetic predisposition in polygenetic IgAN remains uncertain, and familiar forms are extremely rare [39]. Some genetic factors (6q21, 1q32, 22q12, 17q13, 8q32, 1q13, 9q34, 16q11) have been proposed as influencing renal prognosis [40]. A recent publication identified, in a genomewide scan, a copy number variable region at 3p21.1 that might influence the TLR9 expression levels in IgA nephropathy patients with worse prognosis [41]. Differences in patients with several ethnicities might be detected [42], but without therapeutic consequences, while pharmacogenetic studies have not been conducted. However, the worldwide differences in the incidence in IgAN from 0·8 (Germany [43], Spain [44]) to 10·5 (Australia [45]) per 100 000 patients per year seems to depend upon different referral to renal biopsy more than on ethnicity or genetic factors [46].

Is the prognosis and response on the therapy predictable by initial histological findings?

Histological grading systems were established in IgAN by Lee *et al.* [47]. Histological grading of IgA nephropathy predicting renal outcome: revisiting H. S. Lee's glomerular grading system and Haas *et al.* [48]. In 2009, the 'new' Oxford Classification was proposed [49,50]. Unfortunately, this classification did not include important histological findings, such as crescents with extracapillary proliferation and arterial hyalinosis [51–53], thrombotic microangiopathy [54] or techniques such as immune staining and electronmicroscopy [51], which were relevant and indispensable in the diagnosis [1] and prognosis [1,48,51,52,55–59]. In order of the deficiencies, also confirmed by the authors themselves [51], we do not recommend the Oxford Classification. Clearly, no histological grading correlated with clinical outcomes after therapy in most studies [4,60–70]. However, therapeutic interventions should be based not only or decided upon isolated histological findings [71]. Decrease of kidney function, decline

Table 1. Genomic and non-genomic effects of classical immunosuppressive drugs proven in clinical studies in progressive immunoglobulin A nephropathy (IgAN)

Immunosuppressive drug/intervention	Therapy	Cellular Effects	Humoral Effects
Corticosteroids Unspecific pleiotropic effects on immune system and mesenchymal cells (mesangiocytes, podocytes, angiocytes, smooth muscle cells, and fibroblasts) [3]	Induction, Maintenance	Genomic mechanisms **anti-inflammatory/immunosuppressive effects** *transcriptional* • induction of cytokine receptors (e.g. IL-1RII, IL-2R, IL-10R, TGF-βR), induction of pro- and anti-apoptotic factors, induction of adhesion molecules (e.g. ICAM-1, E-selectin) *post-transcriptional* • modification of mRNA stability *translational* • suppression of ribosomal proteins and translation initiating factors *post-translational* • regulation of protein processing and secretion Non genomic **specific** *classical GR* • cPLA2 inhibition (via src/annexin-1) • tertiary CAM structure (via annexin-1) *nonclassical GR* • interaction with membrane GR (?) • apoptosis (?) • interaction with other receptors • signal transduction, Ca^{2+}, second messengers **non specific** • physicochemical membrane properties (fluidity, 'membrane stabilization'), activity of membrane associated proteins	Genomic mechanisms **anti-inflammatory/immunosuppressive effects** *transcriptional* • induction of anti-inflammatory cytokines (e.g. IL-10, TGF-β) • suppression of cytokines (e.g. IL-1, IL-2, IL-6, IL-12, IFN-γ), chemokines (e.g. MCP-1, IL-8, eotaxin), adhesion molecules • indirect modulation via cytokine/chemokine suppression (e.g. of IL-1β, TNF-α) • suppression of T-cell proliferation (e.g. via IL-2↓) *post-transcriptional* • inflammatory enzymes (e.g. COX-2, $cPLA_2$, iNOS) **antiproliferative effects on non-immune cells** • induction of p21CIP1 (e.g. renal mesangial cells), induction of MKP-1 (e.g. osteoblasts) and MMPs; transrepression Non genomic **specific** *classical GR* • cytosolic interactions (via components of the GR-multiprotein complex?) *nonclassical GR* • interaction with membrane GR (apoptosis?) • interaction with other receptors (IP3, Ca2, proteinkinase C, cAMP, MAPK)
IVIG Polyvalent IgG Immunomodulation by targeting on lymphocytes and elimination of antigens and antiantibodies [4-7]	Induction, less toxic, avoid osmotic nephrosis	Regulation of the proliferation of lymphocytes modulation of T-effector cells *Fab mediated activities* • targeting of specific immune cell-surface receptors • modulation of maturation and function of dendritic cells	*Fab mediated activities* • suppression or neutralization of cytokines • suppression or neutralization of autoantibodies • neutralization of activated complement components • neutralisation of T-cell superantigens

