

Comprehensive overview of autoantibody isotype and subclass distribution



Mikhail Volkov, MD,^a Mariateresa Coppola, MD, PhD,^b Ruth Huizinga, MD, PhD,^c Filip Eftimov, MD, PhD,^d Tom W. J. Huizinga, MD, PhD,^a Anneke J. van der Kooi, MD, PhD,^d Liesbeth E. M. Oosten, MD, PhD,^e Joost Raaphorst, MD, PhD,^d Theo Rispens, PhD,^f Rocco Sciarrillo, PhD,^f Maarten J. Titulaer, MD, PhD,^g Luuk Wieske, MD, PhD,^d René E. M. Toes, PhD,^a Maartje G. M. Huijbers, PhD,^{h,i} Karin A. van Schie, PhD,^{a*} and Diane van der Woude, MD, PhD,^{a*} on behalf of the T2B Consortium *Leiden, Amsterdam, and Rotterdam, The Netherlands*

The presence of autoreactive antibodies is a hallmark of many autoimmune diseases. The effector functions of (auto)antibodies are determined by their constant domain, which defines the antibody isotype and subclass. The most prevalent isotype in serum is IgG, which is often the only isotype used in diagnostic testing. Nevertheless, autoantibody responses can have their own unique isotype/subclass profile. Because comparing autoantibody isotype profiles may yield new insights into disease pathophysiology, here we summarize the isotype/subclass profiles of the most prominent autoantibodies. Despite substantial variation between (and within) autoantibody responses, this unprecedented comparison shows that autoantibodies share distinctive isotype patterns across different diseases. Although most autoantibody responses are dominated by IgG (and mainly IgG1), several specific diseases are characterized by a predominance of IgG4. In other diseases, IgE plays a key role. Importantly, shared features of autoantibody

isotype/subclass profiles are seen in clinically unrelated diseases, suggesting potentially common trajectories in response evolution, disease pathogenesis, and treatment response. Isotypes beyond IgG are scarcely investigated in many autoantibody responses, leaving substantial gaps in our understanding of the pathophysiology of autoimmune diseases. Future research should address isotype/subclass profiling in more detail and incorporate autoantibody measurements beyond total IgG in disease models and clinical studies. (J Allergy Clin Immunol 2022;150:999-1010.)

Key words: Autoantibodies, pathogenic autoantibodies, autoantibody isotypes, IgG1, IgG4, IgE

From ^athe Department of Rheumatology, Leiden University Medical Center, Leiden, ^bthe Department of Molecular Cell Biology & Immunology, Amsterdam University Medical Center, Amsterdam, ^cthe Department of Immunology, Erasmus MC, University Medical Center, Rotterdam, ^dthe Department of Neurology and Clinical Neurophysiology, Amsterdam Neuroscience, Amsterdam University Medical Center, Amsterdam, ^ethe Department of Hematology, Leiden University Medical Center, Leiden, ^fthe Department of Immunopathology, Sanquin Research and Landsteiner Laboratory, Amsterdam UMC, University of Amsterdam, Amsterdam, ^gthe Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, and ^{h,i}the Departments of Human Genetics and ⁱNeurology, Leiden University Medical Center, Leiden.

*These authors contributed equally to this work.

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Corresponding author: Mikhail Volkov, MD, or Diane van der Woude, MD, PhD, Department of Rheumatology C1-R, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, The Netherlands. E-mail: m.volkov@lumc.nl. Or: dvanderwoude@lumc.nl.

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Autoreactive antibodies are the common denominator in many autoimmune diseases. For each specific autoantibody, various isotypes and subclasses can be simultaneously present. The isotypes' and subclasses' constant domains shape most of the antibody effector functions. Thereby, the isotype/subclass profile can potentially influence disease pathophysiology.

Five immunoglobulin isotypes are expressed by human B cells: IgM, IgD, IgG, IgA, and IgE. Furthermore, IgG and IgA are subdivided into additional subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.¹ IgG is the most abundant (~80%; reference values, 7-15 g/L) of the antibodies present in the serum, followed by IgA (15%; 0.6-4 g/L), IgM (5%; 0.6-3 g/L), IgD (0.25%; 0-0.14 g/L), and IgE (detected in trace amounts, 3-423 kIU/L).² Secreted IgD has long been an enigmatic antibody with largely unknown functions. Although these have recently become more clear (reviewed elsewhere³), the function of secreted IgD remains poorly understood. Therefore, this review will not focus on IgD.

A B-cell response typically starts with the secretion of the pentameric IgM, after which a proportion of B cells undergoes isotype switching and starts producing IgG1-4, IgA1-2, or IgE. The type of switch is regulated by cytokines and costimulatory signals provided by T cells in the germinal center and depends on the location and nature of the antigen.⁴ Each isotype and subclass exerts a distinct effector function via its fragment crystallizable (Fc) domain, thereby shaping and tuning the immune response to enable efficient clearance of a wide variety of pathogens.⁵ The 2 main antibody effector functions are complement activation (summarized in Table E1 in this article's Online Repository at www.jacionline.org) and FcR binding through which immune cells are activated. An accumulating amount of evidence suggests

Abbreviations used

CD:	Cluster of differentiation
Dsg:	Desmoglein
Fc:	Fragment crystallizable
FcR:	Fc receptor
FcRn:	Neonatal FcR
GP:	Glycoprotein
MuSK:	Muscle-specific kinase
NC1:	NC1 domain of collagen 4 network
SRP:	Signal recognition particle

that the classical and alternative complement pathways play an important role in the pathogenesis of many systemic autoimmune diseases⁶ and complement inhibitors are being evaluated as potential therapeutic agents.⁷ Various Fc receptors (FcRs) have been described for all classes of immunoglobulins: 5 FcγRs and neonatal FcR (FcRn) for IgG, 2 FcεRs for IgE, FcαR for IgA, FcδR for IgD, and FcμR for IgM.⁸ Engagement of FcRs can affect the antibody serum half-life and induce various proinflammatory, anti-inflammatory, and immune-modulatory effects, which depend on various parameters including the isotype/subclass profile of an antibody. The role of FcRs in autoinflammatory processes has recently been reviewed elsewhere.⁹

Autoantibodies play a key role in the diagnostics of autoimmune diseases as highly specific disease biomarkers. A substantial amount of evidence also points to a major role for some autoantibodies in disease pathogenesis. Already in 1957, Witebsky et al's postulates¹⁰ were formulated, describing which criteria autoantibodies would have to meet to play a causal role in autoimmune diseases. High sensitivity/specificity parameters together with clear pathogenic properties exhibited by some autoantibodies help improve stratification of autoimmune diseases. Although clinical characteristics play a major role in disease classification for most autoimmune conditions, it is debated whether a pathogenesis-driven approach (eg, based on autoantibody presence) could be more insightful.^{11,12}

Particular isotypes/subclasses may play a specific pathophysiological role and determine a phenotype that may require a different treatment strategy. For example, patients with chronic inflammatory demyelinating polyneuropathy with IgG4-predominant autoantibody responses are poorly responsive to intravenous immunoglobulin but may benefit from rituximab.¹³

In the last decades, a vast body of literature on autoantibodies has been published. Several publications have aimed to summarize the existing data with a specific focus on a disease group or a specific isotype/subclass^{14–16}; however, a broad overview summarizing the existing data on the presence and role of autoantibody isotypes and subclasses across different diseases is lacking. We hypothesize that knowing the isotype/subclass profiles of various autoantibodies may yield valuable insights regarding the pathophysiology and potential interrelatedness of different autoimmune disorders usually scattered across the medical and academic areas. Grouping diseases by dominance or absence of particular isotypes/subclasses could help identify common effector mechanisms that drive the disease pathogenesis and thus could be used for targeted therapy. Examples of this could be complement components, specific FcRs or cytokines known to stimulate production of specific isotypes/subclasses.^{5,17}

Isotype/subclass profile can also be pathophysiologically linked with the breach of tolerance and the antigen(s) playing a role in this process⁴; thus, investigation of autoantibody isotype/subclass profiles may also help understand the mechanisms of autoimmunity induction and thus make a step toward prevention of autoimmunity. Moreover, a broad overview of this topic may identify knowledge gaps, which can simply direct future research and allow more detailed stratification of patients based on their isotype/subclass profiles. Therefore, we here give a comprehensive survey of the literature, covering a large variety of autoimmune diseases and autoantibodies with a specific focus on the autoantibodies that have been shown to play a direct pathogenic role.

