关于IgG4 RD的几个问题

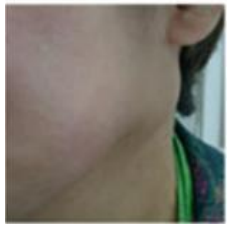
仁济风湿
叶霜
2019.6广州

CNS

Hypophysitis

Pachymeningitis

Mikulicz's disease (14%)



Dacryladenitis

Sialadenitis

Chronic thyroiditis (8%)

Hilar lymphadenopathy (9%)

Interstitial pneumonia (8%)

Mastopathy

Aortitis

Sclerosing cholangitis (60%)

Pseudotumor (2%)

Autoimmune hepatitis (AIH)

Type 1 AIP n=60 (100%)

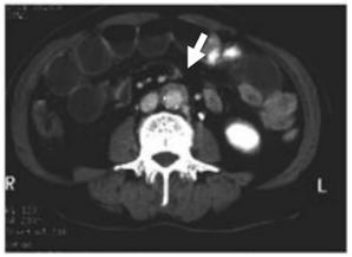
Renal involvement

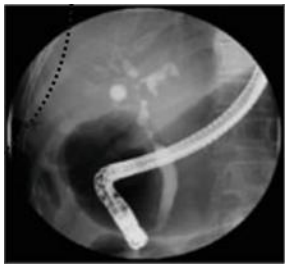
Interstitial nephritis (8%)

Rretroperitoneal fibrosis (10%)

GI tract ?

Prostatitis





Q1: IgG4RD临床分型？

- Group 1 (31%), Pancreato-Hepato-Biliary disease;
- Group 2 (24%), Retroperitoneal Fibrosis and/or Aortitis;
- Group 3 (24%), Head and Neck-Limited disease
  - female (OR~10)
  - Asian (OR~6)
- Group 4 (22%), classic Mikulicz syndrome with systemic involvement.
  - Higher IgG4 concentration (*9)

Ann Rheum Dis. 2019 Mar;78(3):406-412
Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. (n=765)

Q2. 关于血清IgG4的水平：是>2*UNL还是>135mg/dl？

Medicine®

OBSERVATIONAL STUDY

OPEN

Diagnostic Performance of Serum IgG4 Levels in Patients With IgG4-Related Disease

Kuang-Hui Yu, MD, Tien-Ming Chan, MD, Ping-Han Tsai, MD, Ching-Hui Cheng, BS, and Pi-Yueh Chang, MS

2901 IgG4-RD and 2740 non IgG4-RD

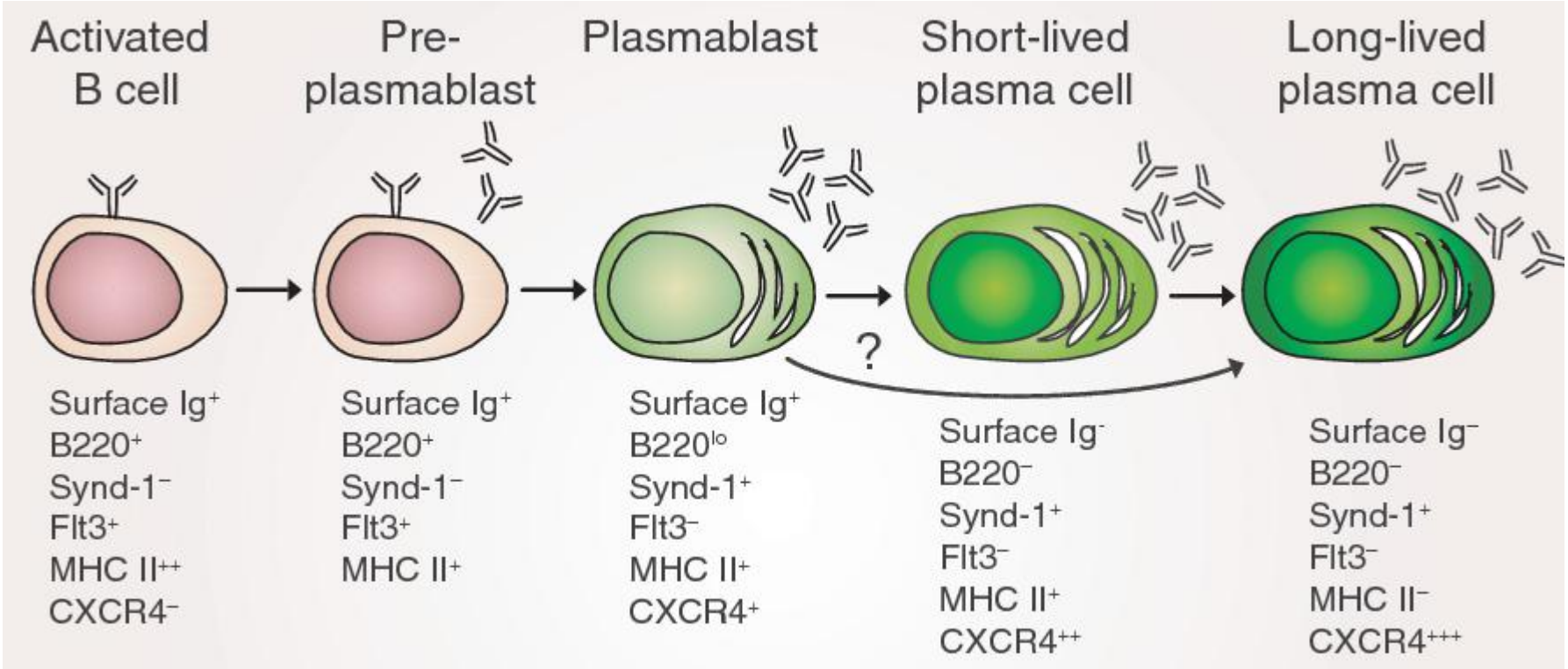
TABLE 2. Characteristics of the 2740 Non-IgG4-RD Subjects and Range of Diseases With Elevated Serum IgG4 Levels

Diseases	Cases, n	Cases %	IgG4 >135 mg/dL*, n (%)	IgG4 >201 mg/dL†, n (%)
Pancreatic cancer	199	7.3	36 (18.1)	13 (6.5)
Pancreatitis	459	16.8	89 (19.4)	39 (8.5)
Cholangiocarcinoma	63	2.3	13 (20.6)	5 (7.9)
Cholangitis	134	4.9	17 (12.7)	8 (6.0)
Gastrointestinal malignancy	51	1.9	20 (39.2)	10 (19.6)
Lymphoma	32	1.2	11 (34.4)	8 (25.0)
Other malignancy	286	10.4	45 (15.7)	15 (5.2)
Allergic disease	31	1.1	13 (41.9)	10 (32.3)
Systemic lupus erythematosus	109	4.0	9 (8.3)	2 (1.8)
Rheumatoid arthritis	433	15.8	131 (30.3)	82 (18.9)
Sjögren syndrome	54	2.0	10 (18.5)	4 (7.4)
Sarcoidosis	2	0.1	0 (0)	0 (0)
Systemic sclerosis	5	0.2	3 (60.0)	2 (40.0)
Vasculitis	1	0.0	0 (0)	0 (0)
Castleman disease	2	0.1	1 (50.0)	0 (0)
Ankylosing spondylitis/psoriatic arthritis	208	7.6	83 (39.9)	64 (30.8)
Other diseases	671	24.5	154 (23.0)	49 (7.3)
Total	2740	100.0	635 (23.2)	311 (11.4)

TABLE 4. Performance of Serum IgG4 Levels in Patients With and Without IgG4-Related Disease, Stratified by Different IgG4 Cutoff Levels

	IgG4* >135 mg/dL	IgG4* >270 mg/dL	IgG4* >405 mg/dL	IgG4† >201 mg/dL	IgG4† >402 mg/dL	IgG4† >603 mg/dL
Sensitivity	86	75	62	80	62	50
Specificity	77	94	98	89	98	99
PPV	18	43	68	29	68	84
NPV	89	98	98	99	98	97
LR+	3.70	12.79	27.11	7.00	36.21	90.77
LR−	0.19	0.26	0.39	0.23	0.39	0.51

Q2-1. 外周血浆母细胞水平是否可作为IgG4相关性疾病新的**诊断/监测指标**？



Published in final edited form as:
Ann Rheum Dis. 2015 January ; 74(1): 190–195. doi:10.1136/annrheumdis-2014-205233.

