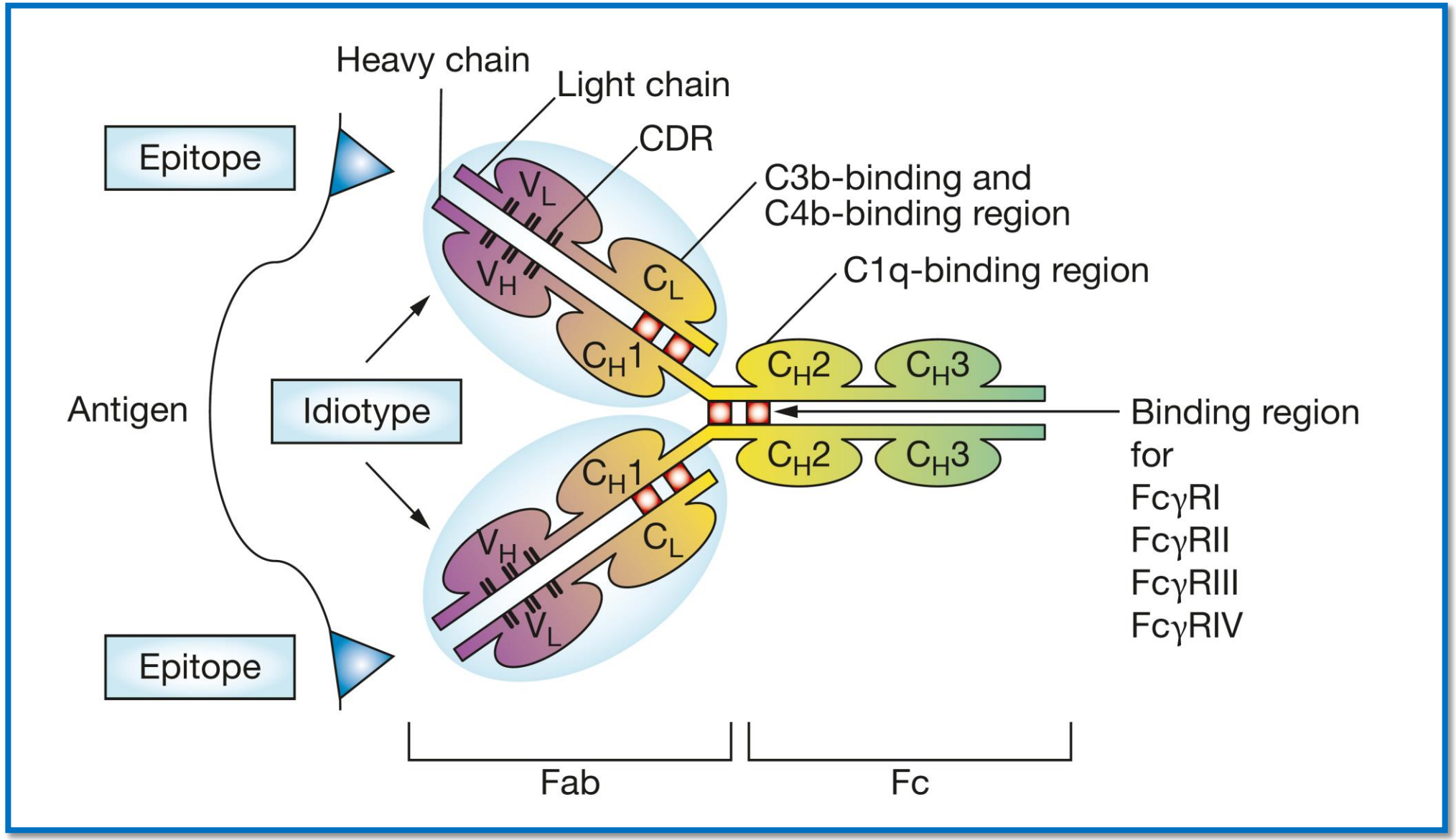
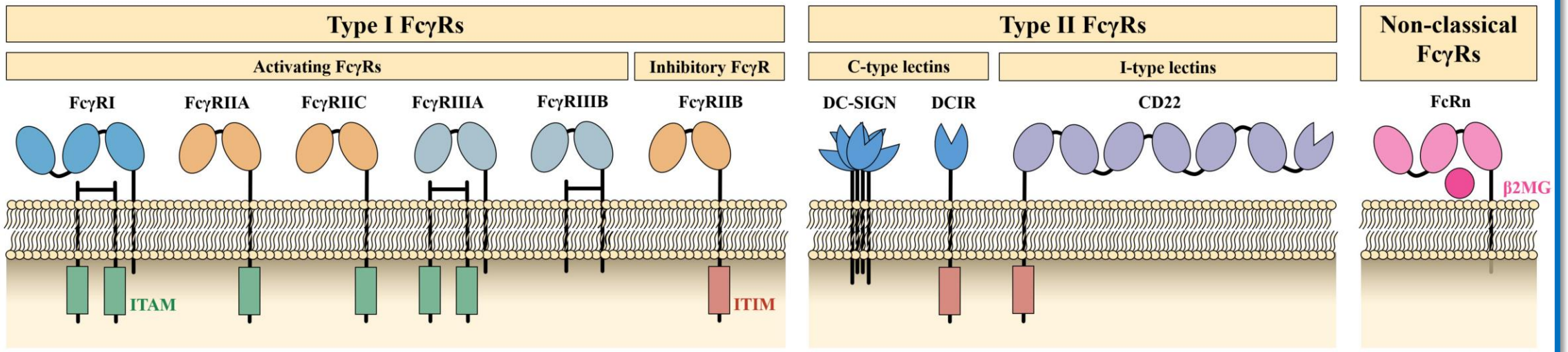
Klinik Pratikte İntravenöz İmmunoglobulinler