METHODS

Autoantibody inclusion criteria

To focus this review on autoantibodies that are clinically relevant, possibly important for disease pathogenesis, and relatively well investigated, we used 5 criteria: (1) the targeted antigen should be defined on a molecular level (eg, a specific protein); (2) a prevalence of the autoantibody in more than 10% of a specific patient group for mutually exclusive antibodies (ie, autoantibodies exclusively found in patients with a specific phenotype, such as antimitochondrial and anti-proteinase 3 antibodies, hardly ever present in the same ANCA-associated vasculitis patients) and more than 50% for concomitantly present antibodies (eg, in systemic lupus erythematosus, where various autoantibodies can be detected in the same patient¹⁸), not specific for a particular ethnicity or geographical region, based on published prevalence studies; (3) a relative consensus in the field regarding autoantibody pathogenicity (reproducible and repeatedly published evidence shown in animal models, *in vitro* assays, and/or newborns from seropositive mothers, supported by the opinion of a respective disease expert from Target2B); (4) presence of published isotype-specific data; and (5) lack of a direct causal association with a different preceding disease or use of a pharmaceutical agent for most patients with the autoantibody response. When fulfilling all of these inclusion criteria, autoantibodies were included in Fig 1 and Tables I and II. Nonincluded autoantibodies/diseases are summarized in Table E2 in this article's Online Repository at www.jacionline.org.

Review composition

Of the 5 existing isotypes, we reviewed IgM, IgG, IgA, and IgE but not IgD, because of the scarce amount of literature on its secreted form. Moreover, because the vast majority of the data investigating IgA did not distinguish between IgA1 and IgA2 subclasses, we only included studies on total IgA.

The information on specific isotypes was presented in tables summarizing the existing data on 3 main aspects: (1) presence of specific autoantibody isotypes in patients, (2) relationship between autoantibody isotypes and various clinical parameters, and (3) signs of *in vitro* or *in vivo* pathogenicity.

Study selection

Articles were identified by a manual search of the literature listed in PubMed, Web of Science, and Google Scholar. Additional articles were found by reviewing reference lists of the already included articles. In view of the large number of disorders and autoantibodies checked for possible inclusion (27 disorders and more than 72 autoantibodies), the full methodology of systematic review was not used to make the project feasible to perform by a small team.

The studies were selected on the basis of presence of data related to this review: assessment of positivity for specific isotypes/subclasses, correlation of antibody levels with clinical parameters, and evidence of *in vitro* or *in vivo* pathogenicity. Eligibility was determined by reviewing the title, the abstract, and then the data presented in the full article. Fig 1 and Table I include only those studies that assessed autoantibodies in at least 10 patients. Only those

0%		1%-10%		10%-40%		40%-70%		>70%		Not enough data	
DISEASE	AUTOANTIBODY	IgM	IgA	IgE	IgG						
					IgG total	Within IgG-positive population					
						IgG1	IgG2	IgG3	IgG4		
BLISTERING DISEASES											
PEMPHIGUS VULGARIS	Anti-Dsg3	0% ^{E1, 2}	0%-72% ^{E2, E3, E4, E5}	0%-13% ^{E2, E4}	74%-100% ^{E2, E3, E6, E7}	33%-88% ^{E2, E4, E6, E7}	33%-57% ^{E2, E7}	7%-57% ^{E2, E7}	62%-100% ^{E2, E4, E6, E7}		
	Anti-Dsg1	0% ^{E2}	7% ^{E2}	32% ^{E8}	53%-59% ^{E2, E6, E7}	10%-31% ^{E2, E6, E7}	0%-14% ^{E2, E7}	0%-38% ^{E2, E7}	19%-59% ^{E2, E6, E7}		
PEMPHIGUS FOLIACEUS	Anti-Dsg1	0%-6% ^{E2, E8}	0% ^{E2}	44% ^{E8}	100% ^{E2, E6}	63%-100% ^{E2, E6}	0% ^{E2}	0% ^{E2}	100% ^{E2, E4, E6, E7}		
		FS: 12%-58% ^{E8, E9}	FS: 0% ^{E9}	FS: 81% ^{E8}	FS: 61%-91% ^{E9}	FS: 72%-79% ^{E10, E11}	FS: 31% ^{E11}	FS: 0% ^{E11}	FS: 90%-100% ^{E10, E11}		
BULLOUS PEMPFIGOID	Anti-BP180	- ^{E12}	88%-100% ^{E13, E14}	22%-100% ^{E13, E15-24}	72%-100% ^{E13, E14, E16, E17, E19, E21, E22}	50%-91% ^{E15, E17}	20%-44% ^{E15, E17}	26%-44% ^{E15, E17}	67%-71% ^{E15, E17}		
NEPHROLOGICAL DISEASES											
ANTI-GBM DISEASE	Anti-α3 NC1	-	-	-	93%-100% ^{E25, E26}	78% ^{E26}	76% ^{E26}	29% ^{E26}	63% ^{E26}		
IDIOPATHIC MEMBRANOUS NEPHROPATHY	Anti-PLA2R	-	-	-	47%-74% ^{E27-30}	75%-92% ^{E28, E30}	5% ^{E28}	71% ^{E28}	93%-100% ^{E28, E30, E31}		
NEPHROLOGICAL/ RHEUMATOLOGICAL DISEASES											
ANCA-ASSOCIATED VASCULITIS	Anti-PR3	15% ^{E32}	27%-47% ^{E33, E34}	- ^{E35}	GPA: 75%-80% ^{E36}	85%-100% ^{E37, E38}	18%-25% ^{E37, E38}	45%-69% ^{E37, E38}	58%-85% ^{E37, E38}		
	Anti-MPO	50%-67% ^{E39, E40}	EGPA: 6% ^{E41}	- ^{E35}	MPA: 68%-86% ^{E36}	94%-100% ^{E37, E38, E42}	30%-77% ^{E37, E38, E42}	25%-73% ^{E37, E38, E42}	67%-85% ^{E37, E38, E42}		
SYSTEMIC LUPUS ERYTHEMATOSUS	Anti-dsDNA	25%-57% ^{E43, E44, E45, E46}	19%-49% ^{E43, E44, E45, E46}	11%-40% ^{E45, E47}	37%-71% ^{E43-46, E48}	76% ^{E49}	10% ^{E49}	86% ^{E49}	0% ^{E49}		
RHEUMATOLOGICAL DISEASES											
PRIMARY SJÖGREN'S SYNDROME	Anti-SSA/Ro	76% ^{E50}	45%-84% ^{E50, E51}	-	43%-100% ^{E50-55}	92%-100% ^{E56, E57}	0%-28% ^{E56, E57}	12%-79% ^{E56, E57}	0%-56% ^{E56, E57}		
	Anti-SSB/La	76% ^{E50}	50%-80% ^{E50, E51}	-	21%-91% ^{E50-55}	96% ^{E57}	58% ^{E57}	65% ^{E57}	23% ^{E57}		
0%		1%-10%		10%-40%		40%-70%		>70%		Not enough data	
DISEASE	AUTOANTIBODY	IgM	IgA	IgE	IgG						
					IgG total	Within IgG-positive population					
						IgG1	IgG2	IgG3	IgG4		
NEUROLOGICAL DISEASES											
IMMUNE-MEDIATED NECROTIZING MYOPATHY	Anti-SRP	-	-	-	38% ^{E58}	81% ^{E59}	≤24% ^{E59}	5% ^{E59}	29% ^{E59}		
MYASTHENIA GRAVIS	Anti-AChR	-	-	-	50%-85% ^{E60, E61}	100% ^{E62}	33% ^{E62}	64% ^{E62}	39% ^{E62}		
MUSK-MYASTHENIA GRAVIS	Anti-MuSK	90%* ^{E63}	-	-	100%†	39% ^{E64}	39% ^{E64}	44% ^{E64}	100% ^{E60, E64-66}		
MULTIFOCAL MOTOR NEUROPATHY	Anti-GM1	33%-85% ^{E67-77}	5% ^{E70, E73}	-	0%-38% ^{E68, E70-73, E78}	-	-	-	-		
GUILLAIN-BARRÉ SYNDROME	Anti-GM1	8%-14% ^{E70, E72, E79, E80-84}	0%-28% ^{E70, E79, E81, E84, E85}	-	9%-50% ^{E70, E72, E79-84, E86, E87}	76%-94% ^{E88-90}	0%-6% ^{E88-90}	19%-52% ^{E88-90}	0%-44% ^{E88-90}		
MILLER FISHER SYNDROME	Anti-GQ1b	3%-69% ^{E70, E91-94}	28%-69% ^{E70, E92}	-	57%-100% ^{E70, E91-95}	38% ^{E95}	54% ^{E95}	54% ^{E95}	0% ^{E95}		
NEUROMYELITIS OPTICA SPECTRUM DISORDERS	Anti-AQP4	0%-27% ^{E96-98}	- ^{E99}	- ^{E99}	52%-89% ^{E100-106}	100% ^{E100, E107}	33% ^{E100}	0% ^{E100}	7% ^{E100}		
MOG ANTIBODY DISEASE	Anti-MOG	9% ^{E108}	9% ^{E108}	-	100%†	100% ^{E109}	23% ^{E109}	41% ^{E109}	14% ^{E109}		
AUTOANTIBODY-POSITIVE AUTOIMMUNE ENCEPHALITIS	Anti-NMDAR*	CSF: 0%* ^{E110}	CSF: 41%* ^{E111}	- ^{E112}	CSF: 79%-80% ^{E113, E114}	CSF: 92% ^{E110}	CSF: 15% ^{E110}	CSF: 23% ^{E110}	CSF: 0% ^{E110}		
					CSF/Serum: 30% ^{E115}	Serum: 82% ^{E116}	Serum: 18% ^{E116}	Serum: 27% ^{E116}	Serum: 0% ^{E116}		
					Serum: 67% ^{E113}						
	Anti-LGI1	-	-	-	CSF: 4% ^{E113}	CSF: 60% ^{E117}	CSF: 15% ^{E117}	CSF: 3% ^{E117}	CSF: 93% ^{E117}		
					CSF/Serum: 13%-24% ^{E114, E115}	Serum: 18%-87% ^{E117-120}	Serum: 0%-42% ^{E117-119}	Serum: 0%-16% ^{E117-119}	Serum: 81%-100% ^{E117-120}		
					Serum: 5% ^{E113}						