Table 1. *Continued*

Immunosuppressive drug/intervention	Therapy	Cellular Effects	Humoral Effects
		Fc dependent activities • blockade of the FcRn • blockade of activating FcγR • upregulation of inhibitory FcγRIIB • immunomodulation by sialylated IgG • selection of B-cell populations	
Cyclophosphamide *Alkylating agent inhibitor of proliferation and function* [8]	Induction, toxic, cumulative dose	Inhibition of the proliferation of B-, e.g. naïve B-cells, and T-cells and of inflammation	Decrease of antibody production and cytokines
Azathioprine Antimetabolite *Inhibition of Proliferation*[9]	Failed in maintenance (more T-cell targeting?), phototoxicity, hepatotoxicity, bone marrow depression	Non specific inhibition of the purine synthesis Mostly T-cells blockade of antigen recognition by T-cells	Indirect, following T-cell hit mild decrease of serum IgA levels
Mycophenolic Acid *Antimetabolit* *Inhibition of the proliferation of activated lymphocytes in the G1-S phase (B- and T-cells) and smooth muscle cells* [8,10-14]	Maintenance, bone marrow depression	Specific inhibition of the proliferation of B- and T-cells by blockade of the de novo purine synthesis Induction of apoptosis of activated T-lymphocytes Inhibition of antigen presentation of dendritic cells Inhibition of migration Proliferation of smooth muscle cells Expression of adhesion molecules (VLA-4, E- and P- Selectin, VCAM-1) Expression of CD 154 and CD 28	Decrease of antibody production, cytokines and anti-inflammatory effects

of GFR (> 12 ml/min/year) and/or refractory proteinuria (> 1·0 g/day) with age-related normal macroscopic morphology, normal kidney size and parenchyma/pyelon ratio and specific findings in renal histology (mesangial hypercellularity, crescents or adhesions) [47,48,51,54,71–73] require further immunosuppressive interventions after symptomatic therapy.

Assessment of progression and subsequent treatment decision

Due to the heterogeneity of progression the of IgAN, risk-adjusted precise homogeneous patient selection for treatment decisions in study inclusion, or interpretation of the outcomes of progressive patients, are the most important criteria in study design (Table 2, Fig. 2) [33,34,64,74]. In all kidney diseases, the recommended standard in the assessment of renal function is the individual linear regression analysis of the time-dependent course of estimated GFR (eGFR; ΔGFR) or inverse serum creatinine before and after therapy, especially in IgAN [5,35,60–62,64,69,74–83] (Table 2, Fig. 2). Doubling of serum creatinine is not recommended in the determination of the loss of renal function (ΔGFR), because the loss of renal function calculated by serum creatinine (eGFR) is not linear between 110 and 40 ml/min [84–86]. The reason for this is that a linear decline in 'true' GFR does not result in a straight line as a reciprocal of serum creatinine analysis. This is because the filtration of serum creatinine is influenced, in proportion, by increased tubular secretion of serum creatinine as renal function declines. Thus, basing outcome analysis on reciprocal serum creatinines only provides a false picture of changes in 'true' GFR. Furthermore, doubling of eGFR as an end-point is not recommended regarding the interindividual differences in the time dependent decline of renal function in such a heterogeneous disease.

Clearly, only progressive patients should be treated with high-risk immunosuppressive therapy in a professional setting, e.g. cyclophosphamide [36].

Therefore, progressive loss of renal function or the decrease of estimated GFR (eGFR; ΔGFR) could be differentiated in four grades or stages: (i) approximately 20–30% or less of the patients: stable disease with physiological decrease of renal function (ΔGFR < 1·5 ml/min/year) and low-grade proteinuria below 1 g/g day with renin angiotensin system blocker (RAASB); (ii) approximately 50% of the patients with intermediate and progressive disease ΔGFR > 1·5–30 ml/min/year or more than 3 ml/min within 3 months; (iii) approximately 10% of the patients with rapidly progressive forms and the presence of crescents in renal histology (RPGN) and a ΔGFR > 3 ml/min/month or > 30 ml/min/year; and (iv) approximately 7% of the patients with a nephrotic syndrome (proteinuria > 3·5 g/g, plus hypoalbuminaemia and oedema).

However, in most meta-analyses and randomized controlled studies (RCTs) this criterion, focusing on the heterogeneity of IgAN, was neglected (Table 1) [33,35,64,74,83,87–91]. Table 1 presents an extensive overview of all publications regarding several immunosuppressive therapies of progressive IgAN concerning evidence-based medicine (EBM) level (≥ 1b) and is stratified by renal risk factors: stage of chronic kidney disease (CKD) and the assessment of the loss of renal function before and during the study period (ΔGFR) with linear regression analysis (ΔGFR). Risk-adapted treatment strategy in order of degree of proteinuria and loss of renal function (ΔGFR) are shown in Fig. 2.

Unfortunately, the low incidence and the heterogeneity of IgAN limit larger trials with results that apply EBM criteria in level 1. Therefore, only one trial in progressive IgAN fulfilled the criteria of EBM level 1 (RCT) and, conversely, a precise, detailed, homogeneous selection of patients with ΔGFR before and during therapy [64].

Point of no return and limitations of immunosuppressive therapy

It has been suggested that untreated patients with a serum creatinine exceeding 2·5–2·7 mg/dl ('the point of no return') will develop end-stage renal disease within a period of approximately 1 year [92,93], but this judgement should be revised with immunosuppressive therapy [4,61–64,77,94,95].