Dr. Uğur KARASU

Pamukkale Üniversitesi Romatoloji

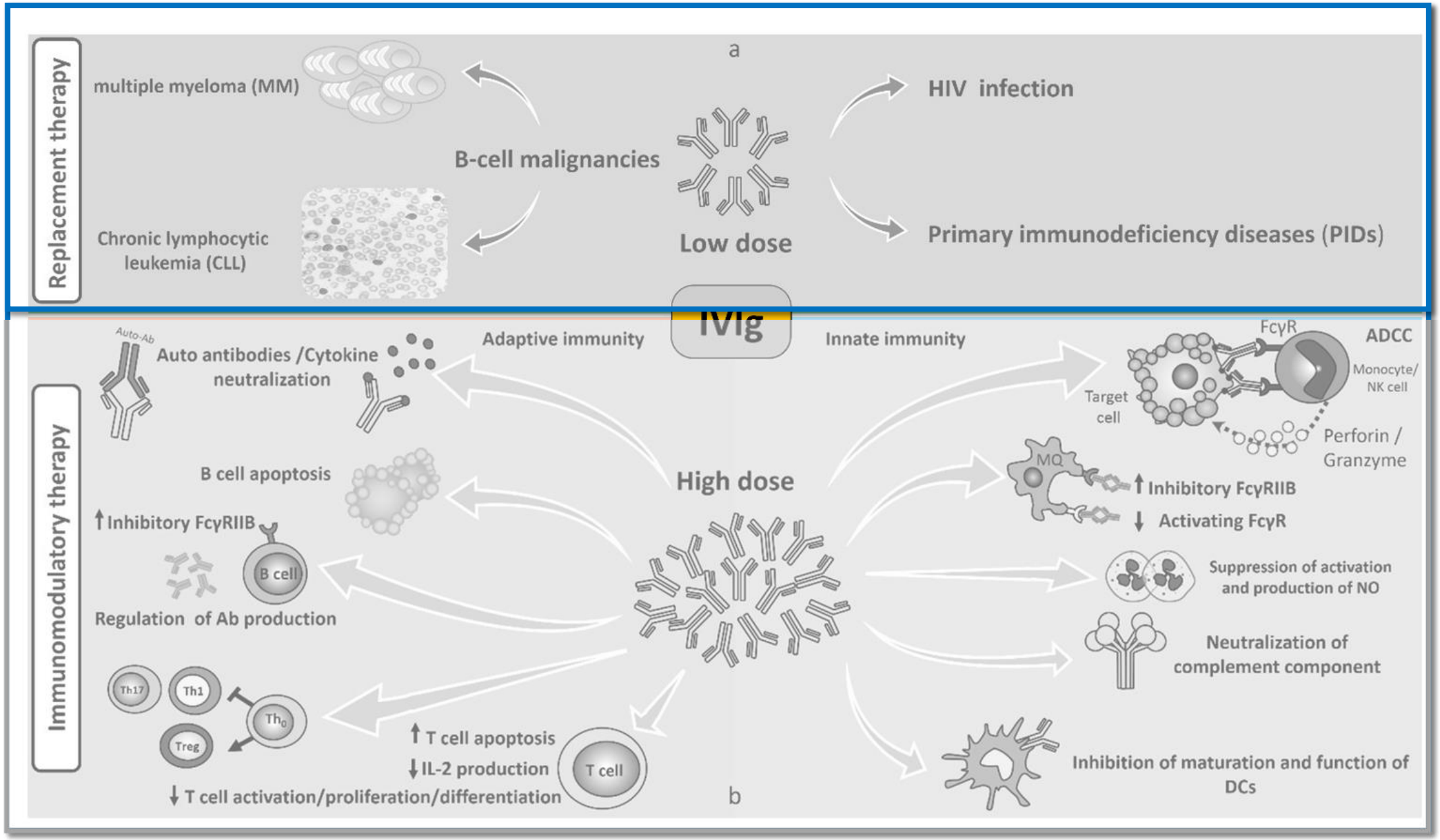


Bayry Et Al. Nature Clinical Practice Rheumatology 2007



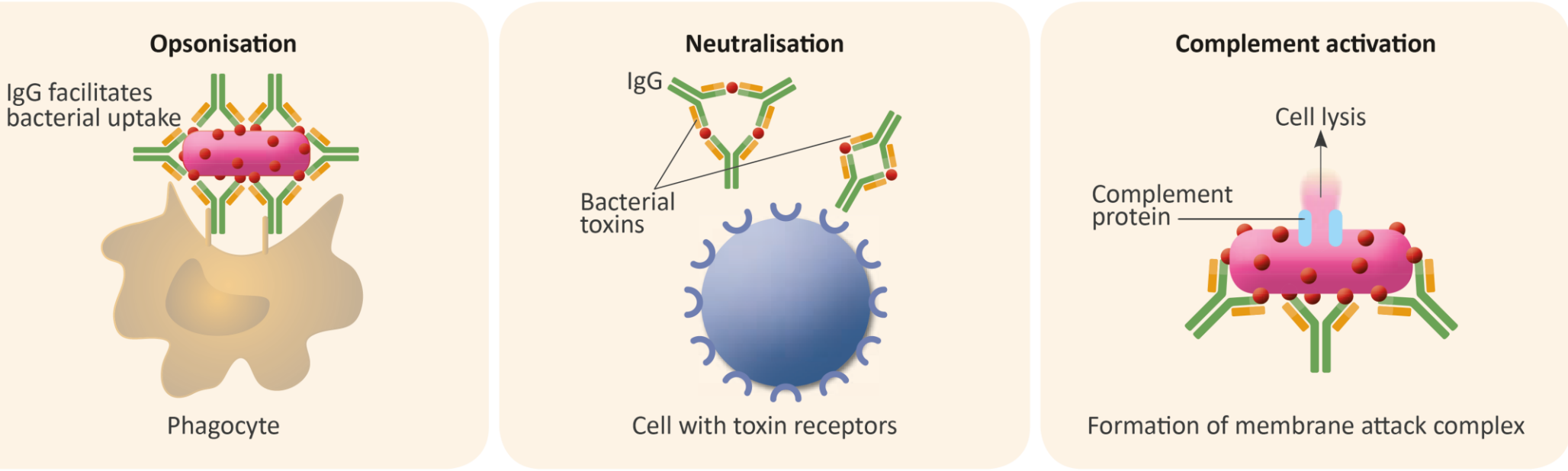
	FcγRI	FcγRIIA	FcγRIIC	FcγRIIIA	FcγRIIIB	FcγRIIB	DC-SIGN	DCIR	CD22	FcRn
Endothelial Cells	-	-	-	-	-	-	+	-	-	+
Dendritic Cells	+	+	+/-	-	-	+	+	+	-	+
Macrophages	+	+	+/-	+/-	-	+	+/-	-	-	+
Neutrophils	[+]	+	+/-	-	+	+/-	-	-	-	+
NK cells	-	-	+/-	+	-	+/-	-	-	-	-
T cells	-	-	-	+/-	-	-	-	-	-	-
B cells	-	-	-	-	-	+	-	-	+	-