FIG 1. Prevalence of autoantibodies isotypes and subclasses in different diseases. Percentage of patients with a particular autoantibody isotype/subclass present in serum is shown, unless indicated otherwise. *BP*, bullous pemphigoid antigen; *PLA2R*, phospholipase A2 receptor; *PR3*, proteinase 3; *MPO*, myeloperoxidase; *SSA/SSB*, Sjögren syndrome antigen A/B; *AChR*, acetylcholine receptor; *GD1b*, ganglioside; *GD1bGM1*, ganglioside GM1; *AQP4*, aquaporin 4; *MOG*, myelin oligodendrocyte glycoprotein; *NMDAR*, N-methyl D-aspartate receptor; *LGI1*, leucine-rich glioma inactivated 1; *β2GPI*, beta 2 glycoprotein I; *ADAMTS13*, ADAM metalloproteinase with thrombospondin type 1 motif 13; *GP*, glycoprotein; *TSAb*, thyrotropin receptor stimulating antibody; *CSF*, cerebrospinal fluid; *EGPA*, eosinophilic granulomatosis with polyangiitis; *FS*, Fogo Selvagem; *GPA*, granulomatosis with polyangiitis; *MPA*, microscopic polyangiitis; *NMDAR*, N-methyl D-aspartate receptor; *PA*, platelet-associated. The reference list for the figure is separate and it can be found in this article's Online Repository at www.jacionline.org. *Diagnosis of anti-NMDAR encephalitis is based on presence of IgG antibodies in CSF; anti-NMDAR IgA and IgM levels were measured in patients with anti-NMDAR IgG positivity in CSF. †These patient subsets are defined by the presence of this antibody.

0%		1%-10%		10%-40%		40%-70%		>70%		Not enough data	
DISEASE	AUTOANTIBODY	IgM	IgA	IgE	IgG						
					IgG total	Within IgG-positive population					
						IgG1	IgG2	IgG3	IgG4		
HAEMATOLOGICAL DISEASES											
PRIMARY ANTI-PHOSPHOLIPID SYNDROME	Anti-β2GPI	21%-51% ^{E121-124}	14%-72% ^{E125}	-	13%-85% ^{E121-124}	18% ^{E126}	100% ^{E126}	14% ^{E126}	4% ^{E126}		
IDIOPATHIC THROMBOTIC THROMBOCYTOPENIC PURPURA	Anti-ADAMTS13	4%-10% ^{E127-130}	20%-21% ^{E127, E129}	-	89%-100% ^{E127-136}	52%-73% ^{E127, E130}	15%-50% ^{E127, E130}	8%-33% ^{E127, E130}	69%-90% ^{E127, E130}		
IDIOPATHIC IMMUNE THROMBOCYTOPENIC PURPURA	Anti-GP IIb/IIIa	Serum: 2% ^{E137}	Serum: 57% ^{E137}	-	Serum: 14%-81% ^{E137-140}	76% ^{E141}	22% ^{E141}	49% ^{E141}	27% ^{E141}		
					PA: 21%-76% ^{E137-140, E142-145}						
	Anti-GP Ib/IX	Serum: 11% ^{E137}	Serum: 66% ^{E137}	-	Serum: 12%-83% ^{E137-140}	-	-	-	-		
					PA: 25%-72% ^{E137, 138-140, E142-145}						
ENDOCRINOLOGICAL DISEASES											
GRAVES' DISEASE	Thyrotropin receptor stimulating antibody (TSAb)	-	-	-	78%-83% ^{E146, E149}	100% ^{E150}	0% ^{E150}	0% ^{E150}	0% ^{E150}		

FIG 1. (Continued).

studies that distinguished seropositive and seronegative individuals were incorporated in Fig 1.

RESULTS AND DISCUSSION

The table structure and general findings

In Fig 1 and Tables I and II, 26 autoantibodies occurring in 21 different diseases were included. Data on autoantibody isotype/subclass prevalence in the respective diseases are summarized in Fig 1. The percentage of positivity for each particular isotype/subclass was included: if more than 1 cohort or 1 study was used, the percentage range was given. Because of the scarcity of the data available for isotypes besides IgG, it was not possible to retrieve data regarding positivity for all isotypes of all antibodies. Data regarding IgM positivity were retrieved for 19 of 26 autoantibodies (73.1%), 17 of 24 (69.2%) for IgA, and only 5 of 24 (19.2%) for IgE. Data on IgG positivity were available for all studies, with data on specific IgG subclasses retrievable for 24 of 26 (92.3%) autoantibodies.

Table I provides information on the association between autoantibodies and clinically relevant characteristics, including disease activity, prediction of relapse, specific clinical phenotypes, and presence in healthy controls. When available, evidence for presence or absence of clinical features was listed per isotype. When a specific isotype/subclass remained stable or reappeared despite treatment and this was associated with subsequent clinical relapse, it was listed as a predictive biomarker in the respective column. IgG is the isotype most routinely measured for diagnostics, and it is also the isotype for which most information is available in the literature. Data regarding correlation with disease activity and relapse prediction were included for 25 of 26 (96.2%) and 14 of 26 (53.8%) autoantibodies, respectively. The availability of the data regarding the other included clinical parameters largely varied among autoantibodies.