Contraindications for immunosuppressive treatment will be: serum creatinine > 4·5 mg/dl (> 480 μmol/l), small kidney size (< 9 cm) in ultrasound, acute or chronic infections (including human immunodeficiency virus, hepatitis B and C virus), carcinoma, leucocyte counts < 3·0/nl, platelet counts < 80/nl, gastrointestinal bleeding, haemolytic anaemia, pregnancy, lactation or women with childbearing potential. In all drug regimens, even in supportive therapy, current information on the contraindications of applicable regulatory documents (summary of product characteristics) should be considered.

Treatment in non-progressive disease and supportive therapy

Symptomatic or common supportive renal therapy, reducing blood pressure and hyperlipidaemia in order to avoid nephrosclerosis, renin–angiotensin–aldosterone blockade and others

Downstream effects, namely glomerular and interstitial fibrosis, may be mediated by monocyte chemotactic protein-1 (MCP-1), interleukin (IL)−6, IL-8, transforming growth factor (TGF)-beta, regulated on activation, normal T cell expressed and secreted (RANTES) and CCR1- and CCR5-positive cells [96,97] and may be reduced by RAASB [98] (Fig. 1).

Table 2. Synopsis of treatment strategies in immunoglobulin A nephropathy (IgAN): imunosuppressive therapy, tonsillectomy and supportive therapy in IgAN stratified by risk factors [stage of renal chronic kidney disease, loss renal function (ΔGFR), arterial hypertension and proteinuria], evidence-based level, study design and inclusion criteria

			Therapy							
			Immunsuppression							
CKD Stage	Proteinuria (g/day)	RR (mm Hg)	CTX	C	MPA/MMF	CsA	IVIG	ACEI or ARB	Tonsillectomy	Fish oil
1	<1	Normal								
	>1	Normal		C+Fish oil: Hogg *et al.* 2006 [179]				ACEI: Praga 2003 [180]	TE+ C: Hotta *et al.* 2001 [110]	+K: Hogg *et al.* 1995 2006 2010 [179,181,182]
				Katafuchi *et al.* 2003 [183]				ACEI+ARB: Tanaka *et al.* 2004 [184]		
				Kuriki *et al.* 2003 [185]				ACEI+ARB: Russo *et al.* 2001 [186]		
				C+TE: Hotta *et al.* 2001 [110]				ACEI: Maschio *et al.* 1994 1996 [100,187]		
				Shoji *et al.* 2000 [188]						
				C+Aza: Yoshikawa and Ito 1999 [189]						
	>1	>125/75		Manno *et al.* 2009 [115]				ARB+HCT: Uzu *et al.* 2005 [190]	Xie *et al.* 2003 [191]	
1–2	> 1		CTX+C+Aza/ HDC+C+Aza *versus* RAASB Rauen *et al.* 2015 [36]	Pozzi *et al.* 1999 [67] C+Aza: Pozzi *et al.* 2010 [66]		Lai *et al.* 1987 [120]				
	>3			Tesar *et al.* 2015 [35]						
					±C: Liang *et al.* 2014 [81]					
1–3	>0·75									
2	n.n.	>125/75		Kobayashi *et al.* 1986, 1988, 1989, 1996 [192–196]						
2–3	>1		CTX±Aza±C: Ballardie and Roberts 2002 [64]		Maes *et al.* 2004 [70]		Rostoker *et al.* 1994 [5]	ARB: Li *et al.* 2006 [82]	Iino *et al.* 1993 [197]	
	>2									

Table 2. *Continued*

CKD Stage	Proteinuria (g/day)	RR (mm Hg)	Therapy							
			Immunsuppression							
			CTX	C	MPA/MMF	CsA	IVIG	ACEI or ARB	Tonsillectomy	Fish oil
3	>1		Woo *et al.* 1987 [198]	C+TE: Sato *et al.* 2003 [199]	+C: Liu *et al.* 2014 [200]		±C Rasche *et al.* 2006a [4]		TE+C: Sato *et al.* 2003 [199]	Donadio *et al.* 1994 1999 2000 2001 [201–204]
				C+Aza: Goumenos *et al.* 1995, 2003 [205,206]	Tang *et al.* 2005, 2010 [68,69]					Pettersson *et al.*1994 [207]
			C+CTX: Roccatello *et al.* 2000 [208] C+CTX: Tsuruya *et al.* 2000 [209]	Peters 2015 [210]						
4	>1	>125/75			Frisch *et al.* 2005 [142]			ACEI+ARB: Nakao *et al.* 2003 [211]	TE+CTX: Rasche *et al.* 1999 [109]	
			CTX±MPA±C: Rasche *et al.* 2006b/2015 [61,63] C±CTX: Tumlin *et al.* 2003 [79] Rasche *et al.* 2003 [62] CTX+TE: Rasche *et al.* 1999 [109]							
	>2	>125/75		Tamura *et al.* 2003 [80]						
n.n.	>2	n.n.			Chen *et al.* 2002 [143]					
n.n.	nephritic syndrom	n.n.			+C: Liu *et al.* 2014 [200]					

Evidence-based level grade 1b is marked in grey and all other studies have been classified as less than 1b. With regard to the heterogeneity of the disease, studies with linear regression analysis (ΔGFR) as the most accurate, standard method in the assessment of the loss of renal function before and during the study period are underlined. AZA, azathioprine; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; C, corticosteroids; CTX, cyclophosphamide; HCT, hydrochlorothiazide; HD, high dose IVIg, high-dose immunoglobulin therapy; MMF, mycophenolate mofetil; MPA, mycophenolic acid; RAASB, renin angiotensin system blocker; RR, blood pressure; TE, tonsillectomy.