Liu et al. Frontiers in Immunology 2020

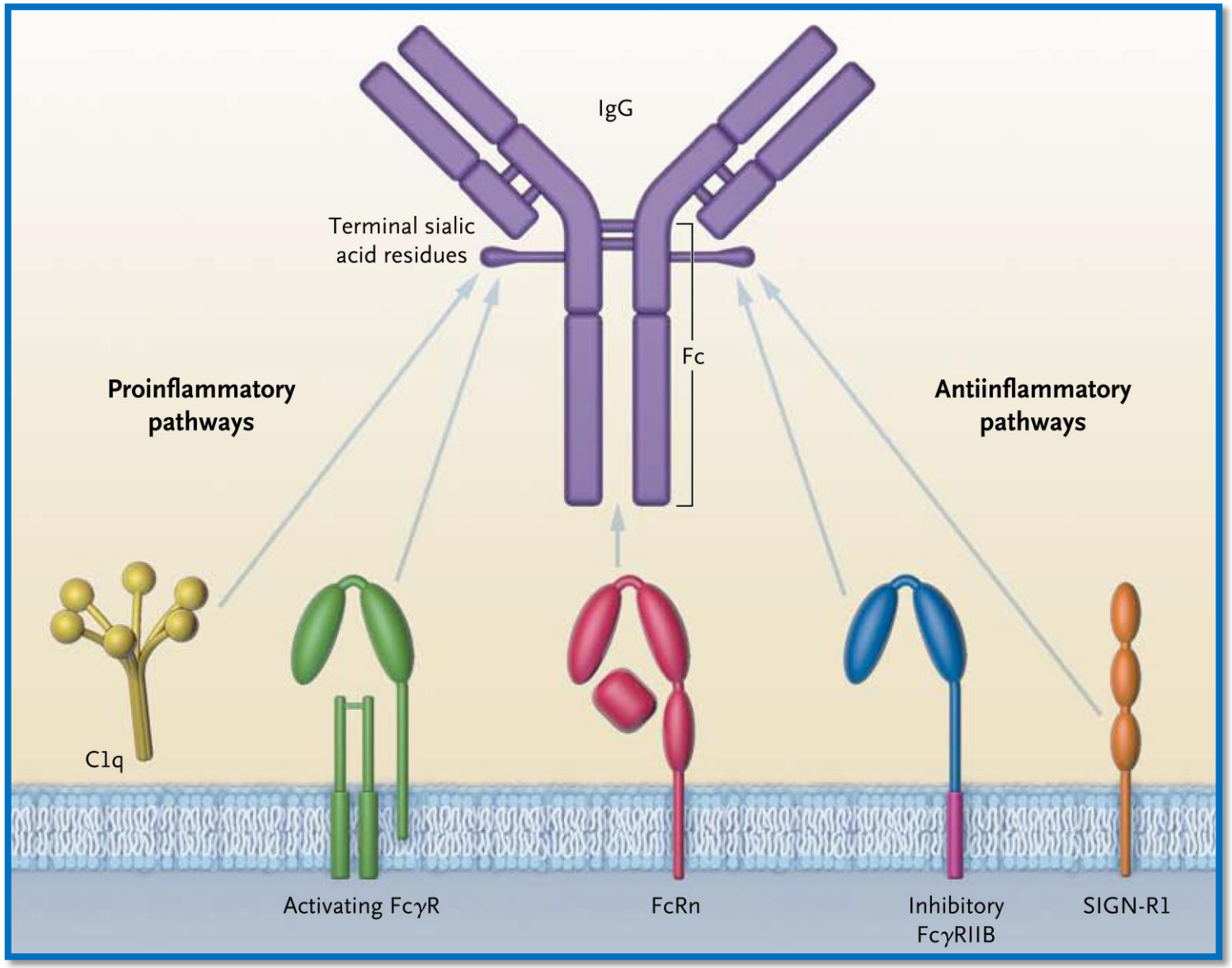


A. H. Mansourabadi, et al. Iran J Allergy Asthma Immunol August 2020