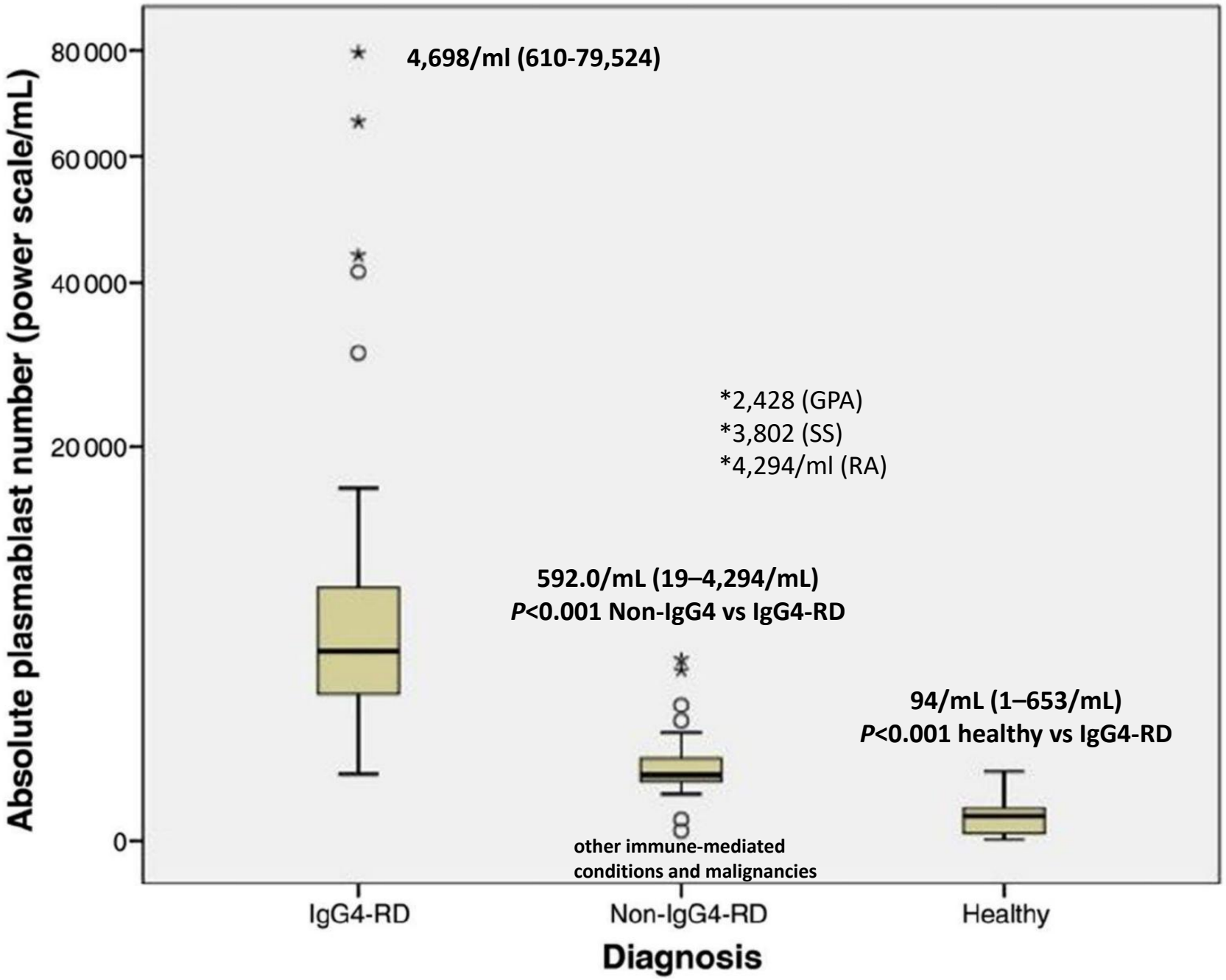
Plasmablasts As A Biomarker For IgG4-Related Disease, Independent Of Serum IgG4 Concentrations

- 37 IgG4-RD (active, untreated)
- 14 healthy controls
- 21 disease controls with active, untreated inflammatory diseases or malignancies
  (5 RA, 4 GPA, 2 pancreatic cancer, 1 DLBC, 3 sarcoidosis, 1 livedoid vasculopathy, 1 SS, 1 PBC, 1 chronic pain, 1 Lyme disease, 1 gout).
- 12 patients treated with RTX (1g*2, 15d)

IgG4 concentration

924 (138~4780 | 59.5 (5.3~123) | p<0.01

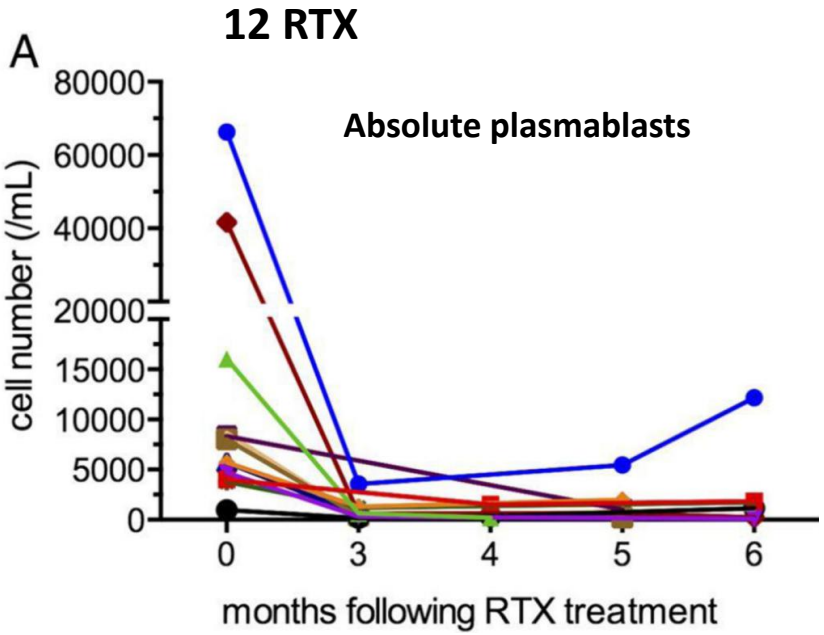
Variable	Elevated Serum IgG4 (n=23)	Normal Serum IgG4 (n=13)	*P*-value
Gender (% male)	65%	69%	0.81
Age (Years)	64	50	0.001
Number of Organs (mean)	2.9	1.7	0.003
Percentage with ≥ 3 organs involved	57%	15%	<0.01
Median PlasmablastCount (#/mL)	3,981	3,659	0.82
Serum IgG4 (mg/dL)	923.6	59.5	0.001
C3 (mg/dL)	82	113	0.005
C4 (mg/dL)	14.9	22.1	0.017
CRP (mg/L)	23.4	3.1	0.008
ESR (mm/hr)	51	11	<0.001

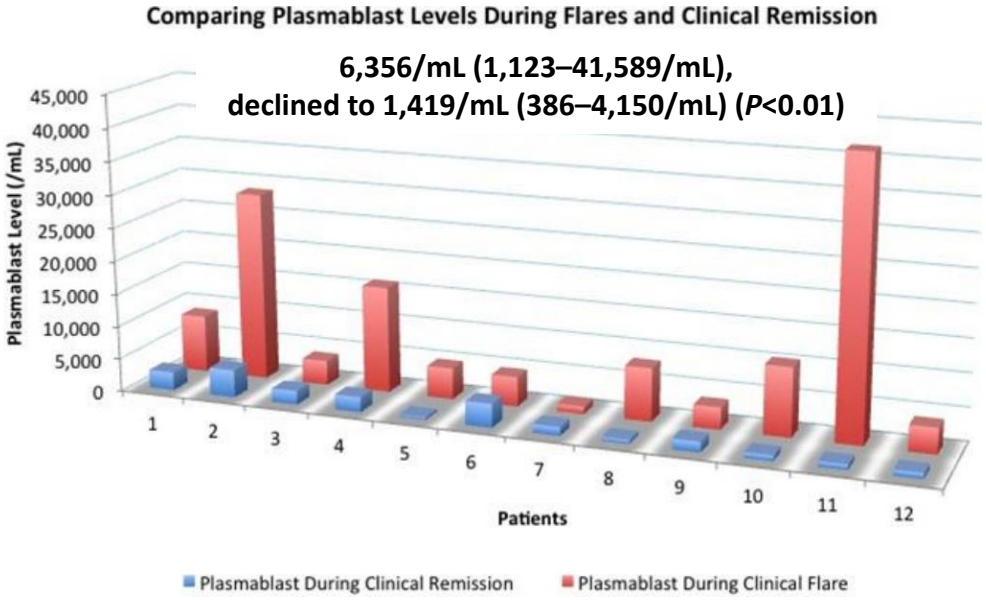

Absolute plasmablast number (power scale/mL)
80 000
60 000
40 000
20 000
0
4,698/ml (610-79,524)
*2,428 (GPA)
*3,802 (SS)
*4,294/ml (RA)
592.0/mL (19–4,294/mL)
P<0.001 Non-IgG4 vs IgG4-RD
94/mL (1–653/mL)
P<0.001 healthy vs IgG4-RD
other immune-mediated conditions and malignancies
IgG4-RD
Non-IgG4-RD
Healthy
Diagnosis