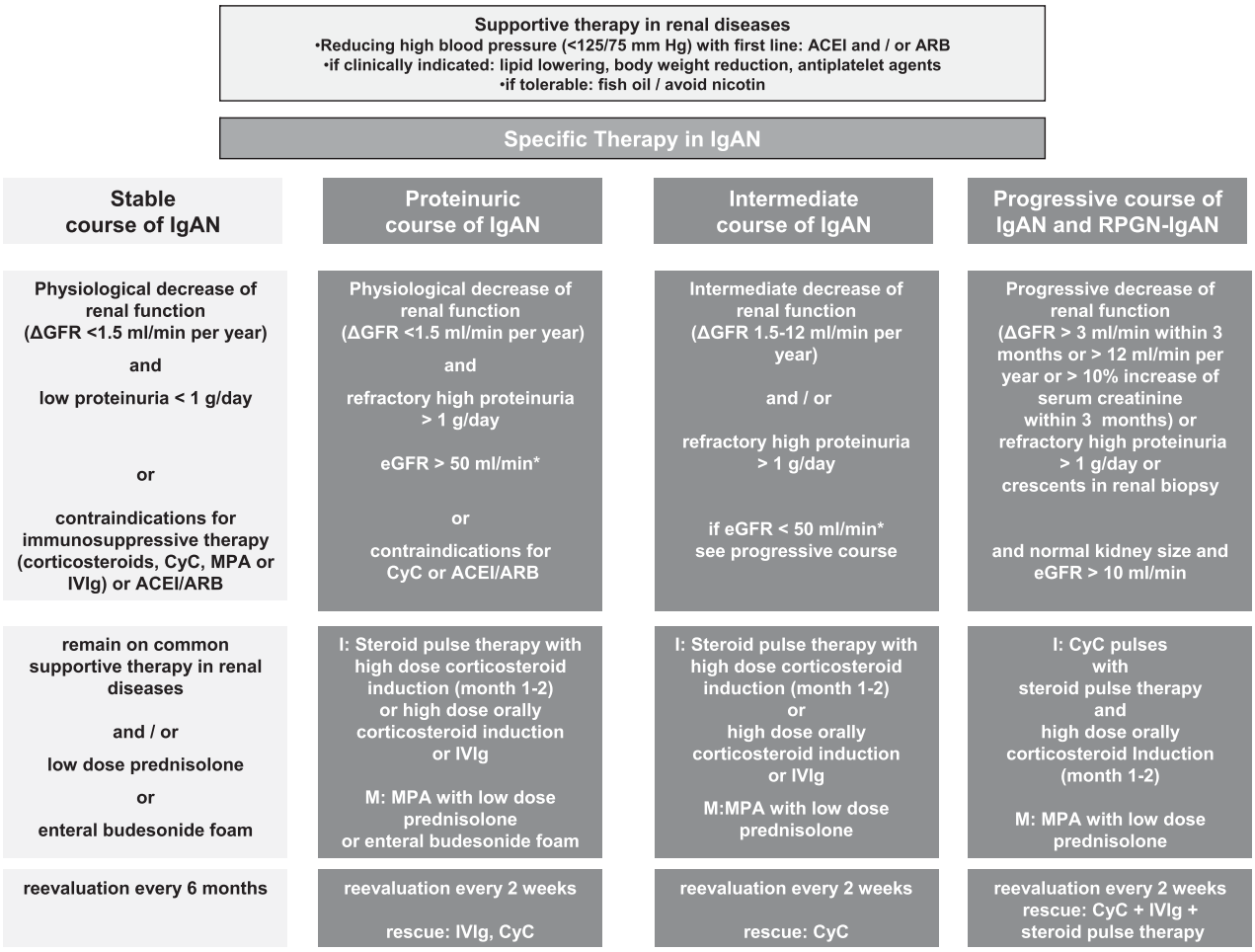

Fig. 2. Risk-adapted treatment strategy in order of degree of proteinuria and loss of renal function (ΔGFR) based on clinical studies (Table 2). Normal kidney size and morphology in ultrasound has to be evaluated before specific immunosuppressive treatment is initiated. Corticosteroids monotherapy showed proven benefit only in patients with mild to moderate impaired renal function (*, Table 2) and the progressive treatment strategy is recommended in patients with severely impaired renal function. In patients with nephrotic syndrome, the proteinuric course treatment regimen will be recommended.