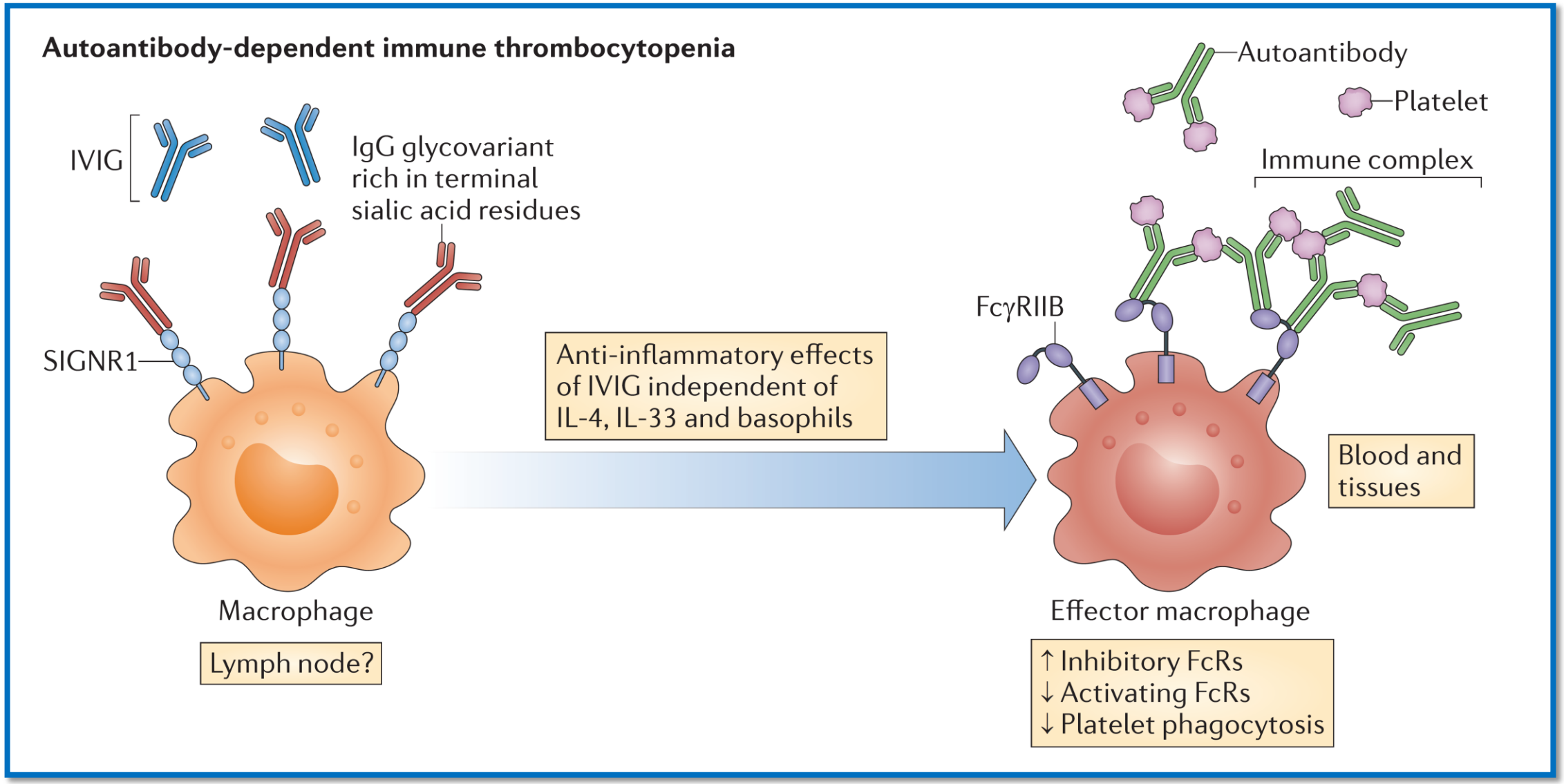
Mechanisms of polyvalent immunoglobulins action to prevent infections
Key role for treatment of primary and secondary immunodeficiency