Data on investigated pathogenic *in vivo* and *in vitro* effects of autoantibodies are stated in Table II. *In vivo* parameters include induction of disease-specific symptoms in animal models after passive or active immunization, and in newborns as a result of passive transfer (via placenta or breast milk) from

autoantibody-positive mothers. For animal models, “passive” implied passive transfer of human (autoantigen-specific) autoantibodies to healthy animals to induce disease-specific symptoms. “Active” mainly implied transgenic models (with spontaneous antibody development) or injection of the human autoantigen in wild-type mice to induce the antibody response and concomitant symptoms. When available, evidence for presence or absence of pathogenic features was listed per isotype. For active immunization studies and studies on pathogenicity of autoantibodies in newborns, a specific isotype responsible for the effect cannot be determined because the underlying response can be driven by other factors besides measured antibodies (including nonmeasured autoantibodies of other isotypes). Because of this, we did not specify the isotype for the active immunization studies, although IgG was often measured. For the newborns, however, IgG was listed because it is highly likely to play the key role in neonatal autoimmune syndromes, because transplacental transfer of immunoglobulins is mainly facilitated by FcRn that binds exclusively to IgG¹⁹ and breast-milk IgA does not enter newborn's circulation.²⁰ Concerning passive transfer, IgG and its subclasses were the sole isotypes investigated, most likely due to their high specificity and technical aspects (stability and predominance in clinical testing and laboratory use). Although animal models are practically irreplaceable in view of demonstrating the direct *in vivo* effects of an antibody, there are 2 important limitations: (1) immunoglobulin isotypes and subclass in animal models are not equivalent to the human ones, although human IgG subclasses do bind to mouse FcγRs with similar binding strength²¹; (2) in animal models, antigen molecules can differ from the human analogues, thus potentially hampering the recognition of the self-protein by the antibodies acquired via passive transfer from human or via immunization with a human antigen. Pathogenic *in vitro* effects included various inhibitory or detrimental outcomes shown on cells or autoantigenic molecules (eg, functioning enzymes). Table II lists these effects for the various isotypes/subclasses, if they were specific for the investigated autoantibody on comparison with other/control antibodies. Data on autoantibody pathogenicity in newborns were represented mostly by case reports/series and systematic reviews summarizing the data.

TABLE I. Clinically relevant effects of various autoantibodies

Disease	Autoantibody	Correlation with disease activity		Prediction of relapse		Association with a clinical phenotype	Presence in healthy controls	Other effects
		Present	Absent	Present	Absent			
Blistering diseases								
Pemphigus vulgaris	Anti-Dsg3	IgG ^{E151,E156; E1,E5,E157; IgE^{E5}}	IgG, IgG1 ^{E157}	IgG ^{E158}	—	—	IgG 0% ^{E159,E160}	IgG associates with HLA-DRB1*04:02 or DQB1*05:03 ^{E161}
	Anti-Dsg1	IgG ^{E152,E156,E162}	—	—	IgG ^{E158}	IgG: cutaneous phenotype ^{E154,E162}	IgG ~0% ^{E159,E160; IgG1^{E163}}	—
Pemphigus foliaceus	Anti-Dsg1	IgG ^{E153; IgG4^{E164}}	—	—	—	—	—	—
Bullous pemphigoid	Anti-BP180	IgG ^{E115,E18,E165-E167; IgG1, IgG4^{E166,E168,E169; IgE^{E17,E18,E20,E24}}}	IgE ^{E170}	IgG1, IgG4 (high levels) ^{E166; IgG (high titer)^{E171}}	—	IgG: erosions and blisters ^{E24}	IgG 0%-4% ^{E159,E172-E174; IgE 4%-7%^{E20,E22,E173,E175}}	—
Nephrological diseases								
Anti-GBM disease	Anti-α3 NC1	IgG ^{E25; IgG1, IgG3^{E26}}	—	—	—	IgG4: predominant lung involvement ^{E176}	—	—
Idiopathic membranous nephropathy	Anti-PLA2R	IgG ^{E27,E29,E177; IgG4^{E30,E31,E178}}	—	IgG ^{E179-E183}	—	—	IgG 0% ^{E184}	High IgG4 titer associates with low chance of spontaneous remission ^{E28}
Nephrological/rheumatological diseases								
ANCA-associated vasculitis	Anti-PR3	IgG ^{E185,E187; IgA, sIgA^{E33}}	IgG ^{E188}	IgG ^{E189-E201; IgG3^{E192}}	IgG ^{E188,E195,E202-E204; IgG1, IgG3, IgG4^{E204}}	—	IgG 3% ^{E205}	IgG associates with stronger prediction of relapse in patients with specific clinical phenotypes ^{E193,E206}
	Anti-MPO	Ig ^{E207; IgG^{E187,E208,E209}}	IgG ^{E185}	IgG ^{E190,E193-E197,E208,E210}	IgG ^{E195,E203,E204; IgG1, IgG3, IgG4^{E204}}	IgM: pulmonary hemorrhage ^{E39}	IgG ~0% ^{E205}	IgG associates with stronger prediction of relapse in patients with specific clinical phenotypes ^{E193,E206}
Systemic lupus erythematosus	Anti-ds-DNA	IgG ^{E46,E211-E213; IgE^{E47,E214}}	—	IgG ^{E212,E215,E216; IgG1^{E216; Ig^{E217}}}	—	IgG: lupus nephritis ^{E218}	IgG 0%-2% ^{E43,E44,E219; 0% (≥65 y/o)^{E220,E221; IgM 0%-3%^{E43,E44,E221; 0%-2% (≥65 y/o)^{E220,E221; IgA 0%-3%^{E43,E44; 7% (≥65 y/o)^{E220}}}}}}	—
Rheumatological diseases								
Primary Sjögren syndrome	Anti-SSA/Ro Anti-SSB/La	IgG ^{E53,E54 IgG^{E53,E54}}	— —	— —	— —	IgG: extraglandular manifestations ^{E53,E222,E223} IgG: extraglandular manifestations ^{E53,E226}	IgG 1%-3% ^{E54,E219; Ig 0%-1%^{E224 IgG 0%-3%^{E54,E219; Ig 0%-5%^{E224}}}}	IgE associates with fetal loss ^{E225} —
Neurological diseases								
Immune-mediated necrotizing myopathy	Anti-SRP	IgG ^{E59}	—	—	—	—	IgG 0% ^{E227}	IgG associates with HLA-DRB1*08:03 ^{E228} , HLA-DRB1*14:01 ^{E229} , poor response to steroid monotherapy ^{E58,E230}
Myasthenia gravis	Anti-AChR	IgG1 ^{E60,E62}	IgG ^{E60,E231; IgG2, IgG3, IgG4^{E62}}	IgG ^{E232}	—	—	IgG 0% ^{E61}	Ig associates with HLA-B8 and HLA-DR3 haplotypes ^{E233}
MuSK-myasthenia gravis	Anti-MuSK	IgG4 ^{E60,E234}	—	—	—	—	IgG: 0%-2% ^{E61,E63 IgG4: 0%^{E64,E235}}	IgG4: HLA haplotype associations ^{E236-E238}
Multifocal motor neuropathy	Anti-GM1	IgM ^{E73}	—	—	—	IgM: disability, axon loss ^{E73}	IgM 0%-9% ^{E72,E239,E240; IgG 0%-2%^{E72,E239,E240}}	—
Guillain-Barré syndrome	Anti-GM1	IgG1 ^{E88; Ig^{E81}}	—	—	—	IgG: motor phenotype ^{E79,E241,E242; IgG, IgM, IgA: axonal phenotype^{E242; IgG1: slow recovery^{E88,E89; IgG3: rapid recovery^{E88}}}}	IgA with preceding diarrhea, anti- <i>C jejuni</i> antibodies ^{E92; IgG1 with preceding gastrointestinal infection, anti-<i>C jejuni</i> antibodies^{E88,E89; IgG3 with preceding upper respiratory tract infection^{E88}}}	
Miller Fisher syndrome	Anti-GQ1b	IgG ^{E93}	—	—	—	IgG: (acute) ophthalmoplegia ^{E91,E243,E244 and ataxia^{E91,E244}}	IgM 0% ^{E239,E240; IgG ~0%^{E239,E240}}	—
Neuromyelitis optica spectrum disorders	Anti-AQP4	IgG ^{E101,E104,E106}	IgG ^{E100,E245,E246; IgG1, IgG2^{E100}}	—	IgG ^{E245}	IgG at onset: optic neuritis ^{E246}	IgG 0% ^{E247}	—
MOG antibody disease	Anti-MOG	—	—	IgG ^{E248; IgG1^{E251}}	Ig ^{E249,E250; Ig^{E252}}	—	IgG 0% ^{E253}	IgG, IgG1 with preceding infection or vaccination ^{E251 High IgG with bilateral optic neuritis^{E254}}
Autoantibody-positive autoimmune encephalitis	Anti-NMDAR	IgG ^{E116,E255,E256}	IgA ^{E111}	—	—	IgA ^{E111} and high IgG titers ^{E256; tumors; high IgG titers: poor outcome^{E256}}	IgG 0%-1% ^{E257-E259; IgM 0%-4%^{E257,E259; IgA 0%-4%^{E257,E259,E260}}}	IgG in CSF correlates better with disease activity than IgG in serum ^{E256}
	Anti-LGI1	IgG1 ^{E120; IgG4 in CSF^{E119}}	—	—	—	IgG1 with cognitive impairment, IgG4 with FBDS ^{E120 Intrathecal synthesis of IgG with worse outcome^{E119}}	Ig 0% ^{E257}	IgG levels are higher in serum than in CSF ^{E261}
Hematological diseases								
Primary antiphospholipid syndrome	Anti-β2GPI	IgG ^{E262-E266; IgA^{E267; IgM^{E264}}}	—	—	—	IgG: thrombosis ^{E268,E269} and heart valve disease ^{E270; IgA: thrombosis^{E268; IgG, IgA: livedo reticularis^{E270}}}	IgG 0%-2% ^{E224,E271; IgA 0%^{E224; IgM 0%-1%^{E224}}}	—