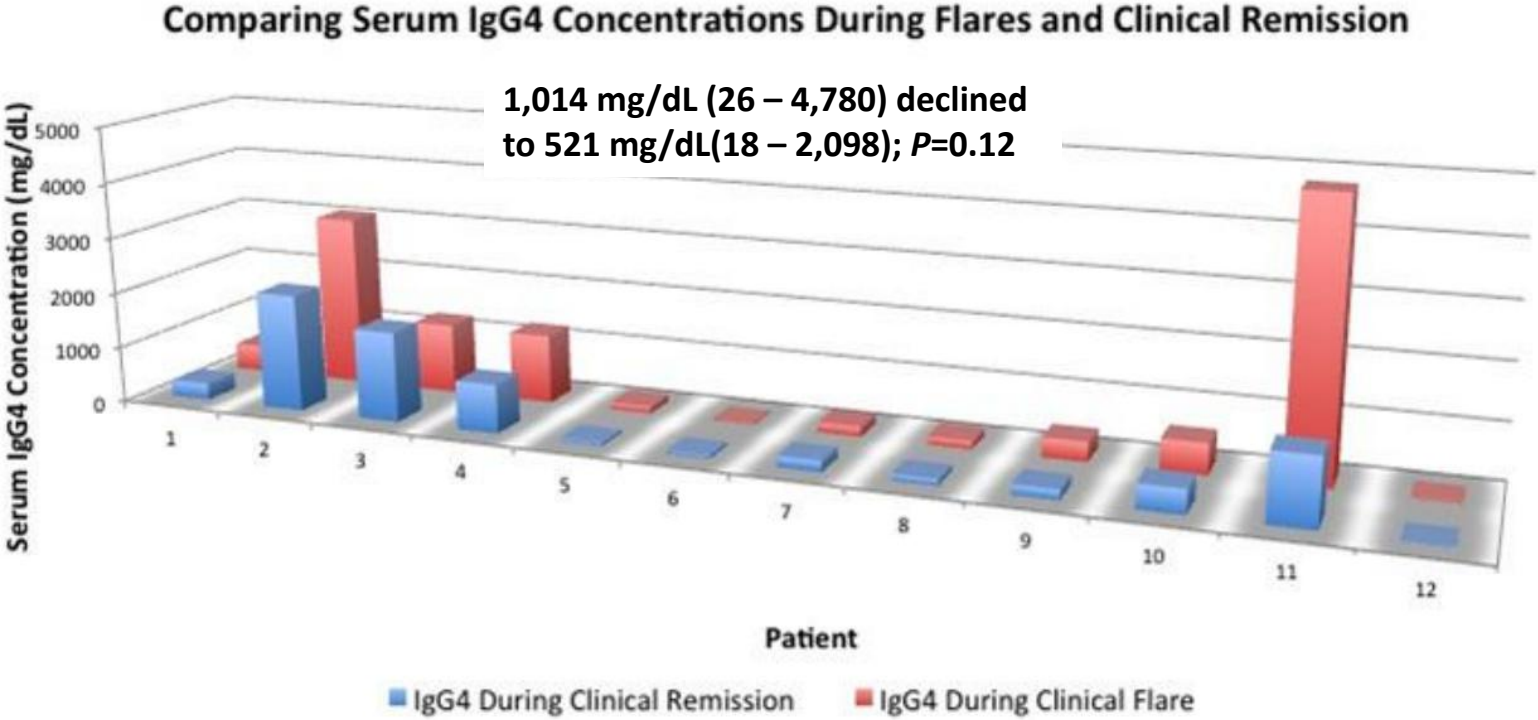
- Plasmablast counts were significantly different between those with multiorgan disease and those with ≤2 organs involved (medians 7,370/mL and 3,435/mL; *P*=0.01).
- Correlation between plasmablast counts and the baseline IgG4-RD RI score was modest (R=0.17, *P*=0.16).

- Plasmablast levels demonstrated excellent performance as a test for IgG4-RD (AUC 0.96, $P<0.05$).

Cutoff of Plasmablast	Sensitivity	Specificity	PPV	NPV
900/ml	95%	82%	86%	97%
2000/ml	87%	91%	91%	87%


A
12 RTX
Absolute plasmablasts
cell number (/mL)
80000
60000
40000
20000
15000
10000
5000
0
0
3
4
5
6
months following RTX treatment


Comparing Plasmablast Levels During Flares and Clinical Remission
6,356/mL (1,123–41,589/mL),
declined to 1,419/mL (386–4,150/mL) (P<0.01)
Plasmablast Level (/mL)
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
1
2
3
4
5
6
7
8
9
10
11
12
Patients
Plasmablast During Clinical Remission
Plasmablast During Clinical Flare


Comparing Serum IgG4 Concentrations During Flares and Clinical Remission
1,014 mg/dL (26 – 4,780) declined
to 521 mg/dL(18 – 2,098); P=0.12
Serum IgG4 Concentration (mg/dL)
5000
4000
3000
2000
1000
0
1
2
3
4
5
6
7
8
9
10
11
12
Patient
IgG4 During Clinical Remission
IgG4 During Clinical Flare

- Circulating plasmablast count is a more robust diagnostic marker than are serum IgG4 concentrations.
- In several patients, rising plasmablast levels during periods of partial or complete remission preceded overt clinical flares
- The utility of plasmablast levels as biomarkers of disease activity and predictors of flare requires further investigation.

Q3. 关于影像：18F-FDG-PET/CT

Characterizing IgG4-related disease with ^{18}F-FDG PET/CT: a prospective cohort study

Jingjing Zhang · Hua Chen · Yanru Ma · Yu Xiao · Na Niu · Wei Lin · Xinwei Wang · Zhiyong Liang · Fengchun Zhang · Fang Li · Wen Zhang · Zhaohui Zhu

Eur J Nucl Med Mol Imaging (2014) 41:1624–1634
DOI 10.1007/s00259-014-2729-3

1. 全身评估
2. 指导活检
3. 诊断
4. 疗效监测

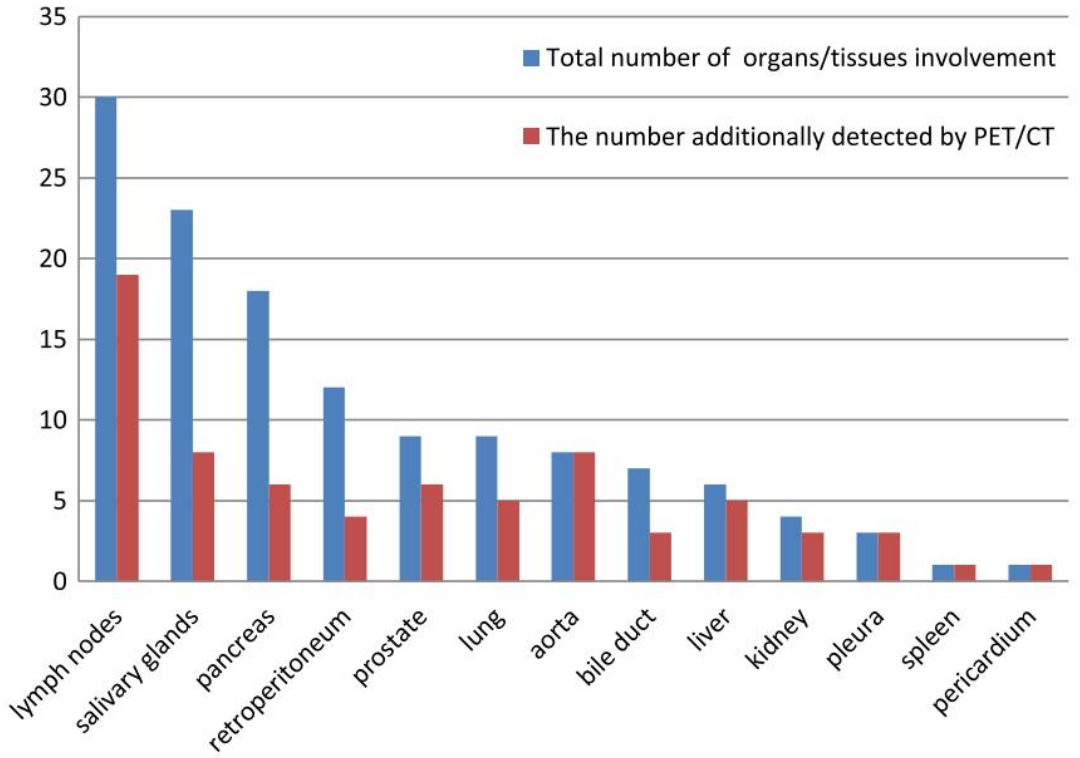
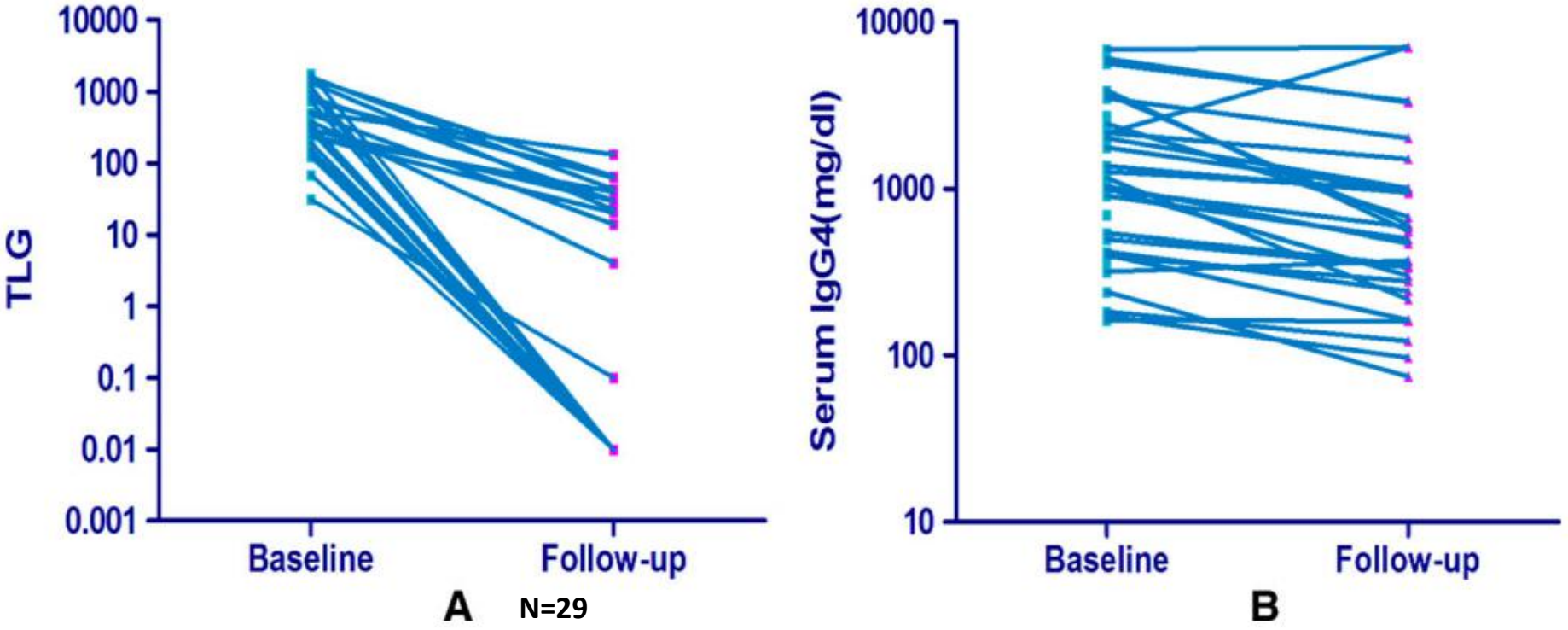


