



IGG-4 ASSOCIATED DISEASE

5TH SEMINARY OF LAREIDAB

11TH CONGRESS OF AMIWIT

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INTRODUCTION

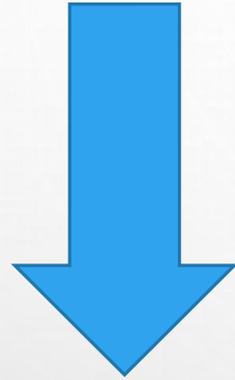
- LA MALADIE ASSOCIÉE AUX IGG4, N'A ÉTÉ ÉTABLIE COMME UNE ENTITÉ DISTINCTE QU'AU COURS DES DEUX DERNIÈRES DÉCENNIES.
- MALADIE FIBRO-INFLAMMATOIRE A MÉDIATION IMMUNITAIRE.
- PEUT TOUCHER N'IMPORTE QUEL ORGANE AVEC UNE PRÉDILECTION POUR CERTAINS D'ENTRE EUX.

ÉPIDÉMIOLOGIE

- PRÉVALENCE 1:100000.
- SOUVENT APRÈS L'ÂGE DE 50 ANS.
- SEXE RATIO: 3/1 (H/F).

PHYSIOPATHOLOGIE

- IMPLICATION DES LB ET DES PLASMOCYTES.



- ACTIVATION DES LYMPHOCYTES T CYTOTOXIQUES CD4+.

- FORMATION DE MASSES INFLAMMATOIRES ET DES TISSUS FIBROTIQUES.



FACTEURS DE RISQUE

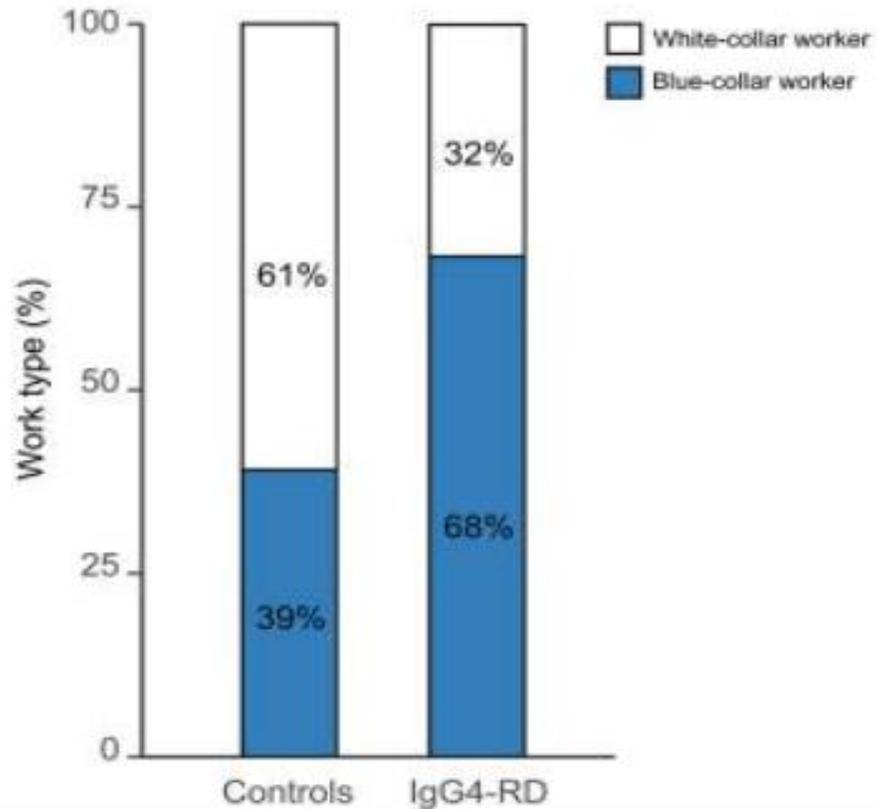
1. TABAC:

- ÉTUDE CAS-TÉMOIN, RATIO 1:5 APPARIÉS SELON LE SEXE, L'ÂGE ET LA RACE.
- IL Y AVAIT UNE PLUS GRANDE PROPORTION DE FUMEURS ACTIFS PARMIS LES CAS D'IGG4-RD (11 %) QUE PARMIS LES TÉMOINS (6 %), OR 1,79.
- EN ANALYSANT LES SOUS-GROUPES, CETTE ASSOCIATION ÉTAIT FORTEMENT SIGNIFICATIVE AVEC **LA FRP [OR 6,93 (IC À 95 %) 2,78, 17,26), $P < 0,001$]**, ET LE **SEXE FÉMININ [OR 3,79 (IC À 95 % 1,71, 8,39), $P = 0,001$]**

2. COLS BLEUS:

Blue-collar work is a risk factor for IgG4-RD of the biliary tract and pancreas

Proportion of people performing blue-collar and white-collar work across cases with IgG4-RD (n = 101) and controls (n = 303)



Conclusions

- A history of blue-collar work was reported by 68% of people with IgG4-RD of the biliary tract and pancreas, compared to only 39% of controls [OR 3.66, 95% CI 2.18-6.13]
- Toxic exposure to selected occupational contaminants (e.g., asbestos, gases, fumes, mineral dusts) may drive autoimmunity in IgG4-RD
- Blue-collar work may explain the striking male predominance among patients with IgG4-RD of the biliary tract and pancreas

ANTICORPS DANS LA MALADIE A IGG4

- ANTICORPS CONTRE LA GALECTINE 3, LAMININE 111 ET L'ANNEXINE A11.
- CES AUTOANTICORPS ÉTAIENT CONSIDÉRÉS COMME DES MOLÉCULES ANTI-INFLAMMATOIRES.