In patients with stable disease without progression in linear regression analysis of serum creatinine (or eGFR) only supportive therapy with ACE inhibitors (ACEI), angiotensin receptor blockers (ARB), cholesterol lowering and fish oil were proposed in the former KDIGO clinical best practice guidelines for glomerulonephritis by Eckardt *et al.* from 2012 [99]. However, corticosteroids have also demonstrated proven benefit in all studies in stable disease (Table 2). Further, in progressive disease, taking into account the risk of worsening renal function and hyperkalaemia, ACEI and/or ARB should be prescribed in lowering intraglomerular pressure and avoiding interstitial sclerosis [100] with a secondary effect on the loss of renal function, e.g. proteinuria as a surrogate parameter, due to nephrosclerosis [101].

Only 7% of the patients with IgAN have proteinuria in the nephrotic range and normal renal function. High-dose corticosteroid induction is beneficial, and in refractory cases or in maintenance therapy, mycophenolic acid or leflunomide [102–104] and in RAASB-resistant disease adrenocorticotrophic hormone [105] will also be beneficial.

Tonsillectomy and mucosa-associated lymphoid tissue (MALT)

Due to the proposed mucosal origin, tonsillectomy was performed in reducing the contact of potential antigens with the mucosa-associated lymphoid tissue (MALT), inhibition of the migration of B and T cells in the locoregional lymphatic nodes and decrease of the total systemic amount of pIgA. Furthermore, tonsilla palatina has been mentioned as a potential trigger for the systemic response (Fig. 1). After tonsillectomy the episodes of macrohaematuria might have been reduced [106–108], but there was no clear benefit in reducing the disease progression [77,90,109].

However, tonsillectomy affected only a part of the widespread MALT. Hence, in combination with steroid pulses [110–112], possible effects have been described in patients with mild renal impairment and proteinuria < 1 g/g (CKD G1-2 A3) [71]. In patients with progressive disease or renal impairment, tonsillectomy could provoke acute renal injury with irreversible detoriation of renal function, and should be avoided [77,109,110].

Topical corticosteroids for suppression of the MALT system

Topical application of enteric budesonide foam targeted to the ileocecal region had a significant effect on urine albumin excretion, accompanied by a minor reduction of serum creatinine and a modest improvement of eGFR [113]. However, systemic budesonide absorption is approximately 10–20% [114].

High-dose corticosteroid induction therapy and long-term application of systemic corticosteroids decreases proteinuria and risk of renal failure

In two large randomized trials, corticosteroids, high-dose intravenous pulses and low-dose corticosteroid maintenance reduced proteinuria and the risk of renal failure in proteinuric patients with mild impaired renal function significantly (serum creatinine/creatinine clearance in control *versus* study group: 88 *versus* 98 μmol/l/87 *versus* 93 ml/min) and proteinuria (1·8 *versus* 2·0 g/day; Table 2) [65–67]. These results were confirmed in a large RCT trial (97 patients, follow-up 8 years) with high-dose corticosteroid induction over 6 months and ramipril *versus* ramipril monotherapy in patients without progression and mild renal impairment, but without maintenance therapy [115]. Recently, a large retrospective cohort study demonstrated that continuous application of corticosteroids in addition to ACEI or ARB prolongs renal survival time significantly, in contrast to RAASB monotherapy [35,116].

Cyclophosphamide and high-dose corticosteroid pulses with azathioprine maintenance in patients with non-progressive disease

In the STOP-IgAN trial, patients with mild renal impairment, no sign of progression and persistent low-degree proteinuria were treated after a 6-month run-in phase of maximum intensified renal supportive therapy (RAASB) in an RCT with cyclophosphamide orally, corticosteroid pulses and only supportive therapy stratified by proteinuria (supportive care *versus* supportive care plus CyP or high-dose corticosteroid pulses: serum creatinine 76/76 μmol/l; GFR 57/61 ml/min, absolute change in eGFR over 36 months −4·7/–4·2 ml/min per 1·73 m^2 body surface area (BSA) per year, estimated loss of renal function 1·6 *versus* 1·4 ml/min per 1·73 m^2 BSA per year, mean annual change in the slope of the reciprocal of serum creatinine concentration −0·02 *versus* −0·01 mg/dl, proteinuria 1·6/1·8 g/day, protein creatinine ratio 1·0–1·1. g/g). However, in this heterogeneous cohort, cyclophosphamide or high corticosteroid pulses demonstrated significant effects on the primary end-point (full clinical remission). Full clinical remission was defined as proteinuria with a protein-to-creatinine ratio of < 0·2 and stable renal function with a decrease in the eGFR of < 5 ml/min per 1·73 m^2 from the baseline eGFR at the end of the 3-year trial phase. The secondary end-point, defined as a decrease in the eGFR of at least 15 ml/min per 1·73 m^2 from the baseline eGFR, was not significant [36]. This trial is discussed controversially, even in study design and statistical power (δ value < 0·3), patient selection (inhomogeneous, no information of ΔGFR before therapy and after therapy), inclusion criteria (proteinuria as a sequelae or surrogate parameter of nephron loss), observation time (only 3 years) and the lack of any kind of renal histology [33,74,83,117–119]. Clearly, cyclophosphamide and corticosteroids will not ameliorate the physiological loss of renal function, even in patients with IgAN, and should be limited in IgAN to patients with a defined decrease of renal function (ΔGFR).