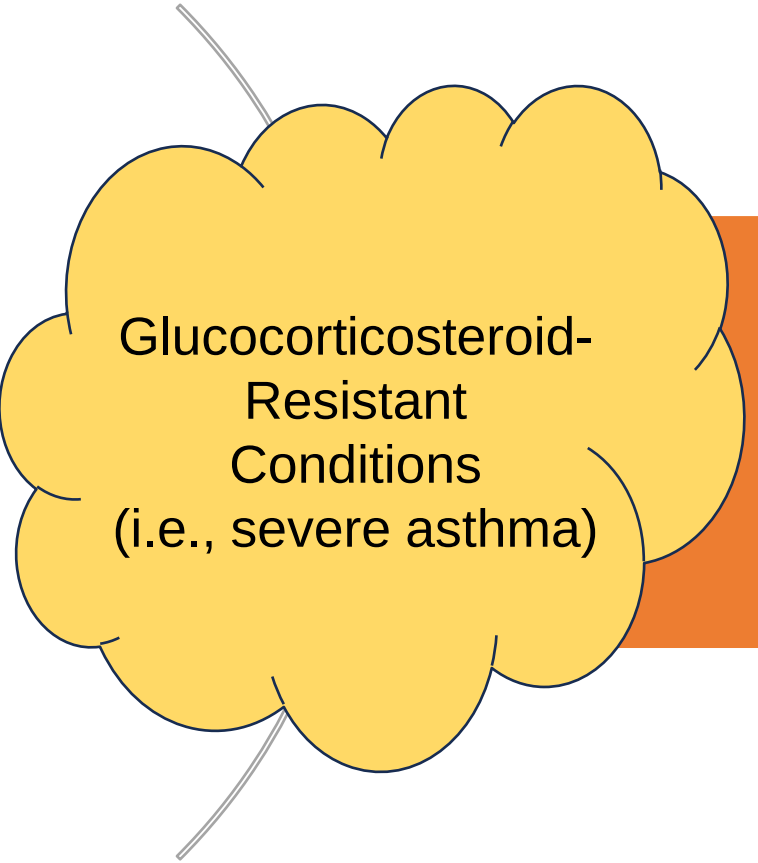
J G Peter, *S Afr Med J* 2014



Erwin W. Gelfand N Engl J Med 2012

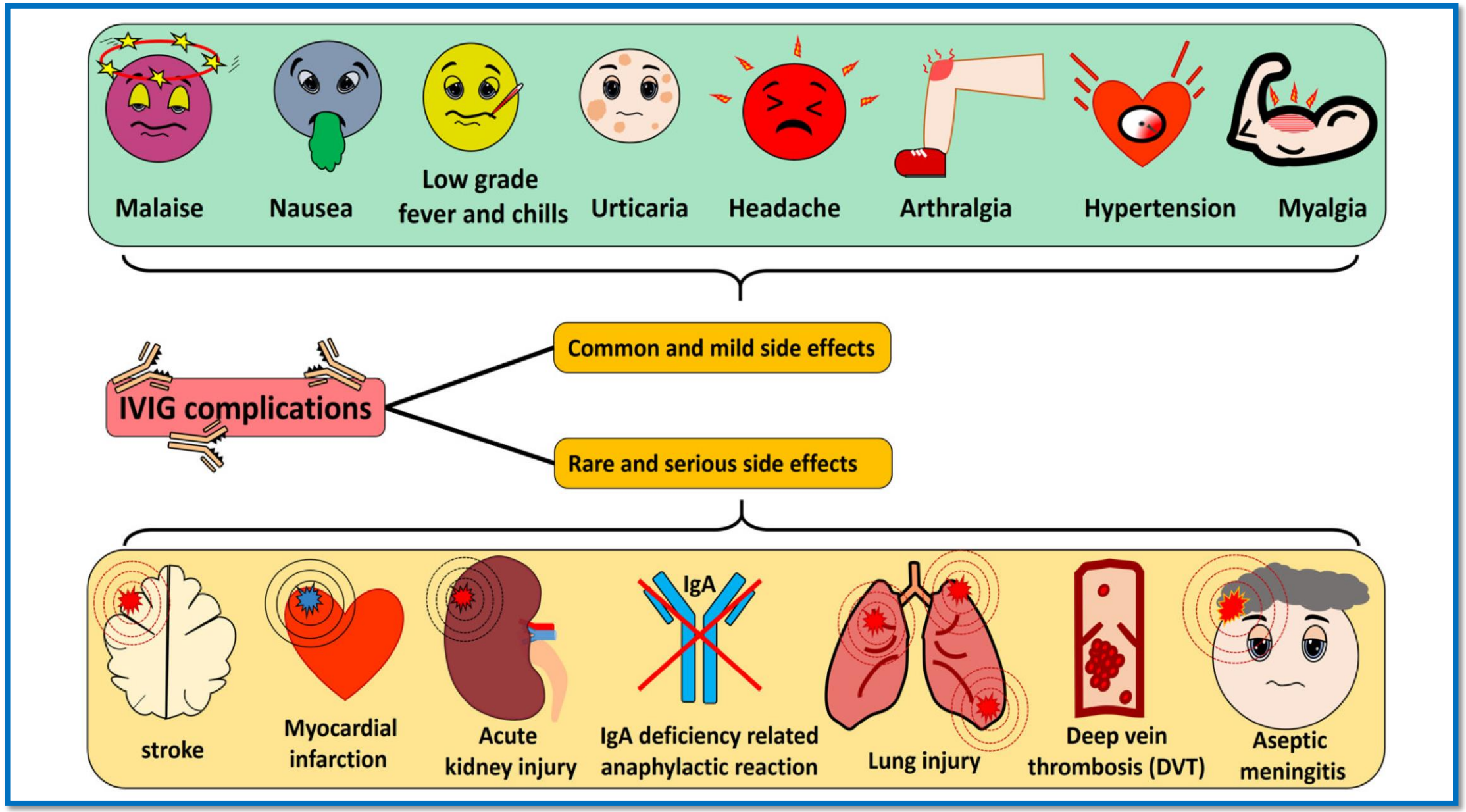


Inessa Schwab And Falk Nimmerjahn Nature Reviews | Immunology 2013



Glukokortikoid-reseptör bağlanmasını iyileştirerek glukokortikoidlere yanıtı iyileştirebilir

Spahn, J.D.; J. Allergy Clin. Immunol. 1999



A. H. Mansourabadi, et al. Iran J Allergy Asthma Immunol August 2020

Table 2 | Adverse events associated with IVIg and SCIg therapies

Adverse events	Risk factors	Manifestations	Mechanisms	Prevention and treatment strategies
IVIg				
Inflammatory reactions[115]	Fast infusion rate Allergic or anaphylactic reactions IgA deficiency	Mild reactions* Moderate reactions‡ Severe reactions§	Anaphylactoid reactions Immune complex formation Anti-complement activity Fc receptor-mediated release of prostaglandins, platelet-activating factor, and cytokines from macrophages and leukocytes Vasoactive contaminants Development of anti-IgA antibodies that react with the IgA molecules in the IVIg preparation	Slow infusion rate as per body weight Product substitution Prophylactic steroids Antihistamines, or anti-inflammatory agents (not very useful) Cautious use of IVIg containing low levels of IgA
Thromboembolic events[116,117]	Age >60 years High dose Fast infusion rate Hypertension Coronary heart disease Type 1 diabetes mellitus Dyslipidemia	Coronary artery disease Transient ischemic attack Infarct Stroke Peripheral thromboembolism	Hyperviscosity Contamination with clotting factors Vasospasm Formation of platelet–leukocyte aggregates	Slower infusion rate Prophylaxis Early treatment of high-risk patients
Renal complications[117]	Age >60 years Type 1 diabetes mellitus Renal disease Sepsis Paraproteinemia Nephrotoxic agents Stabilizers in IVIg preparation (sucrose, maltose, glucose)	Acute renal failure Mild alteration in renal function	Osmotic injury	Adequate hydration Use of correct dose Periodic monitoring of renal function Use of sugar-free stabilizers