Analyse du plasma
des patients IGG4



auto-AC anti-IL1



Médiateurs pro
inflammatoire et
profibrotique

DÉMARCHE DIAGNOSTIQUE

Exclusion criteria for IgG4-related disease

Clinical exclusions	Fever
	Unresponsive to steroids
	Leukopenia and thrombocytopenia
	Peripheral eosinophilia (>3,000 per mm ³)
Serological exclusions	PR3 or MPO-ANCA positive
	Anti-Ro or La positive
	Extractable nuclear antibody positive
	Cryoglobulins
	Other disease-specific antibody
Radiology exclusions	Rapid radiographic progression
	Large bone abnormality (such as Erdheim-Chester disease)
	Splenomegaly
	Concern regarding infection, malignancy, or both
Pathology exclusions	Primarily granulomatous inflammation
	Necrotizing vasculitis
	Malignant infiltrate
	Prominent histiocytic infiltrate
	Prominent neutrophilic infiltrate
	Multicentric Castleman's pathology
	Prominent necrosis
	Inflammatory pseudotumor pathology

MDedge News

Source: Dr. Stone

IgG4-related disease inclusion domains and point assignments

Domains		Points
IgG4 level	Normal	0
	Above normal and less than 2× upper limit of normal	3.7
	2× to 5× ULN	6.1
	Above 5× ULN	10.8
Histopathology and immunostaining	Uninformative biopsy	0
	Dense lymphoplasmacytic infiltrate	3.7
	DLI plus obliterative phlebitis	6.1
	DLI plus storiform fibrosis	13.3
Lacrimal and major salivary gland enlargement	One set of glands involved	5.9
	Two or more sets of glands involved	13.8
Chest and thoracic aorta	Peribronchovascular and septal thickening	3.8
	Paravertebral band-like soft tissue in the thorax	9.8
Pancreas and biliary tree	Diffuse pancreas enlargement (loss of lobulations)	8.0
	Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	10.5
	Pancreas and biliary tree involvement	18.7
Kidney	Hypocomplementemia	5.8
	Renal pelvis thickening or soft tissue or both	8.1
Retroperitoneum	Diffuse thickening of the abdominal aortic wall	4.1
	Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	7.8

MDedge News

Note: A patient must tally at least 19.0 points to receive IgG4-related disease classification.

Source: Dr. Stone

PHÉNOTYPES CLINIQUES

Cluster Analysis of 478 IgG4-RD Patients

Table 2 Phenotypic groups of IgG4-RD (derivation cohort)*

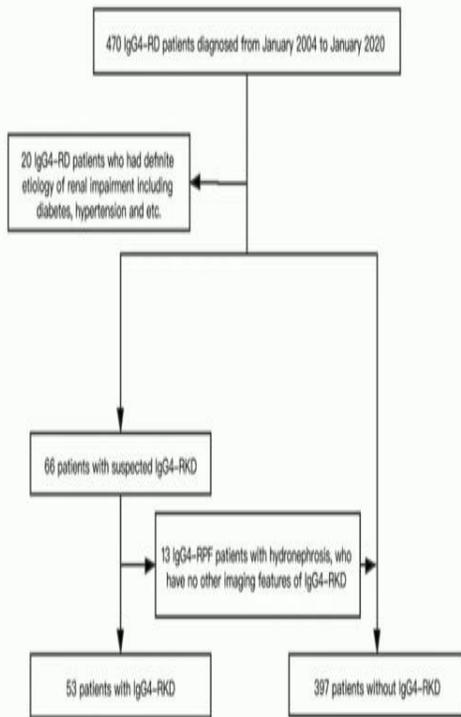
Variables used to identify group†	Group 1 'Pancreato-Hepato-Biliary' (%)	Group 2 'Retroperitoneum and Aorta' (%)	Group 3 'Head and Neck-Limited' (%)	Group 4 'Mikulicz and Systemic' (%)	P value
Pancreas	87	12	15	46	<0.001
Liver	13	1	2	5	<0.001
Biliary	55	<1	<1	27	<0.001
Orbital	<1	3	22	<1	<0.001
Extraocular muscle	<1	1	13	4	<0.001
Sinusitis	3	<1	17	16	<0.001
Parotid gland	2	1	22	49	<0.001
Submandibular gland	15	5	50	77	<0.001
Lacrimal gland	3	3	60	48	<0.001
Renal	11	13	5	36	<0.001
Lung	2	15	7	33	<0.001
Lymph node	15	25	29	67	<0.001
Prostate	1	<1	<1	14	<0.001
Thoracic aorta	1	10	1	3	<0.001
Abdominal aorta	3	22	<1	13	<0.001
Retroperitoneum	4	53	2	8	<0.001

Table 3 Demographics and key covariates according to IgG4-RD phenotype groups (derivation cohort)

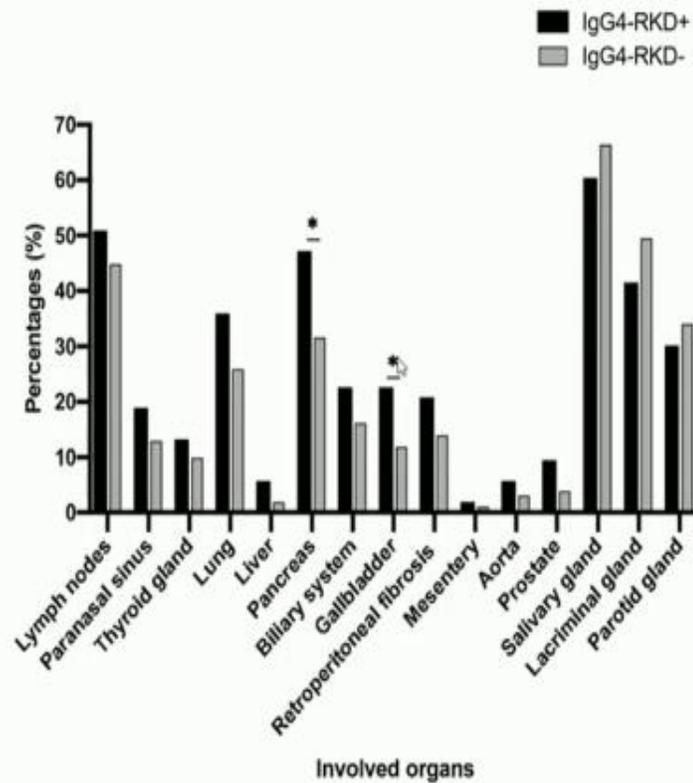
Covariate	Group 1 'Pancreato-Hepato-Biliary'	Group 2 'Retroperitoneum and Aorta'	Group 3 'Head and Neck-Limited'	Group 4 'Mikulicz and Systemic'
Female (%)	21%	25%	70%	22%
Asian (%)	37%	25%	67%	52%
Age at diagnosis (year, mean, SD)	63 (13)	58 (16)	55 (13)	63 (13)
Time to diagnosis (year, mean, SD)	0.9 (1.8)	1.8 (4.0)	2.3 (3.4)	2.0 (3.6)
Serum IgG4 concentration (mg/dL, median, IQR)	316 (147–622)	178 (63–322)	445 (183–888)	1170 (520–2178)