Treatment of progressive disease – classical systemic immunosuppressive therapy

Classical immunomodulatory drugs and interventions: intravenous immunoglobulin (IVIg), corticosteroids, cyclophosphamide and mycophenolate maintenance

In light of the autoimmune pathogenesis, cyclophosphamide, corticosteroids, mycophenolic acid and the less toxic alternative of IVIg are effective in the reduction of the systemic amount of IgA antibodies and local response in the mesangium (Fig. 1). Therefore, in patients with rapid loss of renal function, immunosuppressive therapy is necessary and has to be continued lifelong for kidney survival. The pleiotrophic effects of these drugs promises advantages because several checkpoints of the cascade will be inhibited but toxic effects, except IVIg, must be considered.

T cell-targeted drugs, e.g. cyclosporin, can reduce proteinuria in combination with corticosteroids mediated by glomerular vasoconstriction, but a worsened glomerular filtration rate [120].

Plasmapheresis, in combination with cyclophosphamide and corticosteroids as a short-term intervention, is restricted to rapidly progressive forms, mainly in secondary IgAN, e.g. Henoch–Schoenlein purpura or in p- or c-antineutrophil cytoplasmic antibodies (ANCA)-positive vasculitis. Stem cell transplantation is used only in mice [21–23].

IVIg – non-toxic, limited immunomodulation

In patients with pregnancy, childbearing potential or high cumulative doses with cyclophosphamide, IVIg is a less

toxic alternative with comparable effects in the reduction of ΔGFR from −1·05 ml/min/month to −0·15 ml/min/month ($P = 0·024$) and proteinuria (from 2·4 g/l to 1·0 g/l, $P = 0·015$) [4,5,60–63]. In Kaplan–Meier analysis median survival time was only 4·7 years with IVIg *versus* 10·5 with cyclophosphamide pulse therapy/mycophenolic acid (CyP/MPA). Therefore, IVIg is an option as induction therapy for 6 months. However, 3 years after IVIg, further loss of renal function was observed [4,60,63], and further maintenance therapy will be needed with prednisolone and/or mycophenolate mofetil (MMF)/MPA plus prednisolone [60–63,77].

Corticosteroids are essential in induction and maintenance therapy

Corticosteroids display anti-inflammatory effects and induce apoptosis and show proven benefit in both long-term use and pulse therapy [3,35,65–67,116] (Table 1, Fig. 1). Corticosteroids will be a necessary standard in addition to mycophenolate [60–63], even in other autoimmune diseases [121]. These effects may be responsible for a reduction of the proliferative lesions, glomerular sclerosis and tubular fibrosis in IgAN with a superior renal survival compared with patients receiving only ARB/ACEI [35,36,67,122].

Cyclophosphamide in combination with corticosteroids – advantages of CyP and intensified immunosuppression

Treatment with cyclophosphamide plus steroids has been used with great success for more than 30 years in several publications regarding IgA nephropathy with progressive loss of renal function (Table 2). Cyclophosphamide is a highly potent cytotoxic agent used frequently for cytoreductive induction therapy in autoimmune disease by depletion and inhibition of T and B lymphocytes, but its long-term use is limited due to the high cumulative toxicity [123], therefore further maintenance therapy is needed [64] (Fig. 1, Table 1). In an RCT, Ballardie *et al.* used cyclophosphamide orally 1·5 mg/kg/day adjusted to the nearest 50 mg for 3 months in order to avoid severe leucopenia, anaemia and thrombocytopenia or other side effects with an estimated cumulative dose of 9 g [64]. Continuous oral application of cyclophosphamide has to be monitored weekly by experts, and severe leucopenia with adverse events has been described [36]. Intravenously CyP pulses have shown superiority regarding safety [124] and less toxicity [123–125] by short-term acrolein bladder exposure with fewer cumulative doses [62] with equal [126] or better [124,125] efficacy, as also proved in other autoimmune diseases compared with oral cyclophosphamide.

Intensified and escalated immunosuppression adapted to leucocytes or neutrophils have demonstrated a better outcome in autoimmune diseases [123,127] and in IgAN [62]. We have adjusted the doses to leucocyte count nadir 2 weeks after CyP with a remarkable depression of leucocytes close to 3·5/ml [61–63,77] accompanied by low-dose corticosteroids (5–7·5 mg prednisone/day). However, the majority of our patients (67%, 31 of 47) showed further disease activity 4 months on average after CyP, and further administration of MPA was necessary [61–63,77].