(Continued)

TABLE 1. (Continued)

Disease	Autoantibody	Correlation with disease activity		Prediction of relapse		Association with a clinical phenotype	Presence in healthy controls	Other effects
		Present	Absent	Present	Absent			
Idiopathic thrombotic thrombocytopenic purpura	Anti-ADAMTS13	IgG1, IgG3, IgA ^{E272}	IgG, IgA, IgM ^{E120} , IgG, IgM, IgG2, IgG4 ^{E272}	IgG ^{E272} , IgG4 ^{E127}	IgG ^{E129,E273} , IgM, IgA ^{E129}	—	IgG 4%-5% ^{E136,E274}	IgG associates with mortality ^{E275} ; need for plasmapheresis ^{E272}
Idiopathic immune thrombocytopenic purpura	Anti-GP IIb/IIIa	—	PA IgG ^{E276}	PA IgG ^{E277}	PA IgG ^{E276}	— PA IgG: severe bleeding manifestations ^{E280} and poor response to treatment ^{E280,E281}	PA IgG 0% ^{E139,E141,E278}	Double-positive for PA IgG anti-GP IIb/IIIa and anti-GP Ib/IX associates with severe bleeding manifestations and poor response to therapy ^{E276} ; amount of targeted GPs associates with severity ^{E279}
	Anti-GP Ib/IX	—	PA IgG ^{E276}	PA IgG ^{E277}	PA IgG ^{E276}		PA IgG 0% ^{E278}	
Endocrinological diseases								
Graves' disease	TSAb	IgG ^{E149,E282,E283}	IgG ^{E284}	IgG ^{E285,E286}	IgG ^{E287}	IgG: Graves' ophthalmopathy ^{E283,E284,E288,E289}	IgG 0% ^{E149,E290}	—

The reference list for the table is separate, and it can be found in this article's Online Repository at www.jacionline.org.

ACHr, Acetylcholine receptor; *ADAMTS13*, ADAM metalloproteinase with thrombospondin type 1 motif 13; *ANCA*, antineutrophil cytoplasmic antibody; *AQP4*, aquaporin 4; *BP*, bullous pemphigoid antigen; *β2GPI*, beta 2 glycoprotein I; *CSF*, cerebrospinal fluid; *ds-DNA*, double-stranded DNA; *FBDS*, faciobrachial dystonic seizures; *GBM*, glomerular basement membrane; *GM1*, ganglioside GM1; *GP*, glycoprotein; *GQ1b*, ganglioside GQ1b; *Ig*, immunoglobulin; *PA*, platelet-associated; *LGII*, leucine-rich glioma inactivated 1; *MOG*, myelin oligodendrocyte glycoprotein; *MPO*, myeloperoxidase; *NCL1*, NC1 domain of collagen 4 network; *NMDAR*, N-methyl D-aspartate receptor; *PA*, platelet-associated; *PLA2R*, phospholipase A2 receptor; *PR3*, proteinase 3; *sIgA*, secretory IgA; *SRP*, signal recognition particle; *TSAb*, thyrotropin receptor stimulating antibody.

Autoantibodies that passed some, but not all, of the inclusion criteria were excluded from the review and are listed in Table E2, together with the reason for exclusion.

In the last few years, patients with certain autoantibodies have been suggested to comprise separate disease subsets (eg, muscle-specific kinase [MuSK] myasthenia gravis,²² anti-myelin oligodendrocyte glycoprotein disease,²³ and autoimmune (para-)nodopathies²⁴). For MuSK myasthenia gravis and anti-myelin oligodendrocyte glycoprotein disease, a substantial number of published studies have investigated them as separate disease entities, thus allowing to include them as distinct diseases in our overview. For autoimmune paranodopathies, this remains to be further investigated; thus, we applied our inclusion criteria, which resulted only in anti-NF155 being included in the review.

IgG4: Emerging driver of autoimmunity

Among all the characterized isotypes and subclasses, IgG4 appears to hold a unique position: for 6 of 22 autoantibodies with the IgG-subclass data available, IgG4 was either the most prevalent isotype/subclass or shared the highest prevalence with IgG1. This is striking because IgG4 is the least abundant IgG subclass in serum.⁵

For some of the included autoantibodies, IgG4 was not only widely present (>75%) but also appeared to play a possible driving role in the disease. In these cases, IgG4 correlated with disease activity and exhibited pathogenic properties in animal models and *in vitro* assays. This was the case for anti-desmoglein (Dsg)-3 in pemphigus vulgaris and anti-Dsg1 in pemphigus foliaceus, and anti-phospholipase A2 receptor in idiopathic membranous nephropathy.

Another interesting aspect is the interplay between IgG4 and IgG1 in these diseases. Although IgG1 plays a major role in most autoantibody responses, in the IgG4-dominated responses, IgG1 either had limited prevalence (anti-phospholipase A2 receptor) or was prevalent, but appeared to play a “bystander” role (anti-Dsg3, anti-Dsg1), because IgG1 did not show pathogenic properties or correlation with disease activity.

This evidence for possible pathogenic effects of IgG4 autoantibodies is especially intriguing because IgG4 is often considered

an anti-inflammatory antibody, being unable to activate the classical complement pathway and binding less well to some of the stimulatory FcRs.^{25,26} Furthermore, it is suggested that IgG4 could exert protective effects by outcompeting IgG1 or/and IgE antibodies that are more potent at exerting effector mechanisms, when they target the same antigens.^{27,28} Several hypotheses have been formulated to explain the unexpected role of IgG4 in autoimmune disease pathogenesis. On the one hand, several studies report the activation of complement by IgG4 via the lectin pathway, which has been suggested to play a role in the anti-phospholipase A2 receptor response in patients with idiopathic membranous nephropathy.^{29,30} On the other hand, when binding to certain antigens, IgG4 could exhibit a unique pathogenic effect due to its ability to exchange half of its molecule (antibody-binding fragment [Fab]-arm exchange) and become functionally monovalent.¹⁵ For instance, in myasthenia gravis associated with antibodies against MuSK, monospecific bivalent autoantibodies (that have not undergone Fab-arm exchange) can dimerize MuSK and thus activate MuSK signaling, thereby maintaining muscle strength.³¹ In this setting, the bispecific monovalent IgG4 autoantibodies are detrimental because they block MuSK function, whereas monospecific bivalent IgG1 autoantibodies partly restore it. Similar blocking/inhibiting mechanisms were also shown for other IgG4-mediated diseases.^{32,33}

The enigmatic nature of IgG4-mediated autoimmunity has been reviewed in greater detail elsewhere.^{15,16,34-36} Nevertheless, many physiological and pathological aspects of IgG4 autoantibodies and the IgG4-mediated responses, in general, remain unknown.