L'ATTEINTE RÉNALE AU COURS DE L'IGG4-RD

Retrospective analysis of chart records from Peking University People's Hospital

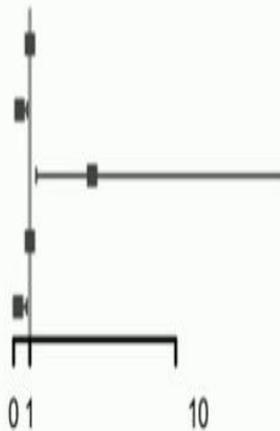


Zeng Q et al. Sci Rep. 2021; 11: 10397



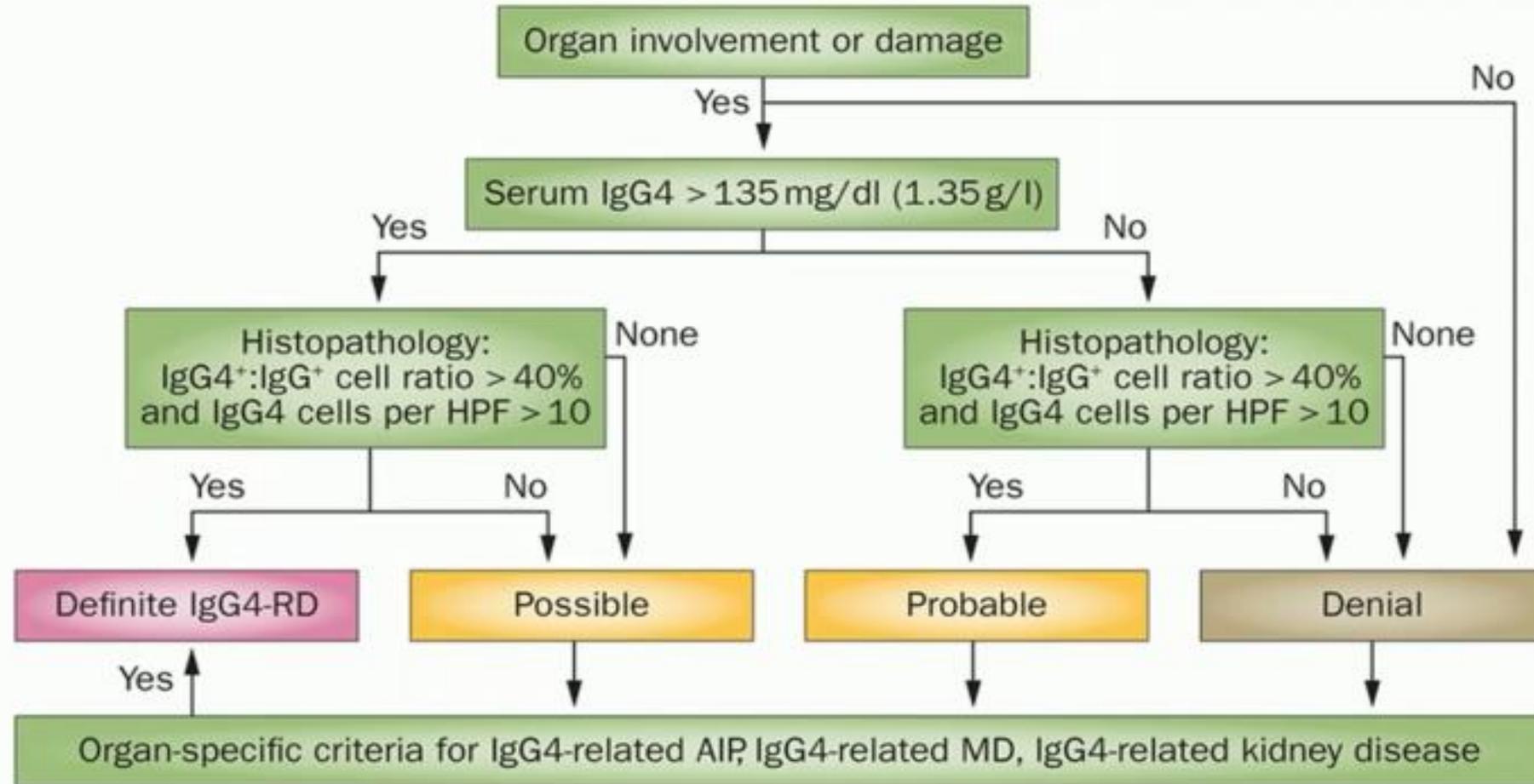
Zeng Q et al. Sci Rep. 2021; 11: 10397

Variables	OR (95%CI)	P-value
Age at diagnosis	1.006 (0.973-1.040)	0.710
Female	0.366 (0.158-0.845)	0.019
Involment of >=3 organs	4.845 (1.395-16.823)	0.013
ESR	1.004 (0.992-1.016)	0.526
C3	0.273 (0.092-0.810)	0.019