Table 2 Summary of the image characteristics that form the pattern of IgG4-related disease on ^{18}F-FDG PET/CT

Image characteristics	Confidence for indication of IgG4-F
1. Diffusely elevated ^{18}F-FDG uptake in organs, mainly involving salivary glands, pancreas, and prostate	
(1) Evenly, symmetrically distributed ^{18}F-FDG uptake in the salivary glands without signs of infection	Strong
(2) Diffusely enlarged pancreas with moderate to intense ^{18}F-FDG uptake without pancreaticobiliary duct obstruction	Strong
(3) Diffusely enlarged prostate with moderate to intense ^{18}F-FDG uptake	Moderate
(4) Broadly involved lymph nodes with moderate to intense ^{18}F-FDG uptake	Moderate
2. Patchy ^{18}F-FDG-avid lesion without signs of infection, mainly involving aorta wall, retroperitoneal region, pancreas, bile duct, liver, kidney, and lung	
(5) Patchy thickness of aorta wall with moderate to intense ^{18}F-FDG uptake not limited to the vascular intima	Strong
(6) Patchy retroperitoneal lesion with moderate to intense ^{18}F-FDG uptake	Strong
(7) Patchy pancreatic lesion	Moderate
(8) Patchy bile duct lesion	Moderate
(9) Patchy liver lesion	Moderate
(10) Patchy lesions in the enlarged irregular kidneys	Moderate
(11) Patchy lung lesion	Weak
(12) Patchy pleural lesion	Weak
(13) Patchy pericardial lesion	Weak
3. Multi-organ involvement, including the following characteristics besides the above-mentioned	
(14) Pancreas nodule or mass	Weak
(15) Kidney nodule or mass	Weak
(16) Lung nodule(s)	Weak
4. Rapid, significant response to steroid-based treatment	
(17) The ^{18}F-FDG-avid lesions had more than 80 % decrease of activity after 2 to 4 weeks of steroid-based treatment at a dosage of 40 mg to 50 mg prednisone per day	Strong



- **A PET VCAR analysis reported complete metabolic remission in 21 cases (72 %), whereas the other eight cases showed partial metabolic response with an 89.0 %±6.4 % decrease in TLG.**
- **Serum IgG4 levels decreased only in 88.6 % (31/35) cases and with less significance. No significant correlation was found between the TLG and the IgG4 level in these patients (r=0.37, P=0.06).**

RHEUMATOLOGY

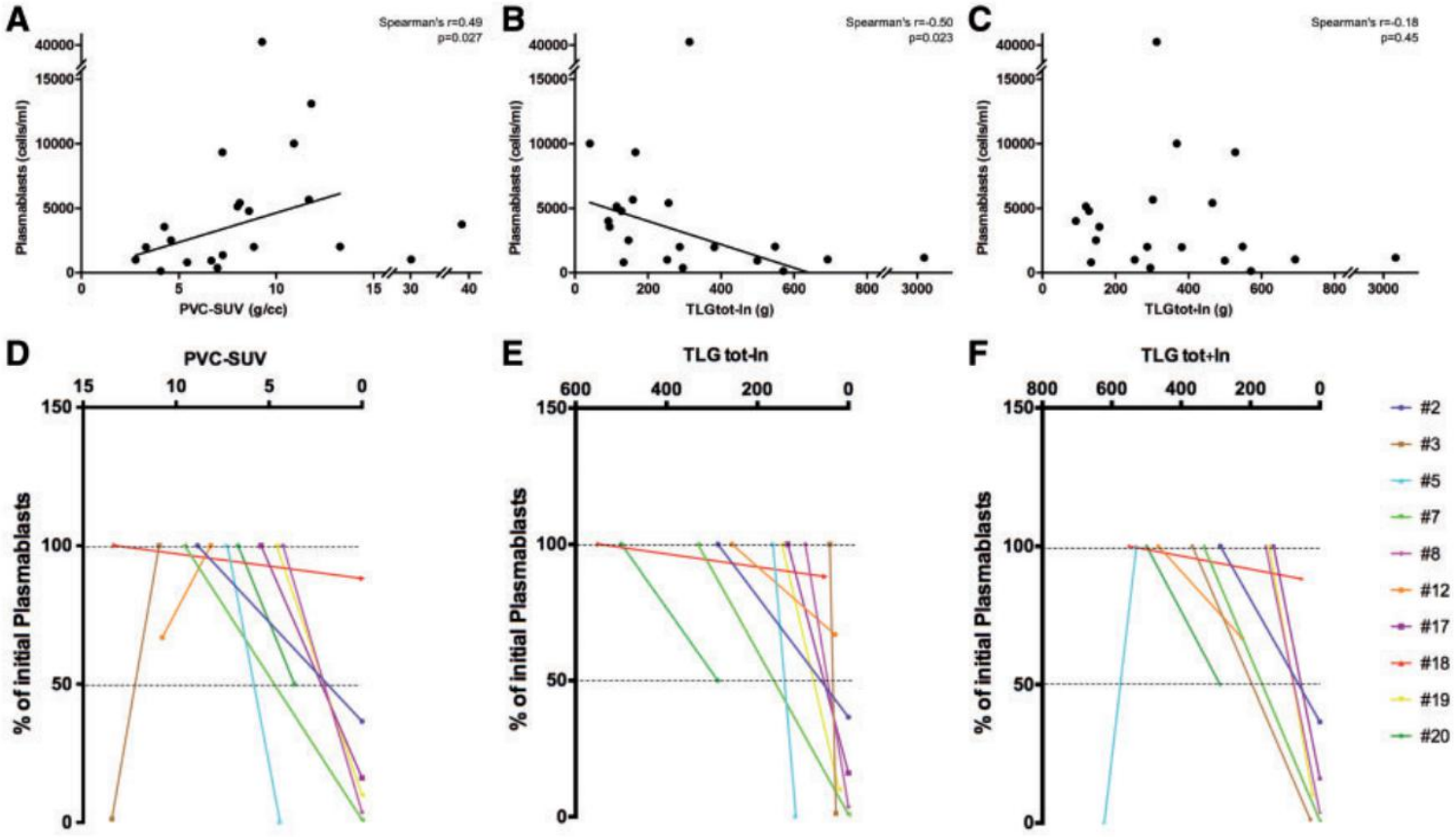
Rheumatology 2017;56:2084–2092
doi:10.1093/rheumatology/kex234
Advance Access publication 7 July 2017