Conversely, in 6 of 22 autoantibodies with data on IgG subclasses, the role of IgG4 appeared negligible (<10% of patients being IgG4-autoantibody-positive). The nature of the antigen and the timing of exposure are likely to play an important role, because IgG4 is considered to be associated with allergens^{37,38} and a T_H2 response,³⁹ and emerge after repeated antigen exposure.⁴⁰ It may be speculated that in disorders characterized by low or absent IgG4 autoantibody levels, these factors are less likely to play a pathogenic role, although more focused research is required.

TABLE II. Pathogenic features of antibodies

Disease	Autoantibody	Evidence of pathogenicity in animal models		Pathogenic <i>in vitro</i> effect		Pathogenicity in newborns	
		Present	Absent	Present	Absent	Present	Absent
<i>Blistering diseases</i>							
Pemphigus vulgaris	Anti-Dsg3	Passive: IgG ^{E91} , IgG1 ^{E292,E293} , IgG4 ^{E293}	Passive: IgG1 ^{E292}	IgG ^{E291,E294-E298} , IgG1 ^{E292,E293} , IgG4 ^{E293}	IgG ^{E291}	IgG ^{E299,E300}	—
Pemphigus foliaceus	Anti-Dsg1	Passive: IgG ^{E291}	—	IgG ^{E291,E301}	IgG ^{E291,E301}	—	—
	Anti-Dsg1	Passive: IgG ^{E302,E303}	—	IgG ^{E295,E303-E305} , IgG1 ^{E306}	IgG ^{E303}	IgG ^{E299,E307,E308}	FS: IgG ^{E309}
Bullouspemphigoid	Anti-BP180	Passive: IgG ^{E310}	—	IgG1, IgG4 ^{E311}	—	IgG ^{E299}	—
<i>Nephrological diseases</i>							
Anti-GBM disease	Anti-α3 NC1	Active: Ig ^{E312,E313} , Passive: Ig ^{E314} , rabbit IgG ^{E315}	—	IgG ^{E316}	—	—	IgG ^{E317}
Idiopathic membranous nephropathy	Anti-PLA2R	Passive: IgG ^{E318}	—	Ig ^{E319} , IgG4 ^{E320}	—	—	IgG ^{E321} , IgG4 ^{E322}
<i>Nephrological/rheumatological diseases</i>							
ANCA-associated vasculitis	Anti-PR3	Active: Ig ^{E323} , Passive: IgG ^{E324}	—	IgG1, IgG3, IgG4 ^{E325,E326}	IgG ^{E326}	—	IgG ^{E327,E328}
	Anti-MPO	Active: Ig ^{E329-E333} , Passive: IgG ^{E334}	—	IgG ^{E335}	IgG ^{E326}	IgG ^{E327}	IgG ^{E327}
Systemic lupus erythematosus	Anti-ds-DNA	Active: Ig ^{E336-E338} , Passive: IgG ^{E339-E342}	—	IgG ^{E342-E346} , IgE ^{E214}	—	—	—
<i>Rheumatological diseases</i>							
Primary Sjögren syndrome	Anti-SSA/Ro	Passive: IgG ^{E347}	—	IgG ^{E348,E349}	—	IgG ^{E350}	—
	Anti-SSB/La	Passive: IgG ^{E347}	—	IgG ^{E348,E349}	—	IgG ^{E350}	—
<i>Neurological diseases</i>							
Immune-mediated necrotizing myopathy	Anti-SRP	Active: Ig ^{E351} , Passive: IgG ^{E351,E352}	—	IgG, Fab ^{E353} , IgG ^{E352}	—	—	—
Myasthenia gravis	Anti-AChR	Active: Ig ^{E354,E355} , Passive: IgG ^{E356,E357} , rat IgG ^{E358,E359}	Passive: IgG4 ^{E360} , Protective effect: IgG4 ^{E361}	IgG, IgG1 ^{E357}	—	IgG ^{E362-E364}	IgG ^{E365,E366}
MuSK-myasthenia gravis	Anti-MuSK	Passive: IgG4 ^{E66,E367,E368} Active: IgG4 ^{E66,E367,E369}	IgG1,IgG2,IgG3 ^{E369}	IgG4 ^{E367} IgG ^{E368}	—	IgG ^{E370,E371}	—
Multifocal motor neuropathy	Anti-GM1	Passive: Serum ^{E372-E374}	Passive: IgM ^{E375}	Ig ^{E374} , IgM ^{E376-E378}	—	IgG ^{E379}	—
Guillain-Barré syndrome	Anti-GM1	Active: Ig ^{E380-E383} , Passive: IgG ^{E384}	Passive: IgG ^{E375}	Ig ^{E377} , Mouse: IgG2b ^{E385}	Mouse: IgG2b ^{E377}	—	—
Miller Fisher syndrome	Anti-GQ1b	Passive: mouse IgM ^{E386}	—	Ig ^{E387-E389} , IgG ^{E389-E394} , IgG1 + IgG2 ^{E389} , IgG3 ^{E389} , Mouse: IgM ^{E388,E395} , IgG2b ^{E396}	IgM ^{E390}	—	—
Neuromyelitis optica spectrum disorders	Anti-AQP4	Passive: Ig ^{E397} , IgG1 ^{E398}	Passive: Ig ^{E397}	IgG1 ^{E96} , IgG ^{E399,E400} IgG, F(ab') ₂ ^{E401} , IgG ^{E405,E408}	—	—	IgG ^{E402}
MOG antibody disease	Anti-MOG	Active ^{E403,E404} Passive: IgG ^{E405-E408}	—	—	—	—	—
Autoantibody-positive autoimmune encephalitis	Anti-NMDAR	Active: Ig ^{E409-E411} , Passive: IgG ^{E412-E418} , Ig ^{E419}	Active: Ig ^{E409}	Ig ^{E373} , IgG ^{E259,E419-E421} , IgA ^{E260}	IgA, IgM ^{E259}	IgG ^{E422-E424}	—
	Anti-LGI1	Natural development: feline Ig ^{E425} , Passive: IgG ^{E426} , IgG4 ^{E261}	—	IgG1 ^{E120} , IgG4 ^{E120,E261} , IgG ^{E261,E426,E427} , Fab ^{E261}	—	—	—
<i>Hematological diseases</i>							
Primary antiphospholipid syndrome	Anti-β2GPI	Active: Ig ^{E428-E430} , Passive: IgG ^{E347,E431,E432} , Fab ^{E433}	—	IgG ^{E434-E437} , IgM ^{E435}	—	IgG ^{E438-E440}	—
Idiopathic thrombotic thrombocytopenic purpura	Anti-ADAMTS13	Passive: IgG ^{E441,E442}	—	IgG ^{E443,E444}	—	—	IgG ^{E445}
Idiopathic immune thrombocytopenic purpura	Anti-GP IIb/IIIa	Active: Ig ^{E446} , Passive: IgG ^{E447-E449}	—	IgG ^{E450,E451} , IgM ^{E452}	—	IgG ^{E453}	—
	Anti-GP Ib/IX	Active: Ig ^{E446} , Passive: IgG ^{E447,E448}	—	IgG ^{E450-E452,E454,E455}	—	—	—
<i>Endocrinological diseases</i>							
Graves disease	TSAb	Active: Ig ^{E456-E458} , Passive: IgG ^{E459} , mouse IgG ^{E460}	—	IgG ^{E461} , IgG1 ^{E462} , Mouse IgG, Fab ^{E458,E460}	—	IgG ^{E463}	—

The reference list for the table is separate, and it can be found in this article's Online Repository at www.jacionline.org.