Concept of sequential therapy – safety maintenance with low risk and toxicity

The concept of sequential therapy, induction and maintenance has already been introduced in the treatment of lupus nephritis [10], ANCA-associated glomerulonephritis [128–131] and other autoimmune diseases. In IgAN, sequential therapy was used in two RCTs and several other studies [60–64,66] (Table 2). In both RCTs, high-dose prednisolone medication orally accompanied the induction therapy for 3 months (Ballardie *et al.* 40 mg for 3 months [64] and Pozzi 0·5 mg/kg/day, alternate-day regimen [66]). Serum creatinine/creatinine clearance in the patients in the Pozzi *et al.* study was almost normal (control *versus* study group: 88 *versus* 98 μmol/l/87 *versus* 93 ml/min); proteinuria (1·8 *versus* 2·0 g/day) was the focus of the treatment and no information was given before therapy regarding the decline of renal function (ΔGFR) [67]. Contrary to Pozzi *et al.* [67], Ballardie *et al.* included patients with moderate to severe impaired renal function (serum creatinine > 130 μmol/l) and a homogeneous progression in linear regression analysis with the equivalent slopes, as in our patients (Ballardie −16·8 to −3·8 ml/min/year and controls −15·6 to −16·5; proteinuria 4·6–4·2 g/day and controls 3·9–0·8 g/day) [64]. We started with a low-dose corticosteroid regimen (20 mg/day prednisolone) and we reduced every 2 weeks to 5 mg/ day until the end of the study [4,60–63,77,109].

In non-progressive IgAN patients after steroid pulses azathioprine (1·5 mg/kg/day), limited for 6 months, provided no additional benefit to steroids alone after a 5-year follow-up, but more side effects have been described [36,66]. However, after cyclophosphamide and corticosteroid induction, maintenance with azathioprine (1·5 mg/kg/day) was continued favourably to the study end. The study by Pozzi *et al.* started in 1987 [65–67] and the study of Ballardie *et al.* in 1991 [64]. The more specific drug, mycophenolic acid, was not available at that time, because MMF has been approved for transplantation since 1996 and free mycophenolic acid (ecMPS) since 2004. Clearly, mycophenolic acid had demonstrated superiority in transplant medicine in preventing acute and chronic rejection to azathioprine [132,133] and in safety [134–137].

Mycophenolic acid

MPA acts by reversible uncompetitive inhibition of inosine 5′-monophosphate dehydrogenase (IMPDH), which is

essential for *de-novo* biosynthesis of guanine nucleotides and lymphocyte proliferation [138–140]. Specifically by MPA, the proliferation of B and T cells is inhibited and the Ig cytokine secretion of B cells is suppressed [11] and the apoptosis of activated T lymphocytes is induced [12]. MPA inhibits the migration of lymphocytes and antigen presentation by dendritic cells [13] (Table 1). However, other forms of important inflammatory response were not influenced by MPA as the expression of activation markers of inflammation, including CD25 and CD69 [14].

MPA was used with different outcomes in several studies with [60–63] and without cytotoxic induction therapy, but in some studies without low-dose prednisolone [68,70,141,142]. However, the patients in these studies were not comparable regarding risk factors, e.g. progression of renal failure in linear regression analysis (ΔGFR), proteinuria and age [68,70,141,142]. This might explain why an RCT in 21 IgAN patients with mild renal impairment without induction therapy and without prednisolone showed no significant effect on the loss of renal function [70,142]. However, a decrease of proteinuria was observed in two RCTs in 31 patients [143] and in 16 patients [68]. Clearly, MPA monotherapy is less effective and corticosteroids are needed additionally for long-term maintenance [35,60–67,121].

Genetic or pharmacogenetic aspects have not been explored in published studies of IgAN patients with supportive or immunosuppressive studies. Hence, only in one study has detailed information of ethnicity been given [61]. Genetic variants of the uridine diphosphate–glucoronyltransferases may enlarge the drug exposition with MMF in the area under the curve and will be responsible for more side effects [144], but larger trials in IgAN patients with MPA/MMF with worldwide scan of this defect have not been published. No signs of less exposure or inosine 5′-monophosphate dehydrogenase suppression between MMF and MPA in our patients were demonstrated in concordance with other studies in a pharmacokinetic/pharmacodynamic study [145].

In our study, sequential MPA maintenance therapy was effective in patients with progressive IgAN in reducing further loss of renal function (ΔGFR) from −0·4 to −0·1 ml/min/month with a trend in reduction of the proteinuria from 1·0 to 0·6 g/l [63]. The full effect of MPA on renal function was observed after an average time lag of 6 months and in reduction of proteinuria after 5 months. Maintenance therapy with MPA and low-dose corticosteroids consolidates the clinical outcome after induction therapy with CyP or steroids over 6 years, while reducing side effects and cumulative toxicity of cyclophosphamide and corticosteroids [10,14,60–63,146,147]. The strengths of our non-randomized study were the homogeneous cohort, the long observation time, the number of treated patients, intraindividual course with ΔGFR before and under therapy and the proven concept of sequential therapy in another RCT with the same criteria, but with azathioprine instead of MPA [64]. However, an RCT with cyclophosphamide and MPA will be needed, but the concept and the realization will be limited by the small number of patients with an incidence of $< 0{\cdot}6/100\,000$/year, decline of resources and support in the health systems for monitoring or study preparations, from governments and pharmaceutical industries and to deny patients a proven and save therapy.