Original article

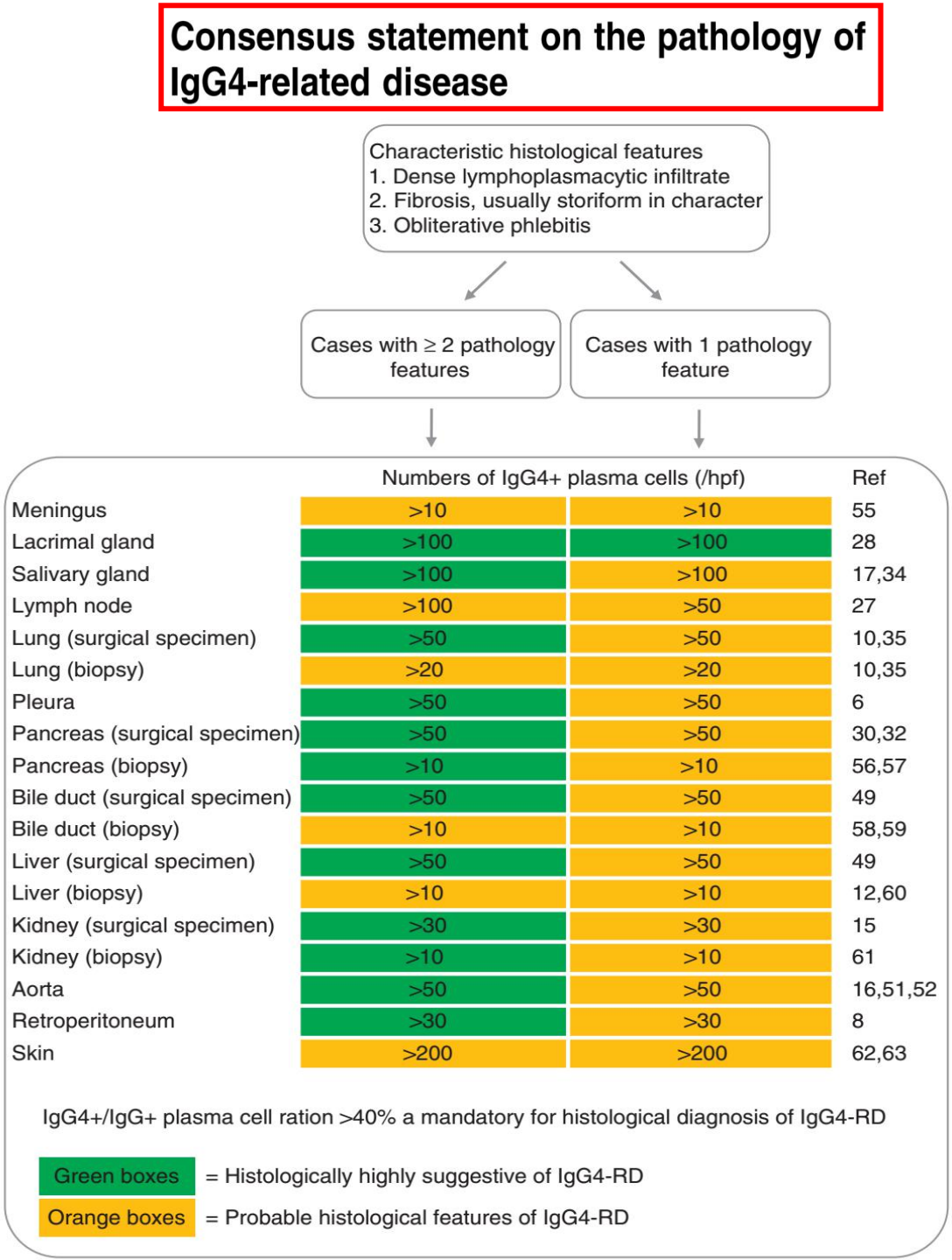
Quantitative measurement of ^{18}F-FDG PET/CT uptake reflects the expansion of circulating plasmablasts in IgG4-related disease

N=20, 10 repeated PET/CT
PK: PET/CT, ESR/CRP, IgG4, RI, plasmablasts

FIG. 2 Correlation between ^{18}F-FDG PET/CT parameters and immunological biomarkers of IgG4-related disease activi



Q4. 关于病理

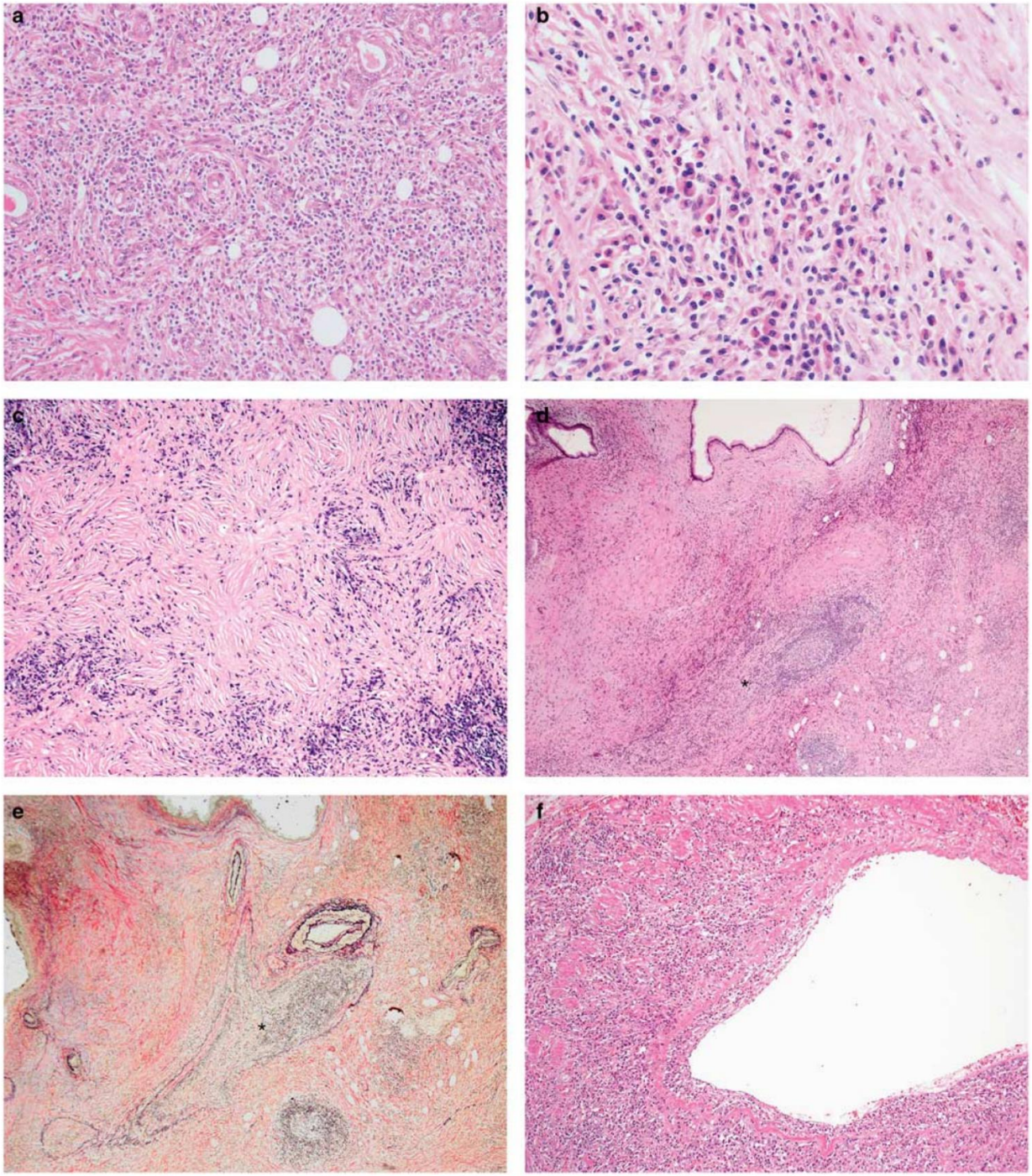


The three major histopathological features associated with IgG4-RD

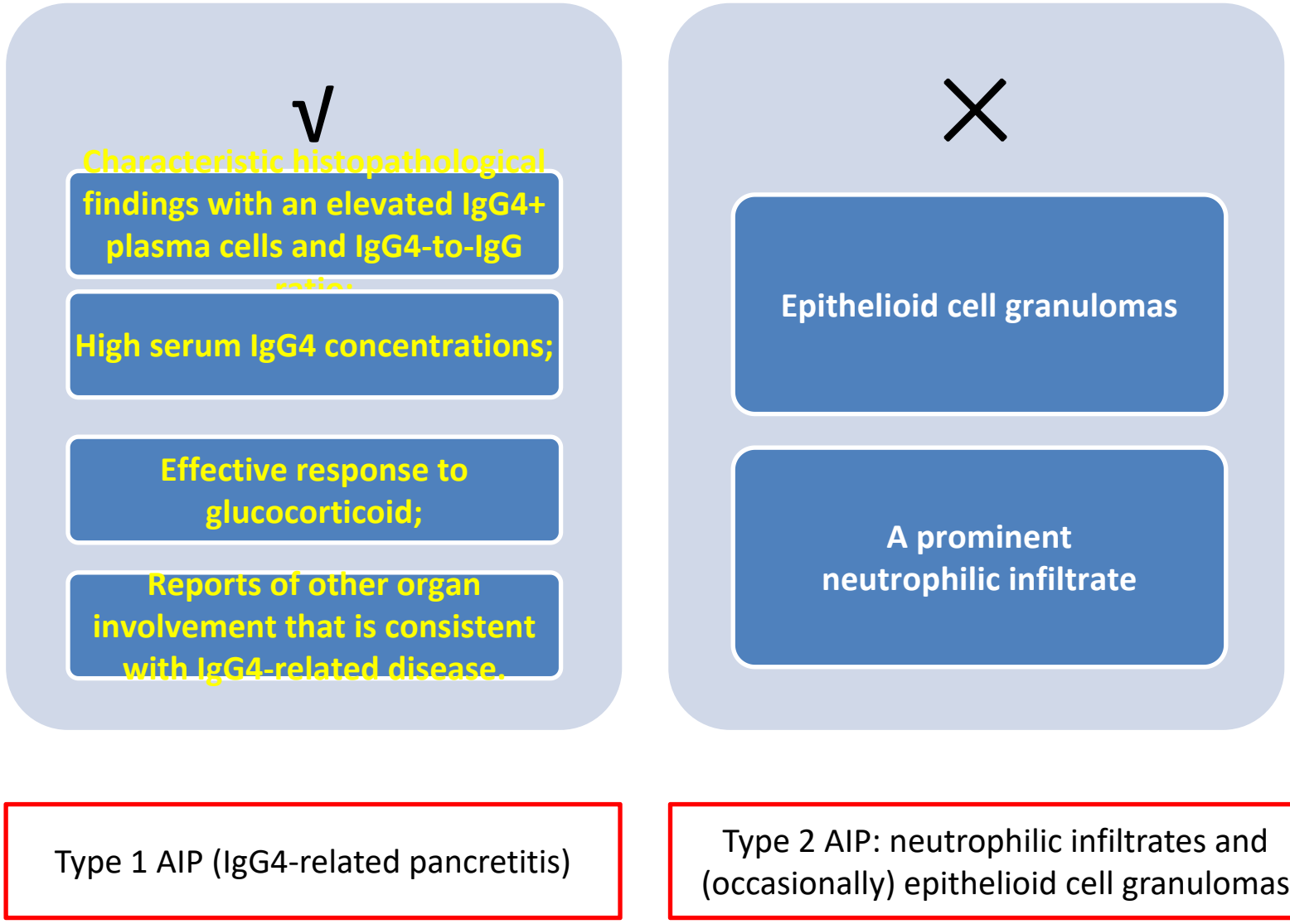
- Dense lymphoplasmacytic infiltrate
- Fibrosis, arranged at least focally in a storiform pattern
- Obliterative phlebitis

Other histopathological features associated with IgG4-RD

- Phlebitis without obliteration of the lumen
- Increased numbers of eosinophils



(a) The salivary gland is extensively infiltrated by lymphocytes and plasma cells.
(b) A moderate number of eosinophils are present.
(c) An irregularly whorled pattern of fibrosis (storiform fibrosis).
(d) Type 1 AIP. The vein (*) is completely obliterated by aggregated inflammatory cell infiltration (obliterative phlebitis).
(e) *100.
(f) Type 1 AIP. The partially obliterated vein shows transmural infiltration by inflammatory cells.