AChr, Acetylcholine receptor; *ADAMTS13*, ADAM metalloproteinase with thrombospondin type 1 motif 13; *ANCA*, antineutrophil cytoplasmic antibody; *AQP4*, aquaporin 4; *BP*, bullous pemphigoid antigen; *β2GPI*, beta 2 glycoprotein I; *ds-DNA*, double-stranded DNA; *FS*, Fogo Selvagem; *GBM*, glomerular basement membrane; *GM1*, ganglioside GM1; *GQ1b*, ganglioside GQ1b; *Ig*, immunoglobulin; *LGI1*, leucine-rich glioma inactivated 1; *MOG*, myelin oligodendrocyte glycoprotein; *MPO*, myeloperoxidase; *NC1*, NC1 domain of collagen 4 network; *NMDAR*, N-methyl D-aspartate receptor; *PLA2R*, phospholipase A2 receptor; *PR3*, proteinase 3; *SRP*, signal recognition particle; *TSAb*, thyrotropin receptor stimulating antibody.

IgE: Bridge between allergy and autoimmunity

Among the various autoantibody isotypes, IgE was the least prevalent, known to be present in 5 of 24 autoantibodies (Fig 1). Although data on IgE autoantibodies are scarce in the available epidemiologic and translational studies, in some specific diseases, IgE autoantibodies have been reported to correlate with disease activity (Table I) and have possible pathogenic effects in animal models and *in vitro* experiments (Table II). In particular, IgE autoantibody levels of anti-Dsg-3, bullous pemphigoid antigen 180, and double-stranded DNA were shown to correlate with disease activity (Table I). Interestingly, for 4 of 5 autoantibodies with IgE presence, high IgG4 prevalence was also observed (Fig 1).

The IgE response is conventionally associated with allergy, and the role of IgE in the pathogenesis of autoimmune diseases is largely unknown and scarcely investigated. One of the underlying reasons for this is the high variability and low reproducibility of the methods used to assess IgE autoantibodies.⁴¹ Because of different conformational states or when bound to mast cells or basophils, IgE may not be detectable by anti-IgE antibodies in certain assays,^{42,43} and the IgG targeting the same autoantigen is usually present in substantially higher concentrations, causing it to interfere with IgE measurement in the assay.⁴⁴ Published prevalences of certain antigen-specific IgE reactivities (eg, anti-bullous pemphigoid antigen 180, Fig 1) appear highly variable, possibly reflecting differences in both sensitivity and specificity of particular assays. In the absence of a “criterion standard” IgE assay, it may be challenging to identify the results most closely reflecting the “true” IgE prevalence among patients.

Despite these technical drawbacks, for certain autoimmune diseases, there is a substantial body of evidence suggesting a pathophysiological role for IgE autoantibodies. The list present in Fig 1 and Tables I and II can be complemented with other diseases in which IgE autoantibodies are reported, such as atopic dermatitis and chronic urticaria.⁴⁵ Intriguingly, most of these diseases are associated with skin involvement. Moreover, for bullous pemphigoid and atopic dermatitis, IgE deposits were found in the skin of the patients and anti-IgE treatment (with omalizumab) showed clinical efficacy.^{46,47} In contrast, several studies reported IgE autoantibodies in diseases without skin involvement such as Graves’ disease (antibodies against thyroid peroxidase) and autoimmune uveitis (antibodies against retinal S antigen), although the evidence regarding the pathogenicity of IgE autoantibodies in these diseases is limited.⁴⁸

The mechanism underlying the role of IgE autoantibodies likely involves mast cells and basophils, because they express high levels of FcεRI and participate in skin lesion formation.⁴⁹ However, there are other mechanisms through which IgE could exhibit pathogenicity, for example, by forming immune complexes and subsequently activating plasmacytoid dendritic cells⁴⁸ or by participating in antigen uptake and HLA class II-mediated presentation to cluster of differentiation (CD)4 T cells.⁴⁵ T_H2 response likely plays an important role in the regulation of IgE autoantibody production and thus links it with the IgG4 response, establishing a link known to be present in allergy.⁵⁰ Overall, IgE represents a promising target for autoantibody research, and further investigation is likely to unravel the role IgE plays in autoimmunity.

Autoantibody-depleting therapeutic methods

Because autoantibodies have been long suspected to be pathogenic, a range of treatments have been implemented to

lower the levels of autoantibodies in blood. These treatments encompass 2 general approaches: extracorporeal methods directly reducing the autoantibody levels (plasmapheresis, immunoadsorption, etc) and pharmaceutical methods affecting the immunoglobulin half-life or production (FcRn-targeting therapy, B-cell and plasma cell depletion).

Extracorporeal methods have been widely used in various autoimmune diseases^{51–53} and, in some conditions, are considered to be the therapy of choice.⁵⁴ However, the extracorporeal methods also have important limitations: the high costs, the required expertise, the invasiveness of the procedure, and the need of the intensive care facilities limit the use in daily practice. So, although these methods can provide a clear indication of the pathogenic properties of autoantibodies, there is a lack of randomized double-blind placebo-controlled studies investigating the efficacy of these methods.⁵⁴ Moreover, in case of plasmapheresis, most plasma proteins are removed, which makes it challenging to attribute the effect exclusively to the depletion of autoantibodies and immune complexes.⁵² Immunoadsorption, however, is more selective and can even result in selective removal of particular isotypes.⁵⁵ The implication of the methods of extracorporeal antibody depletion for various immune-mediated diseases has been reviewed in detail elsewhere.^{52,53}

The most prominent pharmaceutical methods aiming to deplete autoantibodies include targeting B cells, plasma cells, and FcRn. The most widespread method is B-cell depletion via CD20, using rituximab and other anti-CD20 agents.⁵⁶ Importantly, although rituximab therapy appears to lower levels of some autoantibodies, such as anti-proteinase 3^{57,58} and antimyeloperoxidase⁵⁷ or anti-Dsg1,⁵⁹ it hardly affects levels of others, such as anti-SSB/La and anti-SSA/Ro⁶⁰ or anti-acetylcholine receptor.⁶¹ This phenomenon may highlight another important distinction between various autoantibodies and suggests that different autoantibodies may be produced by different types of antibody-producing cells. In particular, rituximab does not deplete long-lived plasma cells⁶² and thus the levels of autoantibodies they produce remain unaffected. Other methods use mAbs and chimeric antigen receptor T cells to target CD19, CD22, CD38, and other B-cell- and plasma-cell-associated markers; these approaches have been recently reviewed elsewhere.⁶³

Another approach that has been emerging in the recent years uses targeted therapy to affect antibody half-life via FcRn. FcRn antagonists, such as efgartigimod and rozanolixizumab, inhibit FcRn-mediated recycling of IgG and thus lower the half-life of circulating (auto)antibodies.^{64–67} Interestingly, this approach is isotype specific, because it targets IgG only.⁵ Finally, some therapies directly target (auto)antibodies of a specific isotype, such as IgG-degrading imlifidase, seemingly efficacious in antineutrophil cytoplasmic antibody-associated vasculitis,⁶⁸ and IgE-blocking omalizumab, showing promising results in chronic spontaneous urticaria^{69,70} and bullous pemphigoid.^{71,72}

Various autoantibody-depleting therapies have been used in clinical practice, and even more methods are currently in development. Most existing methods target autoantibodies in a nonspecific and indirect manner, which makes the effect temporal and/or incomplete. Current developments aim to target the autoantibody responses in an increasingly specific manner, including therapies targeting IgG (via FcRn⁶⁷ and directly⁶⁸) and IgE.⁶⁹ For the already existing approaches and for the potential future therapies targeting specific IgG subclasses, IgM, or

IgA, knowledge of the isotype/subclass profiles, such as the one summarized in this overview, could serve as an asset.

Contradicting data, investigational biases, and gaps Inconsistencies in Fig 1 and Tables I and II.