Hemolysis[90,118]	High dose Blood group other than O Multiparous women	Intravascular hemolysis	Passive transfer of ABO isohemagglutinins to non-O blood group patients Underlying inflammatory state	Blood type cross-matching Determination of anti-A and anti-B antibody titer before infusion Post-transfusion testing for hemolysis within 36 h
Acute meningeal inflammation[119]	Fast infusion rate History of migraine Single high dose of IVIg	Aseptic meningitis	Release of inflammatory cytokines Presence of ANCA-like immunoglobulins	Anti-inflammatory agents

A. H. Mansourabadi, et al. Iran J Allergy Asthma Immunol August 2020

İmmün yetmezlik durumlarında replasman tedavisi

İmmünmodülatuvar ve anti-inflamatuar tedavi

Spesifik infeksiyöz ajanlara karşı hiperimmün tedavi

TABLE I. FDA-approved indications of IVIG

Disease state	No. of FDA-licensed products*	Indication†
PI disease, or primary humoral immunodeficiency	15	Indicated for the treatment of PI states, or for elevation of circulating antibody levels in PI, or for replacement therapy of PI states in which severe impairment of antibody forming capacity has been shown
Idiopathic thrombocytopenic purpura	7	Indicated when a rapid rise in platelet count is needed to prevent and/or control bleeding in idiopathic thrombocytopenic purpura, or to allow a patient with idiopathic thrombocytopenic purpura to undergo surgery
B-cell CLL	2	Indicated for the prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell CLL
CIDP	2	Indicated for the treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse
KD	2	Indicated for the prevention of coronary artery aneurisms associated with Kawasaki disease
MMN	1	Indicated as a maintenance therapy to improve muscle strength and disability in adult patients with MMN
Bone marrow transplantation	0	Indicated for bone marrow transplant patients ≥20 y of age to decrease the risk of septicemia and other infections, interstitial pneumonia of infectious or idiopathic etiologies and acute GVHD in the first 100 d after transplantation
HIV infection	0	Indicated for pediatric patients with HIV infection to decrease the frequency of serious and minor bacterial infections and the frequency of hospitalization, and increase time free of serious bacterial infection