Zeng Q et al. Sci Rep. 2021; 11: 10397

ALGORITHME DIAGNOSTIQUE



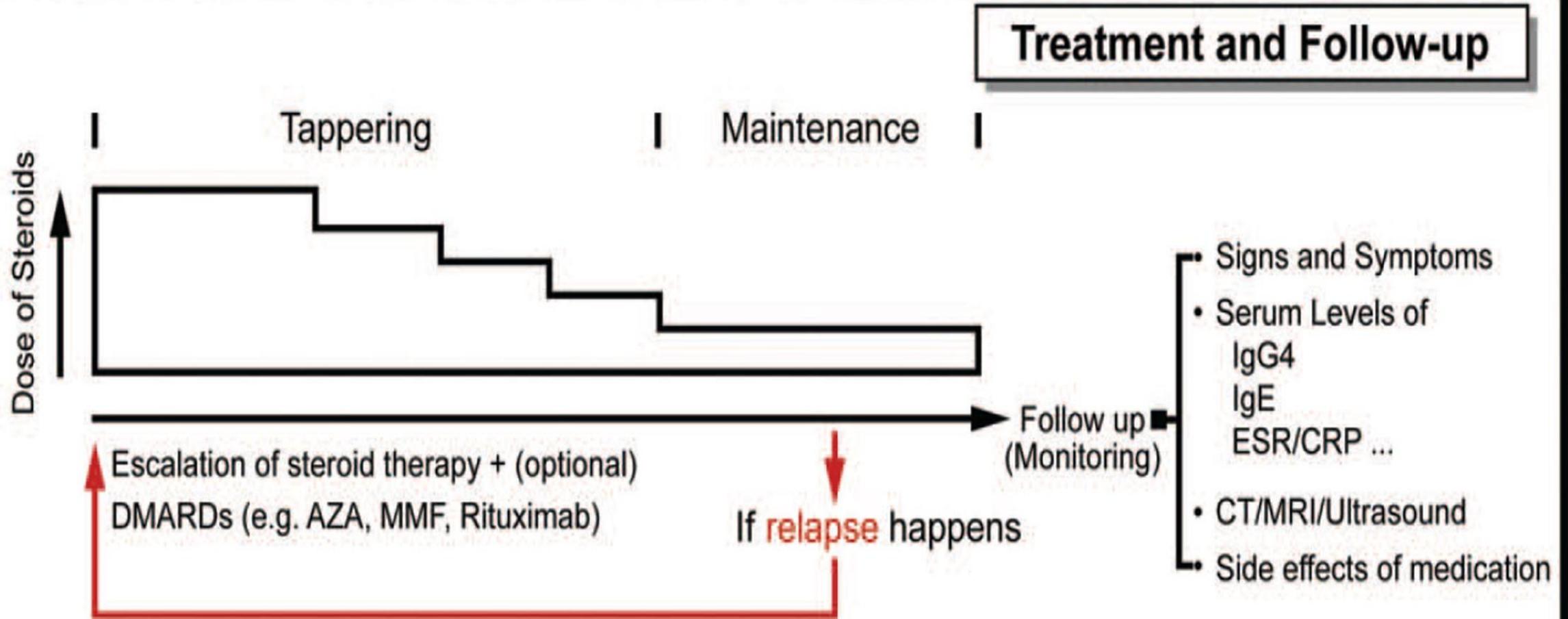
BIOMARQUEURS

Table II. Proposed blood biomarkers recommended for diagnosing and monitoring IgG4-RD according to clinical relevance.

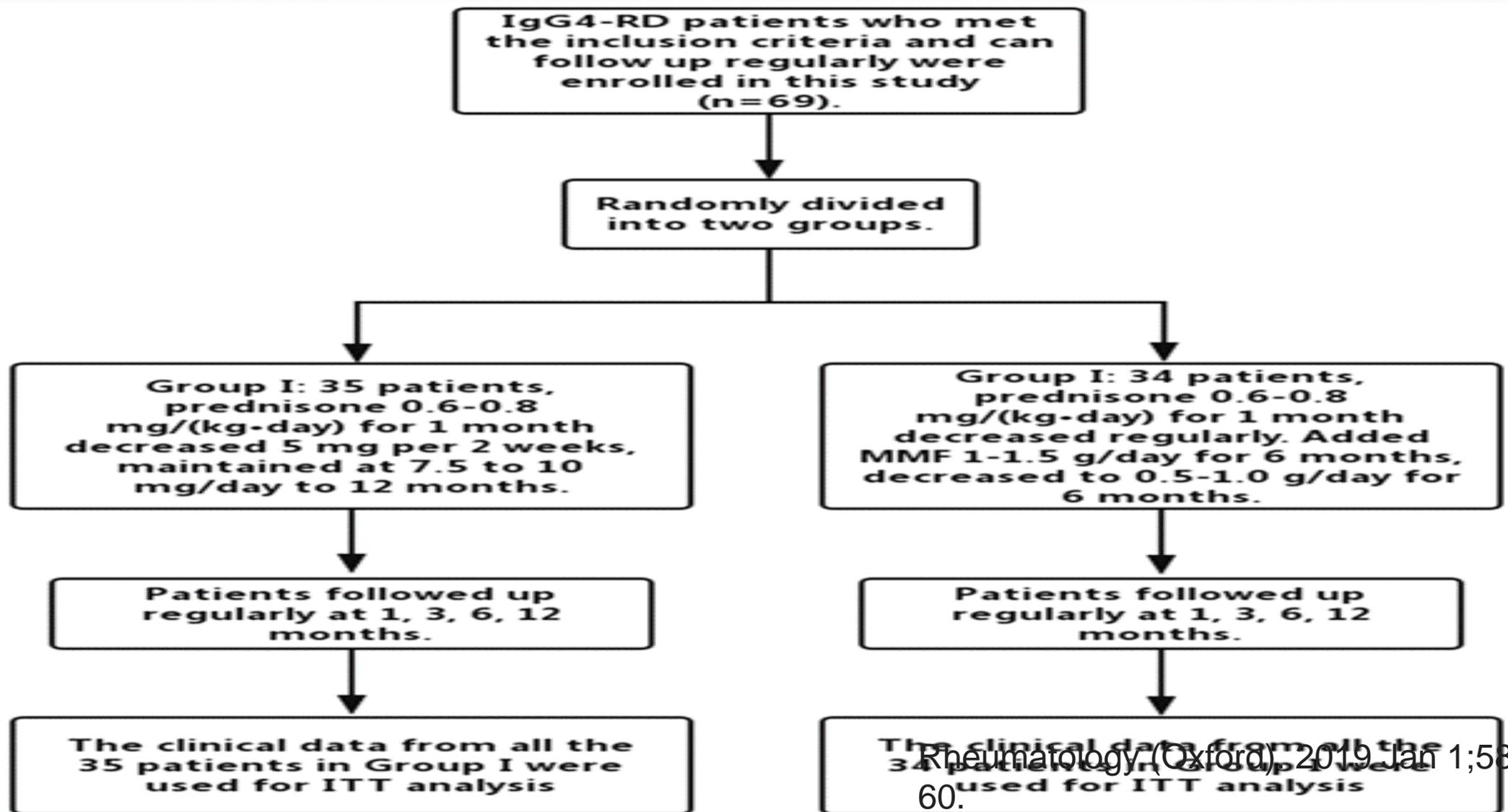
Clinical relevance	Biomarkers recommended in clinical routine	Biomarkers to be considered
Diagnosis	IgG4, IgG2, IgE, C3/C4, sIL-2R, Eosinophils, CRP/ESR	Plasmablasts
Disease activity	IgG4, C3/C4, sIL-2R, CRP/ESR	Plasmablasts
Prognosis	IgG4, IgE, sIL-2R, Eosinophils, CRP/ESR	Plasmablasts, memory B-cells, IgA, TNF- α
Clinical phenotype and organ specific markers	IgG4, IgE, C3/C4, Eosinophils, CRP/ESR	IgG2 (orbital disease), sFLC (renal), IFN α (AIP)
Degree of fibrosis		CCL18, GDF-15, ELF