In Fig 1 and Tables I and II, the existing data are summarized in a concise manner to allow a comparison between diseases and autoantibodies. However, it is important to indicate the presence of possible inconsistencies in the reported literature findings and the variation in the quality of the data presented in the tables. Some isotypes/subclasses were investigated in a large number of high-quality studies, whereas others—present in more rare diseases—were only measured in a limited number of studies with few participants.

The first type of inconsistency involves the large variation in isotype prevalence found among studies, resulting in a large range reported in the table. Another type of inconsistency can be found in Tables I and II: some studies report positive findings, whereas others report negative results. There are various reasons potentially explaining these differences, including variation in implemented methodology (such as antibody assays⁷³), limited patient numbers, and differences in patient characteristics (eg, by disease stage and activity, treatment status, ethnicity, and age). This heterogeneity complicated the use of one of the inclusion criteria we implemented for autoantibody selection: namely, consensus regarding autoantibody pathogenicity. In case of controversial data regarding pathogenicity, we selected autoantibodies for which the evidence of pathogenicity was demonstrated reproducibly and, preferably, corroborated in various experimental setups (Table II).

It is important to note that included studies used various methods, including ELISA, microarrays, immunoblotting, and so forth, with each method demonstrating various degree of technical variation. This can be further illustrated by studies incorporating various methods to measure the same type of autoantibodies, because the results obtained with different methods never fully repeat each other.^{44,74-77} Moreover, for most methods, positivity for an antibody is determined by a cutoff, which is derived from a comparison with a control group; naturally, the exact methods used to calculate the cutoff and the sizes of control groups also differed among studies, thus adding another layer of variation to the data summarized in the tables. Aiming to identify 1 of more specific factors responsible for inconsistencies, we hypothesized that the antibody assays became more sensitive over the years. However, when we performed a separate subanalysis on this effect in Fig 1 data, using the antibodies with the largest variation ranges (IgG anti-SS-A and anti-SS-B, IgE anti-bullous pemphigoid antigen 180, etc), we did not detect a clear link between the prevalence of specific isotypes and the year of the study, which suggested against the presence of such an effect (see Fig E1 in this article's Online Repository at www.jacionline.org). Nevertheless, understanding of the limitations inherent to this kind of data is crucial for the correct interpretation of this overview.

Another important factor causing inconsistencies is directly related to the antibody testing, because most studies use total IgG over specific IgG subclasses when testing for clinical associations (Table I). There are several diseases in which a correlation between total autoantibody-IgG and disease activity has been reported to be both present and absent, depending

on the publication (as in the case of anti-Dsg3,⁷⁸⁻⁸⁴ anti-proteinase 3,⁸⁵⁻⁸⁸ antityeloperoxidase,^{85,87,89,90} anti-aquaporin 4^{77,91-95} IgG). A possible explanation is that when total IgG is used, the contribution of the subclasses might be overlooked. For instance, subclass-specific analysis of anti-Dsg3 in patients with pemphigus vulgaris showed that IgG4, but not IgG1 or total IgG, correlated with disease activity⁸⁴ (Table I).

Furthermore, although pathogenic properties are often demonstrated for IgG in animal models, very limited data exist regarding pathogenicity of (the same) autoantibodies in newborns, the evidence of which is mainly demonstrated in case reports/series. This may seem counterintuitive, because IgG are transferred to the newborns' circulation during pregnancy and "human-to-human" transfer is hypothetically more insightful regarding the direct effect of the human autoantibodies. This is, however, not evident from the literature. The possible reasons for this discrepancy have been reviewed elsewhere⁹⁶ and include 2 main factors: (1) an underdeveloped and more tolerogenic state of the fetal/neonatal immune system and (2) lack of the antigen expression in newborns. A wider investigation of the autoantibody pathogenic properties in newborns in the absence of clear symptoms is further complicated by the ethical challenges of this type of research. The overview presented in the tables of this review, particularly in Fig 1, identifies knowledge gaps across published data and therefore can be a useful tool to guide further research in this direction.

Knowledge gaps regarding IgM and IgA. Considering the short half-life of IgM (5 days against 23 days for IgG⁹⁷) and the limited presence of IgM memory B cells in healthy individuals due to antigen-induced class switching, the presence of IgM in chronic autoreactive responses is intriguing. This could be explained by a continuous initiation of an IgM B-cell response due to repetitive exposure to autoantigens, or by the formation of long-lived IgM-producing plasma cells.⁹⁸ The presence of IgA autoantibodies, however, could indicate a possible pathogenic link with mucosal pathogens.

In the currently available literature, IgM and IgA responses of various autoantibodies are often understudied, which is generally linked to limitations of serological assays detecting IgM and IgA. The implemented assays are notorious for their high background signal, which complicates the discrimination between negative and positive samples. The underlying reasons for this background signal could be the higher avidity due to a larger amount of binding idiotypes (pentameric IgM and dimeric/multimeric IgA), natural antibodies (mostly IgM and IgA present in the absence of antigenic triggering and often exhibiting autoreactivity), and rheumatoid factor (antibody response primarily of IgM or IgA isotype that targets IgG). Rheumatoid factor can often lead to false-positive IgM results,⁹⁹ and it is present in the serum of various patients with autoimmune diseases (systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, etc) as well as in healthy individuals.¹⁰⁰⁻¹⁰² Nevertheless, highly sensitive and specific serological assays and more careful preparation of the samples could help tackle these challenges and test IgA and IgM accurately, such as an IgM antigen binding test,¹⁰³ example of which has also been developed for measuring antibodies against COVID-19.¹⁰⁴

Lack of focus on the Fab-mediated effector functions. Antibody effector functions are usually mediated by the Fc region; however, antibodies can also exert Fab-mediated

detrimental effects by directly or indirectly inhibiting the antigen function or blocking its interaction with other molecules or cross-linking them.¹⁰⁵ This is often (but not exclusively) observed in autoantibodies with the predominant IgG4 subclass, demonstrating particularly high affinity and relatively weak Fc-mediated proinflammatory properties.¹⁰⁶ Although these mechanisms could be relevant for disease pathophysiology, they rely on antigen specificity rather than isotype/subclass composition, thus placing this topic beyond the scope of this review. Nevertheless, it is worth saying that this mechanism often appears to play a role for autoantibodies with the predominant IgG4 subclass, demonstrating particularly high affinity and relatively weak Fc-mediated proinflammatory properties.³⁵

CONCLUSIONS

Autoantibodies are a key tool for investigating various autoimmune diseases, being both a highly specific diagnostic tool in the clinic and a robust instrument for translational research. To our knowledge, this review provides the first and thus far only summary of the existing data on the prevalence and characteristics of isotypes and subclasses of various autoantibodies across different disease groups.

Although certain autoantibody isotypes/subclasses (such as IgG and IgG1) appear to play a major role in most autoantibody responses, each autoantibody to some degree has its own unique isotype/subclass profile. Nevertheless, certain patterns also exist in the isotype/subclass profile, such as prominence of IgG4 and IgE; these patterns may indicate pathophysiological similarities between distinct autoantibody responses and diseases and provide insights regarding translation of the treatment options across diseases. This potential relatedness introduces a novel angle on investigation and stratification of autoimmune responses, different from the conventional approach of grouping diseases on the basis of clinical presentation and/or organ involvement. Antibody-depleting therapies have become increasingly specific, as isotype-specific approaches, including IgG- and IgE-targeting therapies, find implementation in autoimmune diseases and may be complemented by IgA- and IgM-targeting in near future.

Despite the large body of literature dedicated to autoantibodies in various diseases, many aspects regarding non-IgG isotypes and specific IgG subclasses remain understudied for most of the autoantibody responses. As a result, important phenomena related to autoantibody measurements beyond total IgG may have been overlooked. A more in-depth approach to isotype/subclass testing could improve disease models and clinical studies in the future. Moreover, a multidisciplinary approach to autoantibody isotype profiling and translation of methodology across distinct autoimmune diseases may result in novel insights and further increase our understanding of autoimmunity.

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