New Drug Approvals 2021-22

FDA Indications

- belimumab (lupus nephritis)
- apremilast (mild-moderate psoriasis)
- tocilizumab (ILD of systemic sclerosis)
- rilonacept (Recurrent pericarditis),
- IVIG (inflammatory myositis)
- secukinumab (jPsA, ERA)
- tofacitinib in AS, atopic dermatitis
- upadacitinib PsA, AS, atopic dermatitis
- baricitinib (COVID, alopecia areata)
- MTX + Pegloticase (gout)
- canakinumab in Adult Stills Dz
- risakizumab in PsA and Crohns colitis

Prospective, double-blind, randomized, placebo-controlled phase III study evaluating efficacy and safety of octagam 10% in patients with dermatomyositis ("ProDERM Study")

IDIOPATHIC INFLAMMATORY MYOPATHY

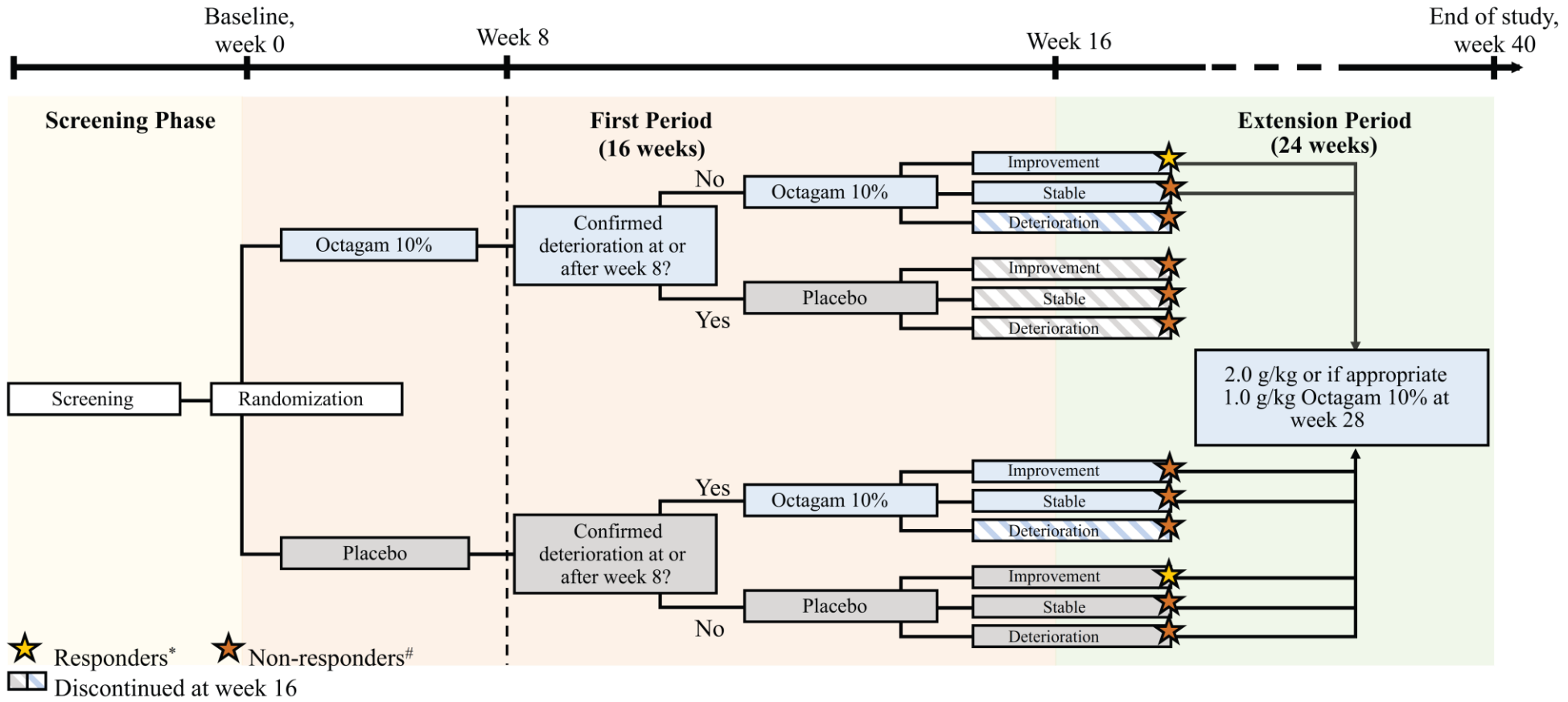


Figure 1. Overview of study design. *Patients with a total improvement score (TIS) ≥20 at week 16 and no prior confirmed deterioration up to and including week 16. #Patients discontinuing from the study due to confirmed deterioration and patients with no response.