Type 1 AIP (IgG4-related pancretitis)

Type 2 AIP: neutrophilic infiltrates and (occasionally) epithelioid cell granulomas

Mod Rheumatol (2012) 22:21–30
DOI 10.1007/s10165-011-0571-z

ORIGINAL ARTICLE

Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011

Hisanori Umehara · Kazuichi Okazaki · Yasufumi Masaki · Mitsuhiro Kawano · Motohisa Yamamoto · Takako Saeki · Shoko Matsui · Tadashi Yoshino · Shigeo Nakamura · Shigeyuki Kawa · Hideaki Hamano · Terumi Kamisawa · Toru Shimosegawa · Akira Shimatsu · Seiji Nakamura · Tetsuhide Ito · Kenji Notohara · Takayuki Sumida · Yoshiya Tanaka · Tsuneyo Mimori · Tsutomu Chiba · Michiaki Mishima · Toshifumi Hibi · Hirohito Tsubouchi · Kazuo Inui · Hirotaka Ohara

Q5. 关于<u>诊断标准</u>？

MODERN PATHOLOGY (2012) 25, 1181–1192

Consensus statement on the pathology of IgG4-related disease

Vikram Deshpande[1,31], Yoh Zen[2,31], John KC Chan[3], Eunhee E Yi[4], Yasuharu Sato[5], Tadashi Yoshino[5], Günter Klöppel[6], J Godfrey Heathcote[7], Arezou Khosroshahi[8], Judith A Ferry[1], Rob C Aalberse[9], Donald B Bloch[8], William R Brugge[10], Adrian C Bateman[11], Mollie N Carruthers[8], Suresh T Chari[12], Wah Cheuk[3], Lynn D Cornell[13], Carlos Fernandez-Del Castillo[14], David G Forcione[10], Daniel L Hamilos[15], Terumi Kamisawa[16], Satomi Kasashima[17], Shigeyuki Kawa[18], Mitsuhiro Kawano[19], Gregory Y Lauwers[1], Yasufumi Masaki[20], Yasuni Nakanuma[21], Kenji Notohara[22], Kazuichi Okazaki[23], Ji Kon Ryu[24], Takako Saeki[25], Dushyant V Sahani[26], Thomas C Smyrk[13], James R Stone[1], Masayuki Takahira[27], George J Webster[28], Motohisa Yamamoto[29], Giuseppe Zamboni[30], Hisanori Umehara[20] and John H Stone[8]

2011 Japan

Table 1 Comprehensive diagnostic criteria for IgG4-related disease, 2011

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)
3. Histopathological examination shows:
(1) Marked lymphocyte and plasmacyte infiltration and fibrosis
(2) Infiltration of IgG4+plasma cells: ration of IgG4+/IgG +cells > 40 % and > 10 IgG4+plasma cells/HPF
Definite: 1) + 2) + 3)
Probable: 1) + 3)
Possible: 1) + 2)

- **Not specific!!**
- **Exclusion criteria is required.**
- **Involvement of at least one typical organ is required.**

- The sensitivity of these criteria were comparatively good for diagnosing IgG4-related MD (83 and 70%) and KD (87 and 85%).
- In contrast, patients with IgG4-related AIP could not be diagnosed by the comprehensive diagnostic criteria (0% for definite, nearly 70% for possible, and 10–30% for unlikely) because biopsies could not be obtained from most of these patients.

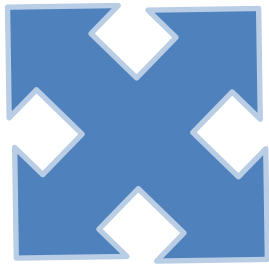
New criteria-exclusion criteria

Clinical

EXCLUSION	MIMICKERS	CASES
FEVER	44 (17%)	1 (<1%)
NO RESPONSE TO STEROIDS	23 (9%)	1 (<1%)
LEUKOPENIA AND THROMBOCYTOPENIA	19 (7%)	1 (<1%)
PERIPHERAL EOSINOPHILIA (>3,000mm^3)	9 (4%)	4 (1%)

Radiology

EXCLUSION	MIMICKERS	CASES
Rapid Radiographic Progression	5 (2%)	0 (0%)
Long Bone Abnormalities (e.g., ECD*)	3 (1%)	0 (0%)
Splenomegaly	14 (5%)	3 (1%)
Concern re: Infectious/Malignancy	4 (2%)	2 (1%)



Serology

EXCLUSION	MIMICKERS	CASES
PR3 or MPO-ANCA+	48 (19%)	2 (1%)
Anti-Ro or La+	51 (20%)	5 (1%)
Extractable Nuclear Antibody +	6 (2%)	0 (0%)
Cryoglobulins	10 (4%)	0 (0%)
Other disease-specific autoantibody	0 (0%)	0 (0%)

Pathology

EXCLUSION	MIMICKERS	CASES
Malignant Infiltrate	26 (10%)	1 (<1%)
Inflammatory Pseudotumor Pathology	2 (1%)	0 (0%)
Prominent Neutrophilic Infiltrate	6 (2%)	0 (0%)
Necrotizing Vasculitis	36 (14%)	0 (0%)
Prominent Necrosis	2 (1%)	0 (0%)
Primarily Granulomatous Inflammation	39 (15%)	0 (0%)
Prominent Histiocytic Infiltrate	7 (3%)	1 (<1%)
Multi-Centric Castleman's Pathology	6 (2%)	0 (0%)

New criteria
-8 weighted inclusion domains

- **Serum IgG4**
- **Histopathology**
- **Immunostaining**
- **Glandular enlargement**
- **Chest & thoracic aorta**
- **Pancreas & biliary tree**
- **Kidney**
- **Retroperitoneum**

Serum IgG4

a. Normal	0.0
b. > Normal but < 2X ULN*	3.7
c. 2X ULN to 5X ULN	6.1
d. >5X ULN	10.8

Pathology

--Histopathology

a. Uninformative biopsy	0.0
b. Dense lymphoplasmacytic infiltrate (DLI)	3.7
c. b + obliterative phlebitis (OP)	6.1
d. DLI + storiform fibrosis	13.3

--Immunostaining

Missing

Involved Organs

Lacrimal & Major Salivary Glands

One set of glands is involved	+ 5.9
Two or more sets of glands are involved	+ 13.8

Chest & Thoracic Aorta

Peribronchovascular and septal thickening	+ 3.8
Paravertebral Band-Like Soft Tissue in the Thorax	+ 9.8

Pancreas & 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/soft tissue	+ 8.1

Retroperitoneum

Diffuse thickening of the abdominal aortic wall	+ 4.1
Circumferential or antero-lateral soft tissue around the infra-renal aorta or iliac arteries	+ 7.8

	Sensitivity	Specificity
New criteria	85.5%	99.2%
Without exclusion criteria	90.0%	88.5%

Q6. 关于病情评估：IgG4-RD RI（ACR2012）

IgG4-RD responder index

Date form completed: (e.g., 7 / July / 2050)

Case number: _____

Scoring rules

Scoring refers to manifestations of disease activity present in the last 28 days

Scoring: 0 Normal or resolved
1 Improved
2 Persistent (unchanged from previous visit; still active)
3 New / recurrence
4 Worsened despite treatment

Definitions

Organ/site score: the overall level of IgG4-RD activity within a specific organ system
Symptomatic: is the disease manifestation in a particular organ system symptomatic? (Y = yes; N = no)
Urgent disease: disease that requires treatment immediately to prevent serious organ dysfunction (Y = yes; N = no)
(presence of **urgent disease** within an organ leads to **doubling** of that organ system score)
Damage: organ dysfunction that has occurred as a result of IgG4-RD and is considered permanent (Y = yes; N = no)

	Activity			Damage
Organ/site	Organ/site score (0-4)	Symptomatic (Yes/No)	Urgent (Yes/No)	Present (Yes/No)
Pachymeninges				
Pituitary gland				
Orbits and lacrimal glands				
Salivary glands				
Thyroid				
Lymph nodes				
Lungs				
Aorta and large blood vessels				
Retroperitoneum, mediastinum, and mesentery				
Pancreas				
Bile duct and liver				
Kidney				
Skin				
Other sclerosis/mass formation				