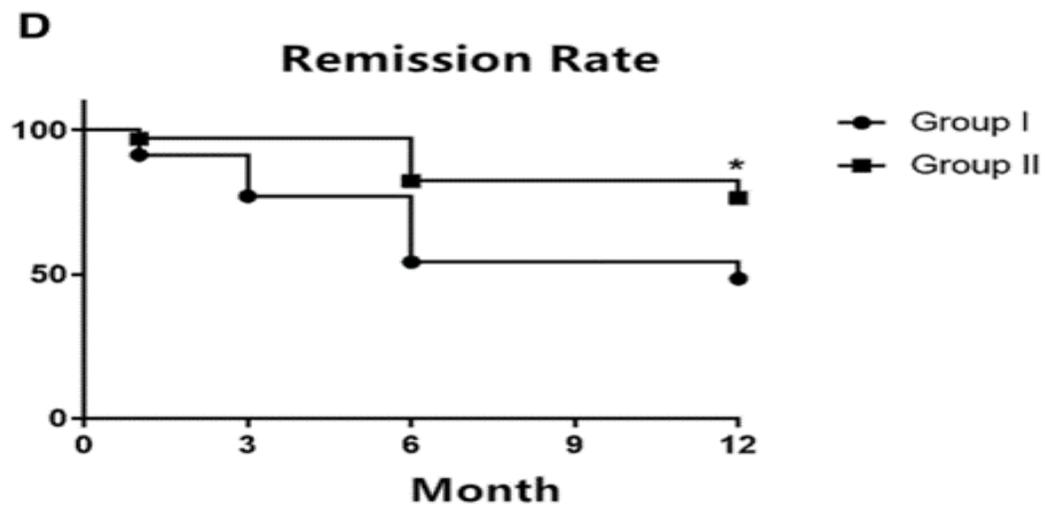
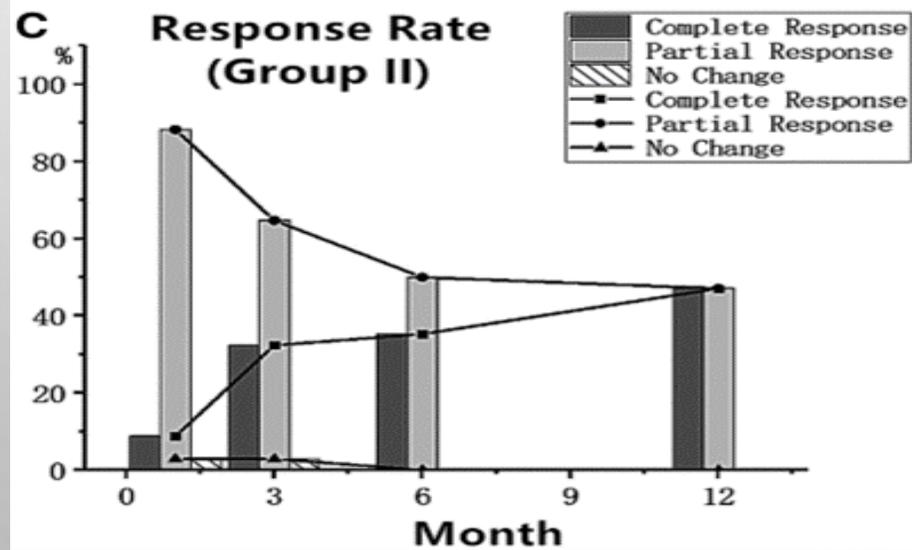
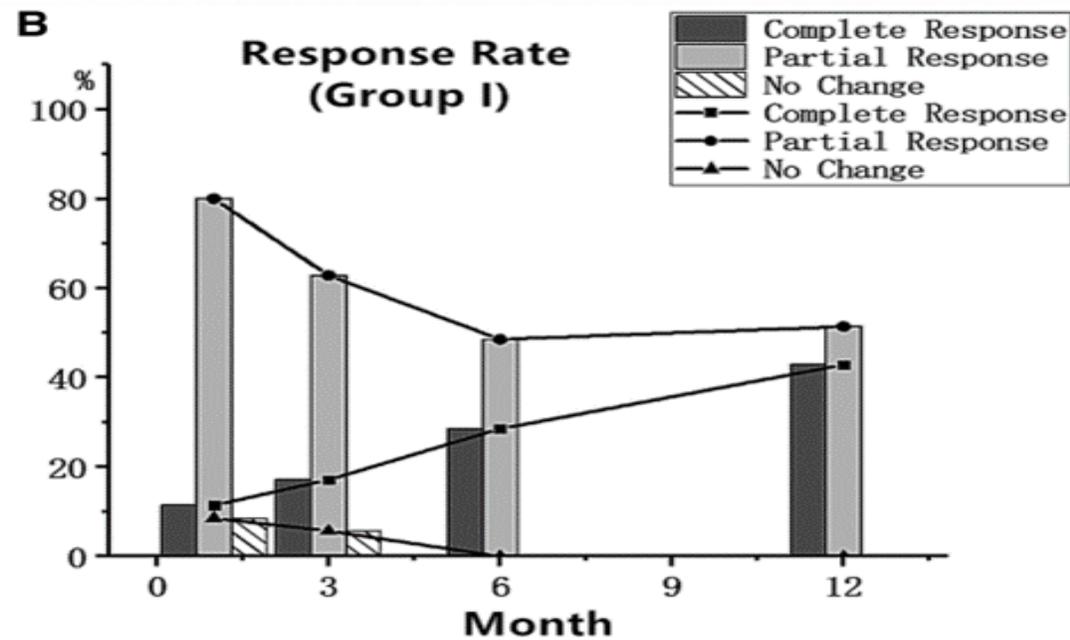
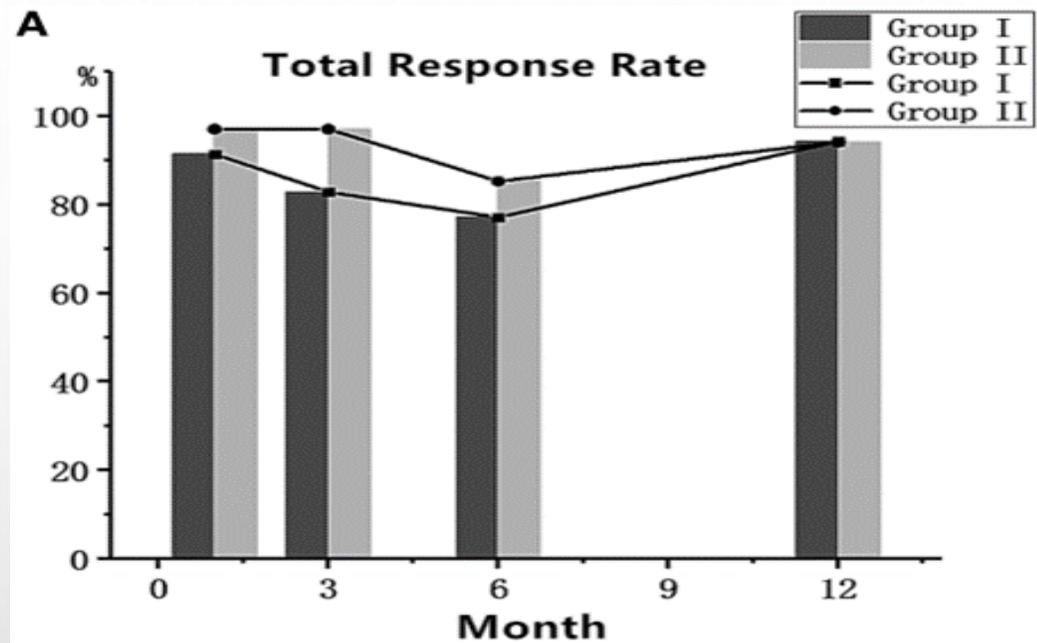
CCL18: C-C motif chemokine ligand 18; CrP: C-reactive Protein; ELF: enhanced liver fibrosis; ESR: erythrocyte sedimentation rate; GDF-15: growth differentiation factor 15; sIL-2R: soluble interleukin-2 receptor; sFLC: serum free light chains.