Targeted inhibition of the generation, formation and deposition of the pathogenic IgA immune complexes and the downstream cascade with new immunotherapies, checkpoint inhibitors and other stratified interventions

Because of the still-unclear pathophysiology, the genetic susceptibility in the production of aberrant glycosylated IgA1 and the multiple targets on several locations, e.g. MALT, systemic immune system, bone marrow and mesangium, and the development of therapeutic strategies in the specific inhibition of the pernicious cascade, are our future challenges (Fig. 1).

Hypothetical strategies – *in-vitro* or animal models

Nanoparticles may protect from the ingestion of potential triggering antigens in the mucosal area [148].

Cleavage of the pathological IgA1 and the IgA1 IC with a specific IgA protease is a controversial topic in casual-specific therapy for IgAN [30,149–154]. However, IgA is one of the most frequent immunoglobulins and is extremely important for the defence and integrity of the surfaces. Therefore, the loss of integrity could be induced [155,156].

Desensitizing may be helpful in reducing pathological IgA1 by shifting plasma cells to IgG-producing cells [157]. Blockade of aberrant glycosylated IgA1 by autoantibodies [16,20,158] or poly-Ig receptors Fcalpha/muR [31] on mesangial cells may attenuate the influence of aberrant glycosylated IgA1 [159].

Hyperexpression of nuclear factor kappa B (NF-kB) is found in IgAN and proteasome inhibitors; e.g. bortezomib will be a therapeutic option in progressive glomerular diseases limited by neurotoxicity [160]. In IgAN the Akt/mTOR/p70S6K pathway and Toll-like receptor (TLR)−9 [161,162] is activated and the inhibitor rapamycin might be an option in the treatment of IgAN [163].

The deposition of IgA in the mesangium may be mediated by the soluble type I IgA receptor (FcalphaRI or CD89) and transferrin receptor (TfR) on mesangial cells [164–166]. This might be inhibited by anti-FcalphaRI Fab [167]. Inhibition of factor Xa by DX-9065a may reduce mesangial proliferation [168].

Secondary IgAN – cytokine inhibition by biologicals

Proinflammatory cytokines play a pivotal role in the inflammatory downstream events and might be a possible target for intervention. Beneficial effects of biologicals were reported in secondary IgA by inhibition: IL-1 with anakinra [169]; I:-6 with tocilizumab [170,171]; TNF with infliximab [172,173] and adalimumab [174].

Biologicals – B cell and complement inhibition in human case reports

Recently, case reports have been published after B cell depletion with rituximab with beneficial response in patients with nephrotic syndrome [175] and RPGN-IgAN after kidney transplantation [176]. Anti-thymocyte globulin (ATG) induction therapy reduces disease recurrence in renal transplant recipients with primary IgA nephropathy [177]. B and T cell interaction will be inhibited by biologicals, e.g. cytotoxic T lymphocyte (CTLA)−4 abatacept, in one patient with rheumatoid arthritis [174]. In a patient with RPGN-IgAN refractory to CyP, corticosteroids and plasmapheresis [178] will offer new aspects in the inhibition of the complement system by humanized anti-C5 monoclonal antibody eculizimab.

However, all these specific interventions will interfere with other important ongoing parallel immune processes and probably inhibit crucial functions of the immune system. Contrary to these specific inhibitions, the advantages of the classical drugs were the multi-modal types of action, long-term experience and cost-effectiveness.

Concluding remarks

καιρὸς δ' ἐπὶ πᾶσιν ἄριστος: Hesiod, ΕΡΓΑ ΚΑΙ ΗΜΕΡΑΙ, 694

Approximately 3000 years ago, Hesiod taught 'why, when and how' interventional therapy in a heterogeneous disease such as IgAN has to be started (καιρὸς). Supportive therapy might be effective in reducing renal fibrosis by lowering intraglomerular pressure. However, in an autoimmune disease with lifelong deposition of altered IgA1 immune complexes, corticosteroid therapy will promise benefit even for mild progressive course and in patients with proteinuria. The right moment (καιρὸς) for immunosuppressive intervention with cyclophosphamide is defined by an accelerated decrease of renal function in linear regression analysis (ΔGFR). Immunosuppressive therapy with cyclophosphamide has been proved (δ' ἐπὶ πᾶσιν ἄριστος) in several trials. Mycophenolate maintenance therapy with low-dose steroids provides a reduction of further progress after cyclophosphamide induction in concordance with other autoimmune diseases. However, the heterogeneity of the disease needs further sufficiently powered, larger, randomized, placebo-controlled clinical studies (δ' ἐπὶ πᾶσιν ἄριστος), with the focus on maintenance therapy with corticosteroids and MMF regarding the loss of GFR in linear regression analysis and the optimal duration of therapy. In future, less toxic and more specific drugs will be needed to prevent prolonged mesangial deposition of the altered IgA and prevent loss of renal function.

Disclosure

None to declare.

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