Descriptor	Level mg/dl	Score
Serum IgG4 concentration		

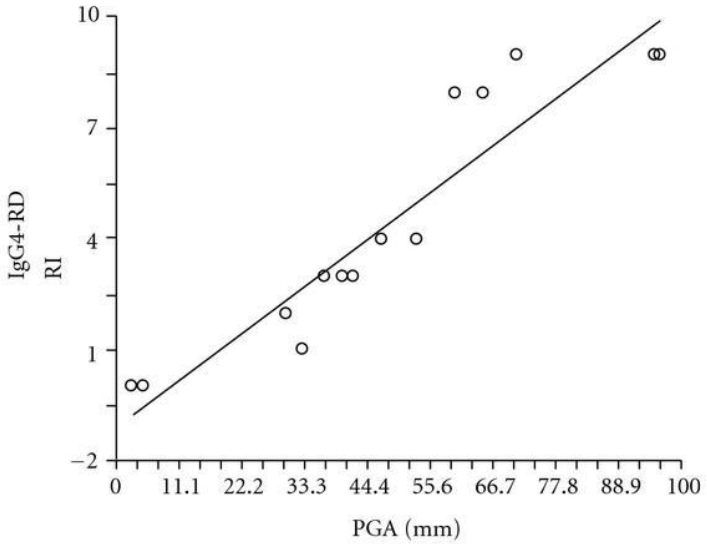
Total activity score

Organ/sites (×2 if urgent) + serum IgG4 score: _____

Total number of urgent organs: _____

Total number of damaged organs: _____

Steroid dose at the time of assessment (prednisone equivalent):
____ mg/day
Cumulative steroid dose in the past 28 days:
____ mg prednisone equivalent



“Damage”

- The severity of fibrosis is dependent on the individual organs involved. Storiform fibrosis. The response to glucocorticoids varies according to the affected organs and the degree of fibrosis.
  - Wait and see: Overall ~20%, 70%~ of lymphadenopathy, 30%~ of salivary glands; Spontaneous resolution: 40%~ of patients (but with higher relapse rates compared to those treated with glucocorticoids) ; may be appropriate in asymptomatic patients with lymphadenopathy or mild salivary gland enlargement.
  - However, uncontrolled disease in certain organs can lead to irreversible damage. Urgent treatment is therefore recommended for the following types of IgG4-RD: aortitis, RPF, sclerosing cholangitis, TIN, pachymeningitis, and pericarditis.

“High risk” patients

- Multi-organ disease,
- Significant elevation of serum IgG4 levels
- Proximal extrahepatic/intrahepatic biliary strictures
- With a history of relapse

- However, as IgG4-RD patients are typically elderly and are at high risk of developing steroid-related complications such as osteoporosis and diabetes mellitus, cessation of the medication should be attempted.
- Cessation of maintenance therapy should be planned within 3 years in cases with radiological and serological improvement.

Prognosis

- The short-term clinical, morphological, and functional outcomes of most IgG4-RD patients treated with steroid therapy are good, although the long-term outcomes are less clear.
- However, there are several unknown factors such as relapse, developed fibrosis, and associated malignancy that influence long-term outcomes.
- 10%~30% manifestations of chronic pancretitis (pancreatic stones, pancreatic calcification, pancreatic atrophy)
- Malignancy concern: Chronic pancreatitis has been reported as one of the risk factors for pancreatic cancer. Case reports of AIP patients developing pancreatic cancer. (2.4%-10%).

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Q7. 关于治疗

- 无症状的患者是否可以暂时观察，暂不进行干预？
- IgG4相关性疾病是否首选需用激素治疗？剂量应为：
- IgG4相关性疾病的治疗是否需加激素助减剂？何时加？（初始、维持、激素无法控制或依赖）
- 激素助减剂您更倾向选择传统免疫抑制剂还是生物靶向药物如利妥昔单抗?
- 您认为糖皮质激素的维持治疗时间应为？维持剂量应为？
- 您认为IgG4相关性疾病的复发常见吗？
- 复发患者的治疗应为？

Standard steroid treatment for autoimmune pancreatitis

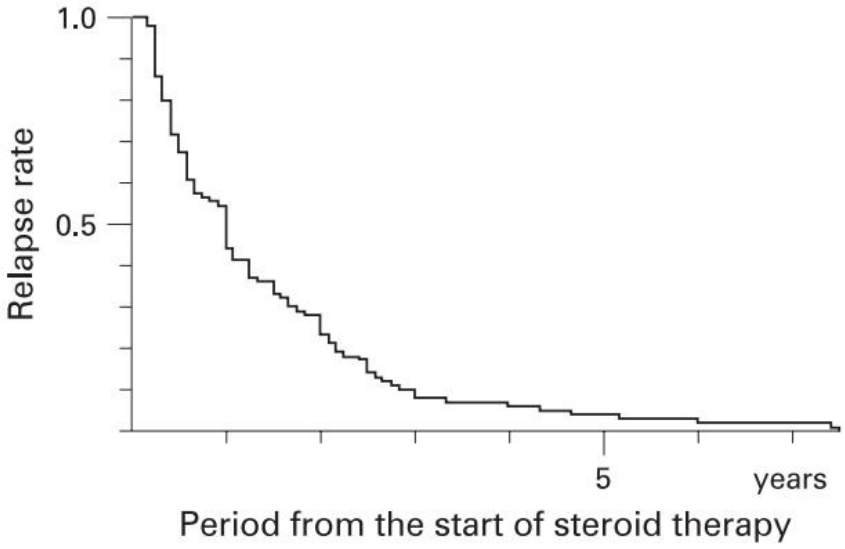
T Kamisawa,[1] T Shimosegawa,[2] K Okazaki,[3] T Nishino,[4] H Watanabe,[5] A Kanno,[2] F Okumura,[6] T Nishikawa,[7] K Kobayashi,[8] T Ichiya,[9] H Takatori,[10] K Yamakita,[11] K Kubota,[12] H Hamano,[13] K Okamura,[14] K Hirano,[15] T Ito,[16] S B H Ko,[17] M Omata[15]

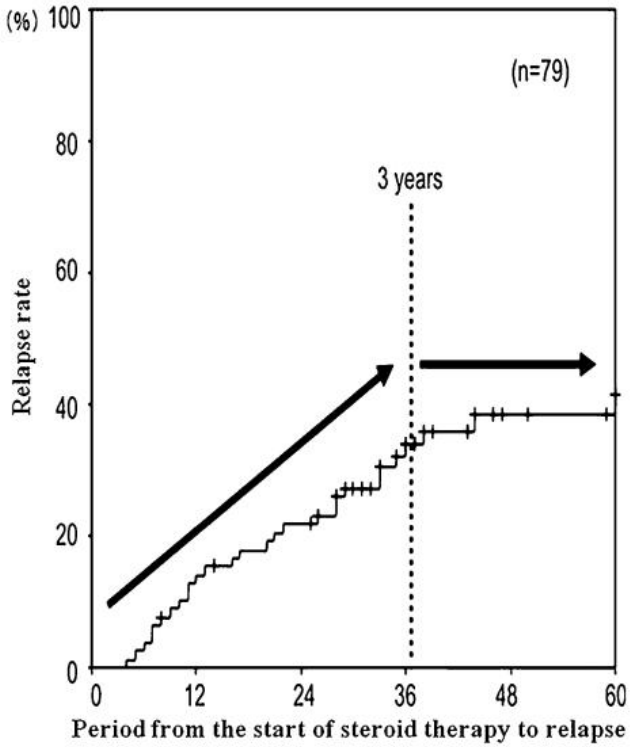
Table 1 Remission and relapse rate in patients with autoimmune pancreatitis treated with and without steroid

	With steroid	Without steroid	p Value
Remission rate	451/459 (98%)	77/104 (74%)	<0.0001
Relapse rate	110/451 (24%)	32/77 (42%)	0.003

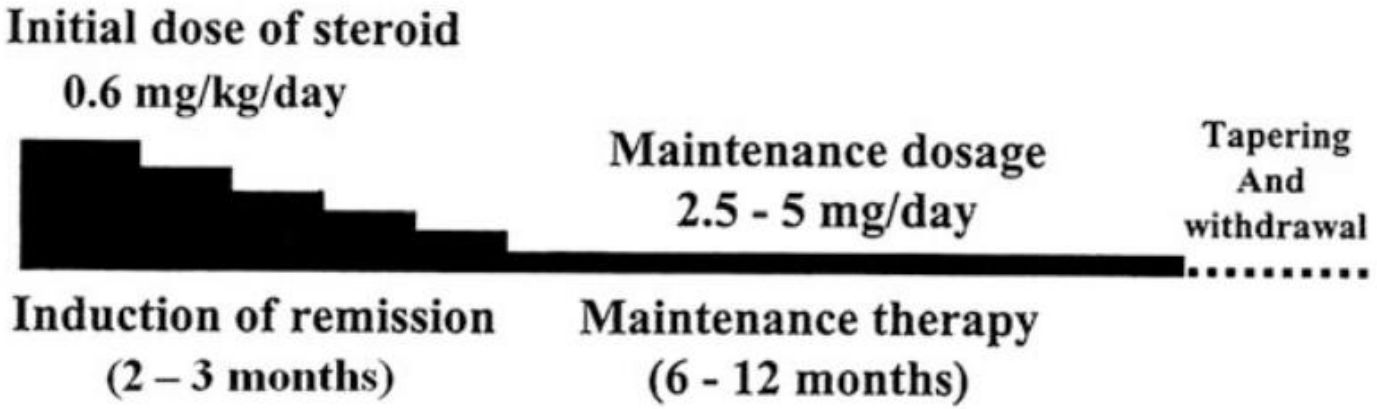
Table 2 Period to yield a remission and relapse rate in patients with autoimmune pancreatitis treated with initial prednisolone of 40 and 30 mg/day