TRAITEMENT

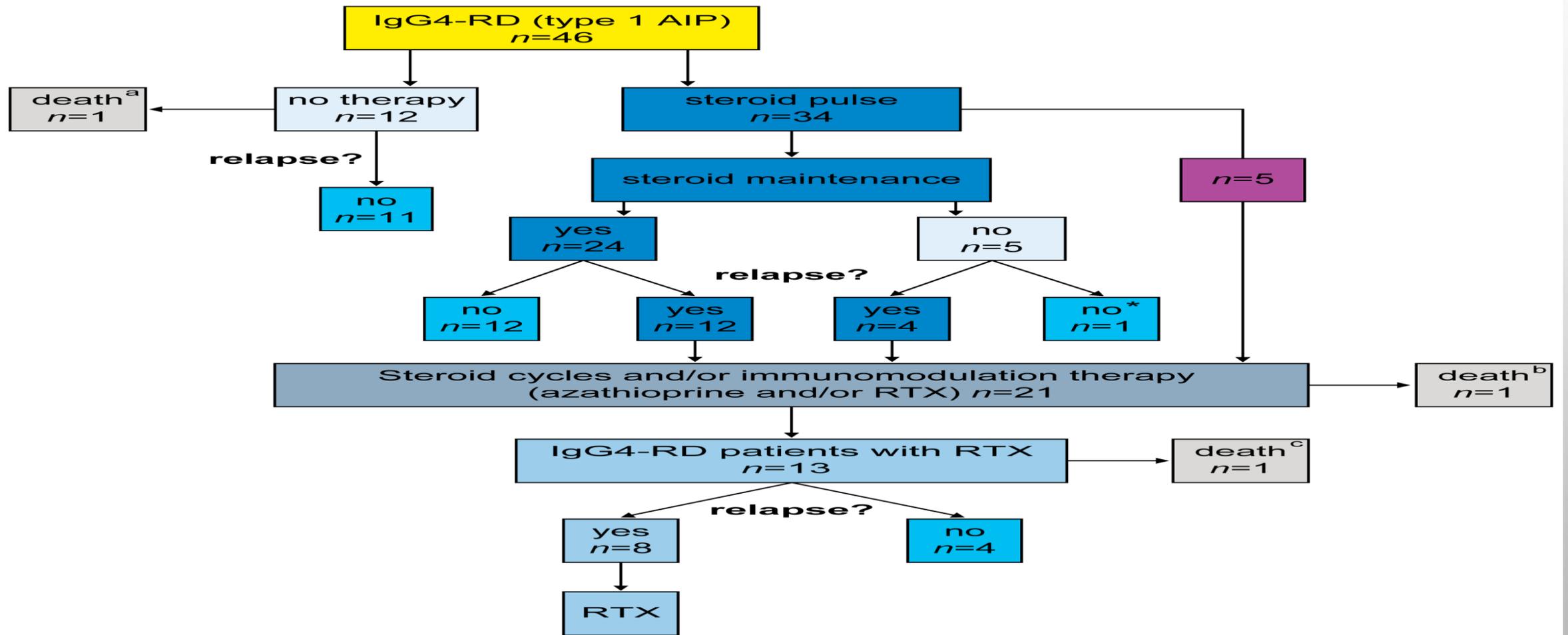


BITHÉRAPIE D'EMBLÉE OU NON ?

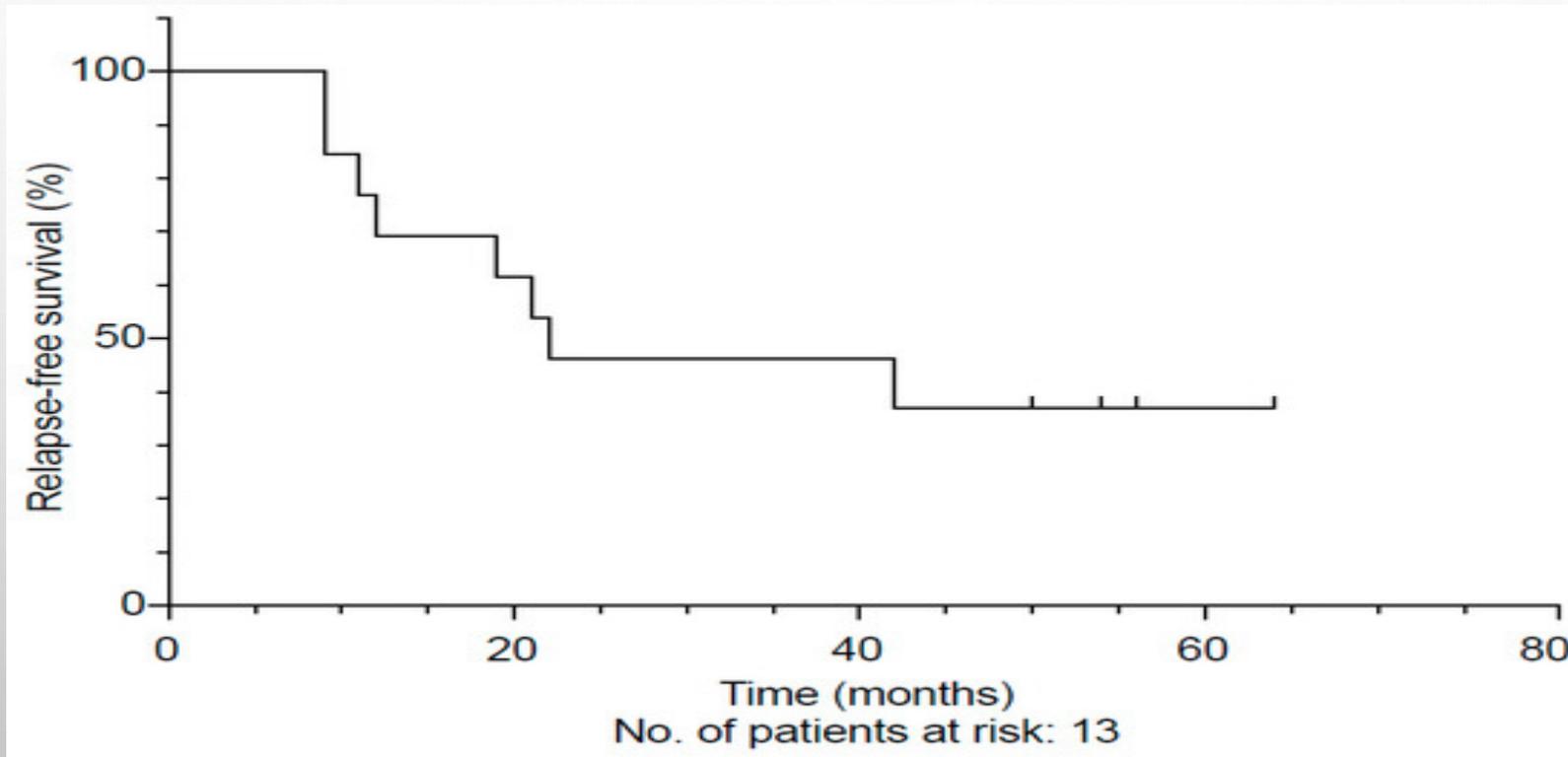




FOLLOW-UP STUDY OF IGG4-RD PATIENTS TREATED WITH RITUXIMAB



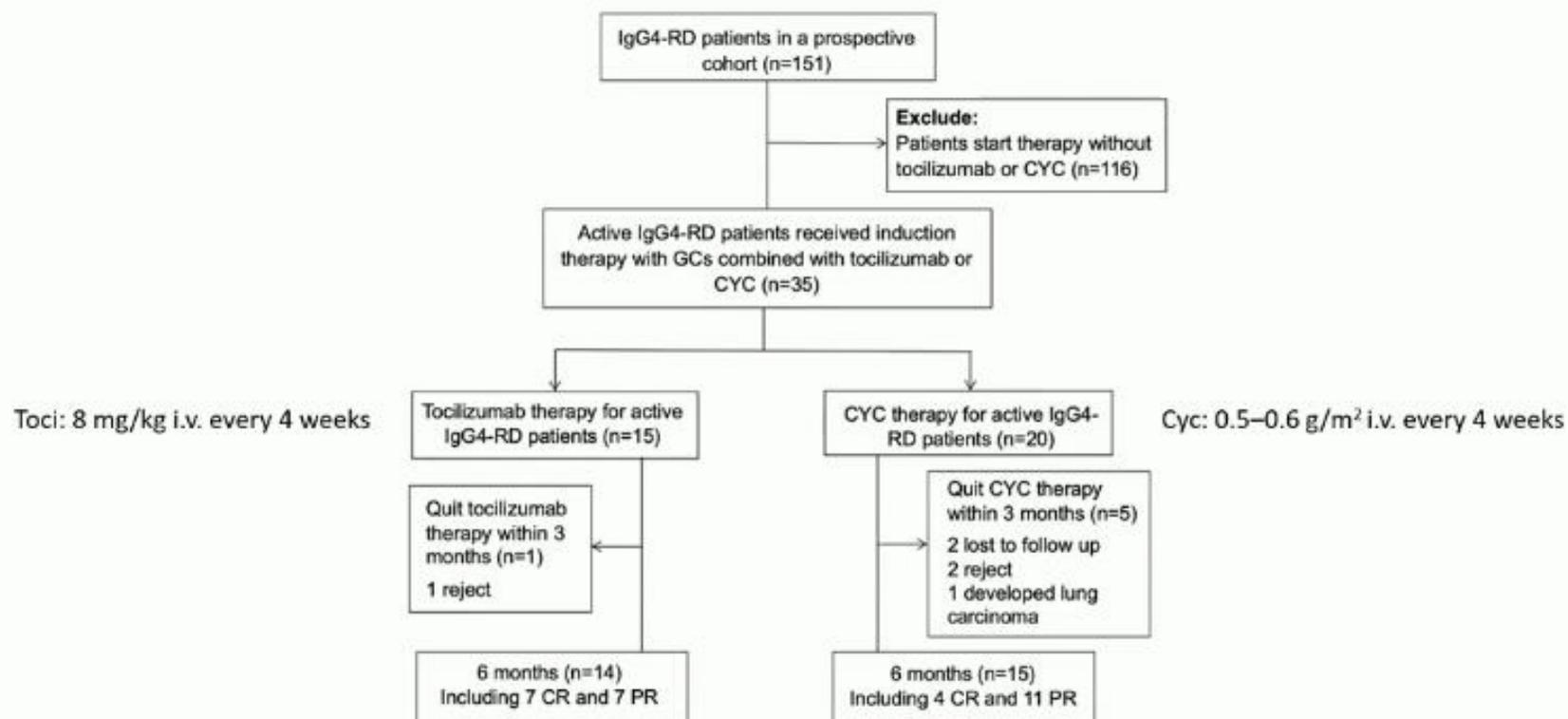
FOLLOW-UP STUDY OF IGG4-RD PATIENTS TREATED WITH RITUXIMAB



TOCILIZUMAB VS CYCLOPHOSPHAMIDE

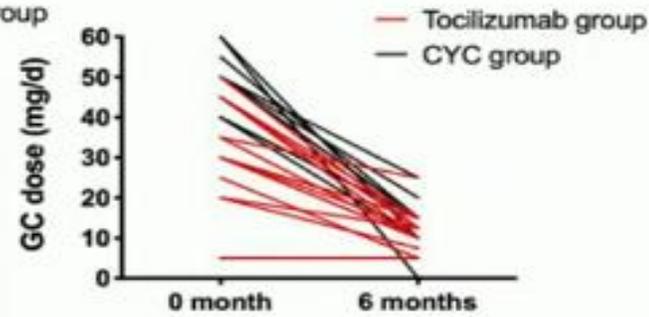
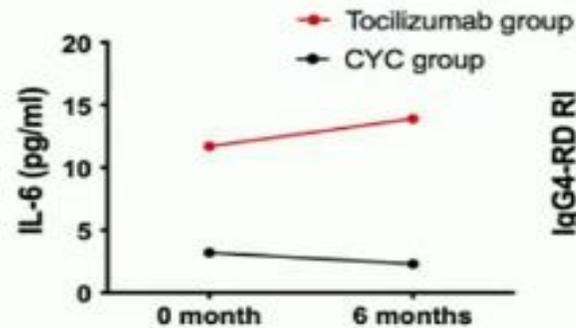
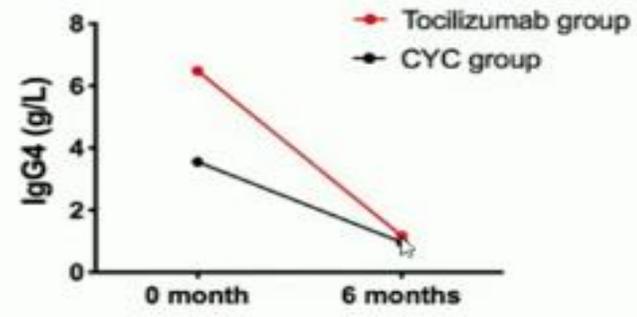
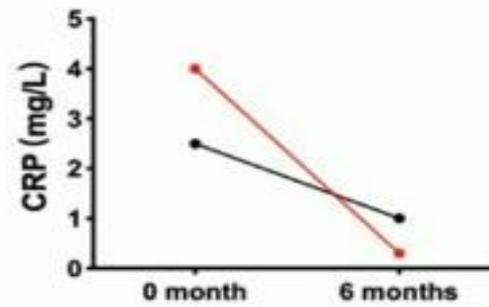
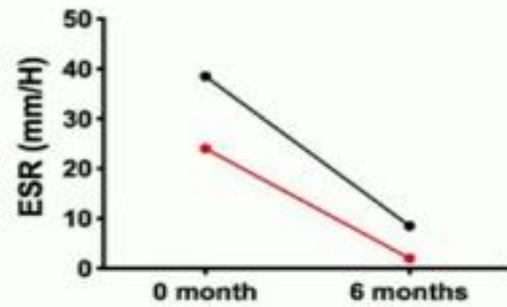
Outcomes of IgG4RD patients on tocilizumab or on cyclophosphamide: Prospective cohort study

Patients from Zhongshan Hospital, Fudan University