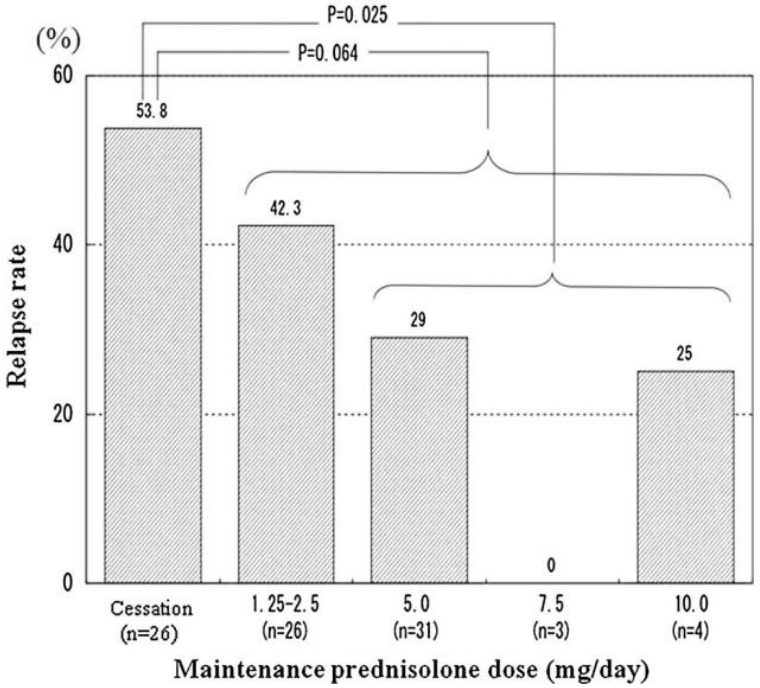
	40 mg/day	30 mg/day	p Value
Period to remission (mean (SD), months)	6.34 (8.13)	6.82 (6.11)	0.401
Relapse rate	31/160 (19%)	65/283 (23%)	0.402





- 32% (32/99)relapsed within 6 months
- 56% (55/99) relapsed within 1 year
- 76% (75/99) relapsed within 2 years
- 92% (91/99) relapsed within 3 years
- Relapse rate: 23%, 63/273 with maintenance treatment
  vs 34%, 35/104 without maintenance ; p = 0.048).





- Similar findings (Korea, UK, US), maintenance therapy with low-dose prednisolone (2.5–5 mg/day) was recommended to prevent relapse

How are relapsers treated? (参照AIP)

- Re-administration or dose-up of steroid is effective. (A)
- In most relapsed cases, remission can be achieved with the same prednisolone dose as the initial dose, although it may be necessary to taper more gradually. (B)
- Application of immunomodulatory drugs is considered for AIP patients who prove resistant to steroid therapy. (B)

IS?

- In cases where the steroid dosage cannot be tapered due to persistently active disease, the addition of immunomodulatory drugs such as azathioprine or mycophenolate mofetil has been considered to be appropriate.

ORIGINAL ARTICLE

Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience

Table 1 Treatment protocols used for steroid, immunomodulator and rituximab (RTX) therapy

	Induction regimen	Taper	Maintenance
Steroids	Prednisone 40 mg daily×4 weeks	5 mg/wk until discontinued	None
Immunomodulator	Azathioprine 2.0–2.5 mg/kg/day (alternate: 6-MP 1 mg/kg/day) (alternate: MMF 750–1000 mg twice daily)	N/A	Continue×12–18 months
RTX	375 mg/m^2 intravenous BSA weekly×4 weeks Coadminister: oral diphenhydramine 50 mg and oral paracetamol 1000 mg once	N/A	Repeat infusions every 2–3 months×24 months (total of 8 additional doses)

6-MP, 6-mercaptopurine; BSA, body surface area; MMF, mycophenolate mofetil.

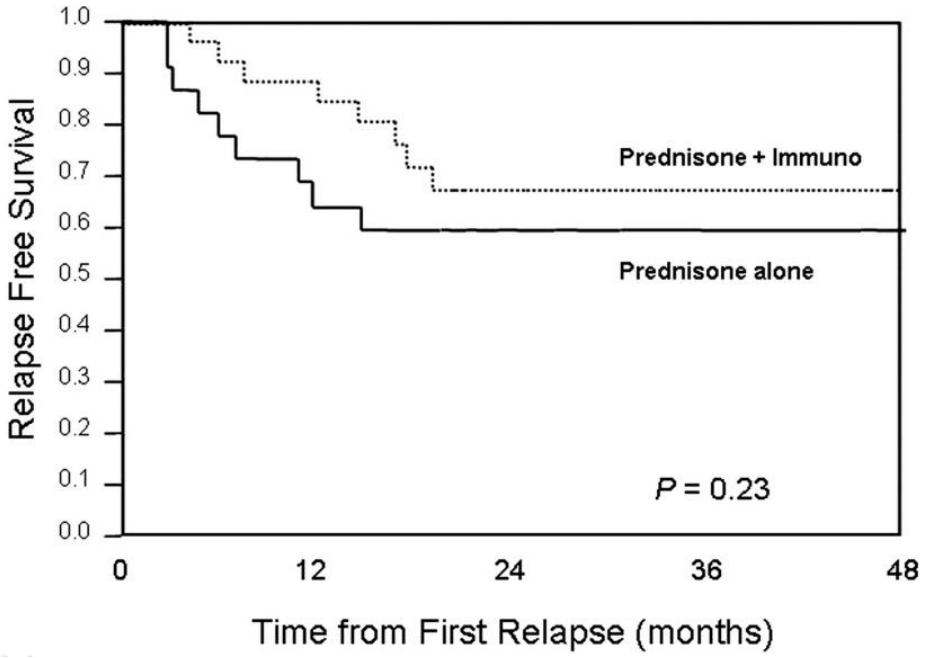


Table 5 Univariate analysis of risk factors for immunomodulator (IM) resistance

	IM responsive (n=21)	IM resistant (n=15)†	p Value*
Age >65 years at diagnosis	10 (48)	8 (53)	0.61
IgG4 >ULN	18 (86)	13 (87)	0.68
IgG4 >2×ULN	7 (33)	6 (40)	0.81
Initial treatment by surgery	3 (14)	0	0.16
Diffuse pancreatic enlargement at presentation	13/19 (68)	7/13 (54)	0.45
Other organ involvement			
OOI ever	12 (57)	14 (93)	0.03
IgG4-relatedSC at presentation	7 (33)	7 (47)	0.34
OOI (other than IgG4-related SC)	6 (29)	12 (80)	<0.01
Retroperitoneal fibrosis	0	7 (47)	<0.01
>6 months duration from diagnosis to IM initiation	15 (71)	8 (53)	0.20

Data presented as n (%), unless otherwise indicated.
*p Values were calculated using the log-rank test from Kaplan–Meier analyses.
†IM resistant column does not include the two patients who did not tolerate treatment.
OOI, other organ involvement; SC, sclerosing cholangitis; ULN, upper limit of normal.

- 12 patients with steroid or IM intolerance/resistance were treated with RTX, an antiCD20 antibody; 10 (83%) experienced complete remission and had no relapses while on maintenance therapy.

RTX

EXTENDED REPORT

Rituximab for IgG4-related disease: a prospective, open-label trial

Mollie N Carruthers,[1] Mark D Topazian,[2] Arezou Khosroshahi,[3] Thomas E Witzig,[4] Zachary S Wallace,[1] Philip A Hart,[2] Vikram Deshpande,[5] Thomas C Smyrk,[6] Suresh Chari,[2] John H Stone[1]

- 30 IgG4-RD patients with two doses of RTX (1000 mg each).
- The participants were either treated with RTX alone (n = 26; 87%) or required to discontinue baseline glucocorticoids (GC) within 2 months (n = 4; 13%).

Table 2 Primary and secondary outcomes

Outcome	Proportion of participants (%)
Primary outcome	23/30 (77%)
Disease response (6 months)	29/30 (97%)
Sustained disease response	22/30 (73%)
Complete remission (6 months)	14/30 (47%)
Complete remission (6 months), exclusive of serum IgG4	18/30 (60%)
Complete remission (any time point)	18/30 (60%)
Complete remission (any time point), exclusive of serum IgG4	20/30 (67%)
Relapses occurring before month 6	3
Relapses occurring between months 6 and 12	4
Time to endpoint	**Duration (days)**
Time to disease response (mean±SD)*	43±37
Time to complete remission (mean±SD)*	198±87
Time to relapse (mean±SD)	210±105
Treatment	
Total prednisone dose equivalent (mg) administered in the 28 days prior to the 6 month study visit (mean, range)	15 (0–280)
Retreatment with RTX for relapses during the 12 months after enrolment	4/30 (13%)

The primary outcome, measured at 6 months

- decline of the IgG4-RD RI ≥2 points compared with baseline;
- no disease flares before month 6;
- no GC use between months 2 and 6.

Complete remission

- RI score of 0 with no GC use.

致谢

- 孙芳芳医生