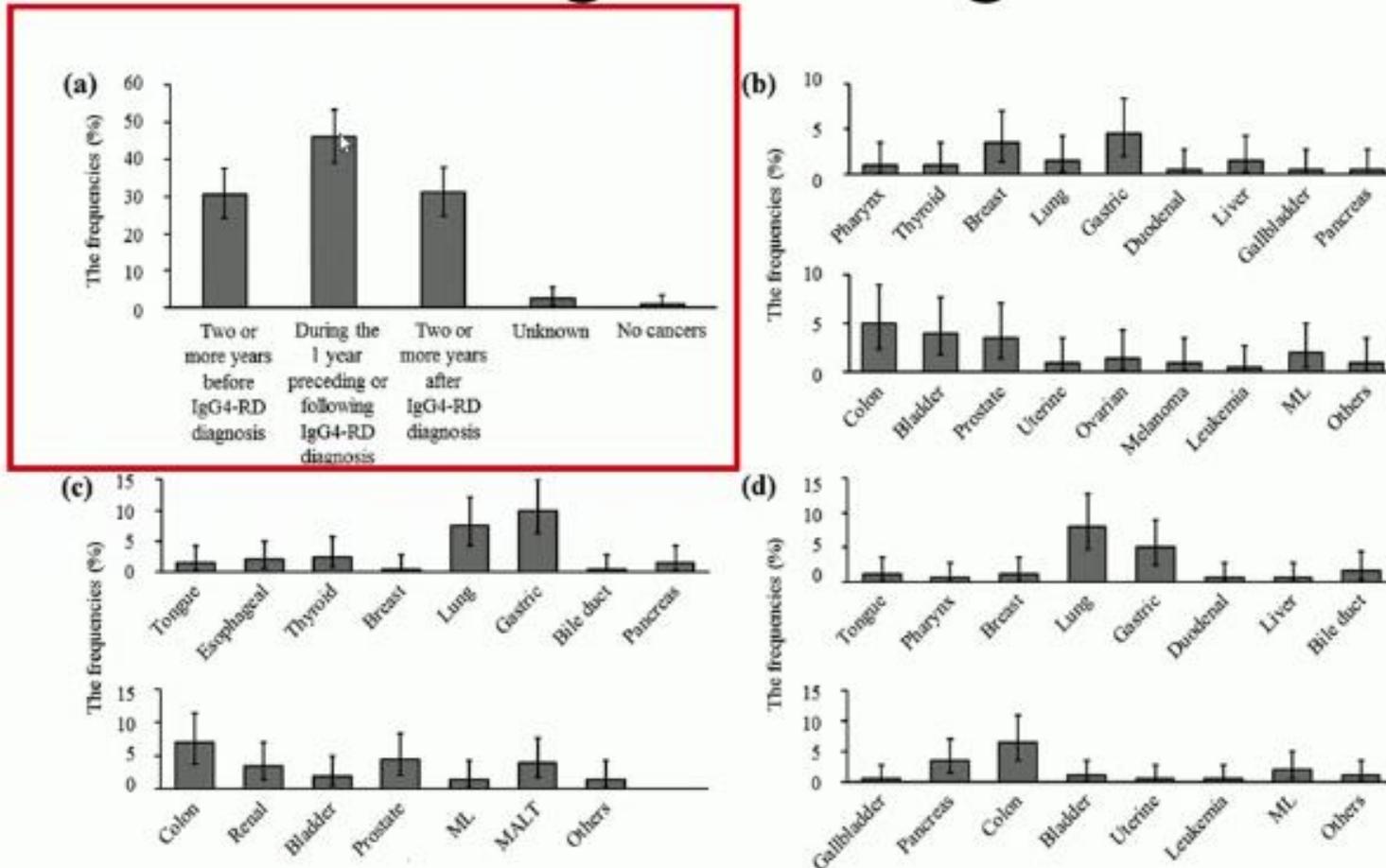
Goal: Prednisone maintenance 0.1-0.2 mg/kg

Outcomes of IgG4RD patients on tocilizumab or on cyclophosphamide



IGG4 ET RISQUE DE MALIGNITÉ

Time between diagnosis of IgG4RD and cancer



CONCLUSION

- L'IGG4-RD N'EST PAS AUSSI RARE QUE L'ON PENSAIT.
- ELLE PEUT GRAVEMENT AFFECTER LA QUALITÉ DE VIE DES PATIENTS OU MÊME METTRE LA VIE EN DANGER LORSQUE CERTAINS ORGANES VITAUX SONT TOUCHÉS.
- BIEN QUE LES STÉROÏDES RESTENT LE PILIER DU TRAITEMENT, LES MÉDICAMENTS ÉPARGNANT LES STÉROÏDES COMME LES DMARDS ET LE RTX DOIVENT ÉGALEMENT ÊTRE ENVISAGÉS DANS CERTAINES CONDITIONS