Aggarwal et al. Medicine 2021

Trial of Intravenous Immune Globulin in Dermatomyositis

IDIOPATHIC INFLAMMATORY MYOPATHY

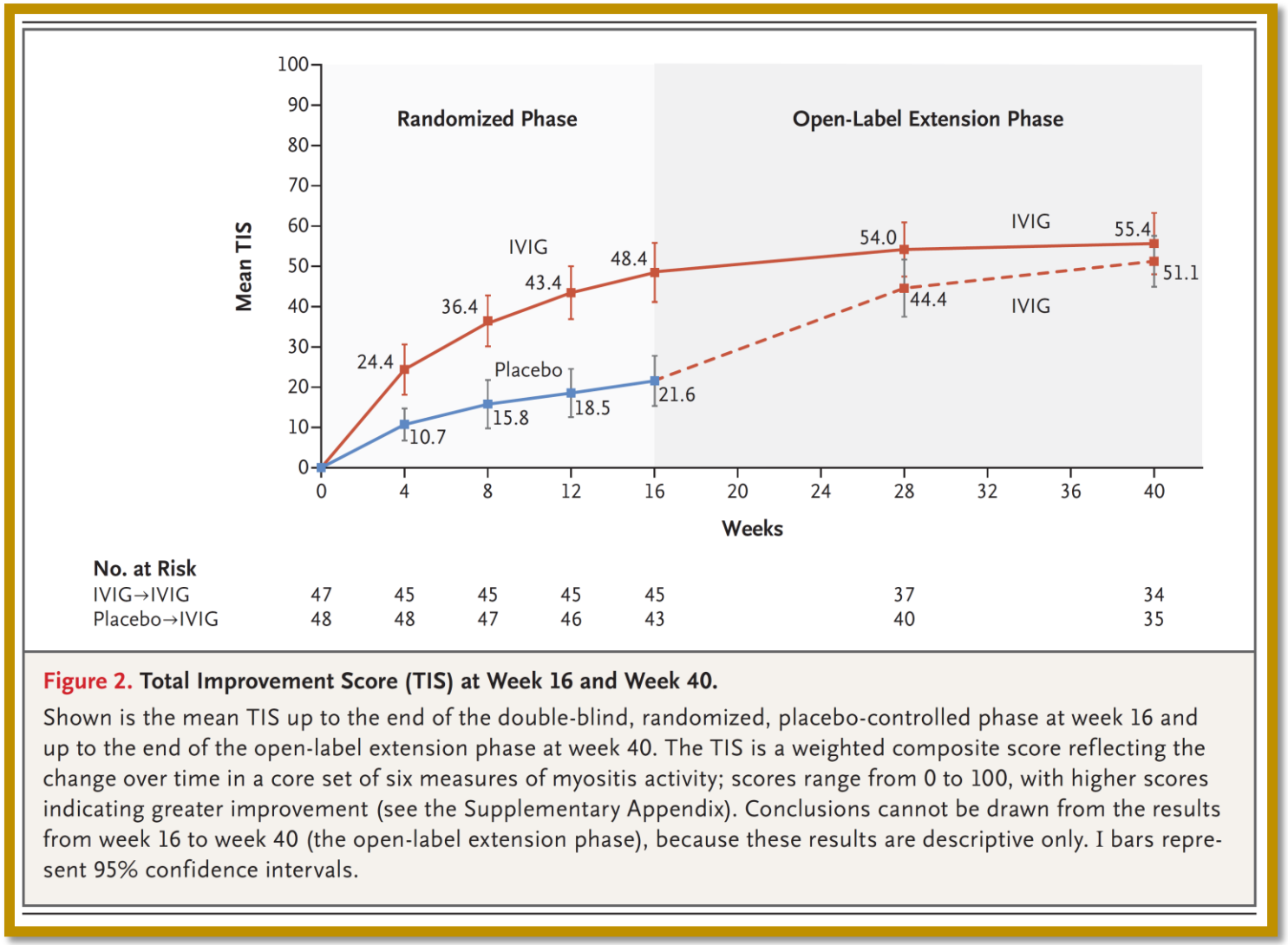


Figure 2. Total Improvement Score (TIS) at Week 16 and Week 40.

Shown is the mean TIS up to the end of the double-blind, randomized, placebo-controlled phase at week 16 and up to the end of the open-label extension phase at week 40. The TIS is a weighted composite score reflecting the change over time in a core set of six measures of myositis activity; scores range from 0 to 100, with higher scores indicating greater improvement (see the Supplementary Appendix). Conclusions cannot be drawn from the results from week 16 to week 40 (the open-label extension phase), because these results are descriptive only. I bars represent 95% confidence intervals.

R. Aggarwal ve ark. N Engl J Med 2022

British Society for Rheumatology guideline on management of paediatric, adolescent and adult patients with idiopathic inflammatory myopathy

IDIOPATHIC INFLAMMATORY MYOPATHY

Number	Statement (unless otherwise specified, recommendation applies to adults and children)	Cited evidence	Strength/ Quality/ Agreement	Number of raters Numerator/denominator
1. How should muscle inflammation be treated?				
4	Intravenous immunoglobulin should be considered as a treatment of severe and/or refractory muscle inflammation.	• Dalakas(31) Cherin(32) • Lam(33) Kampylafka(34)	1 B 100%	21/21

Efficacy of intravenous immunoglobulins (IVIg) in improving skin symptoms in patients with dermatomyositis: a post-hoc analysis of the ProDERM study

IDIOPATHIC INFLAMMATORY MYOPATHY

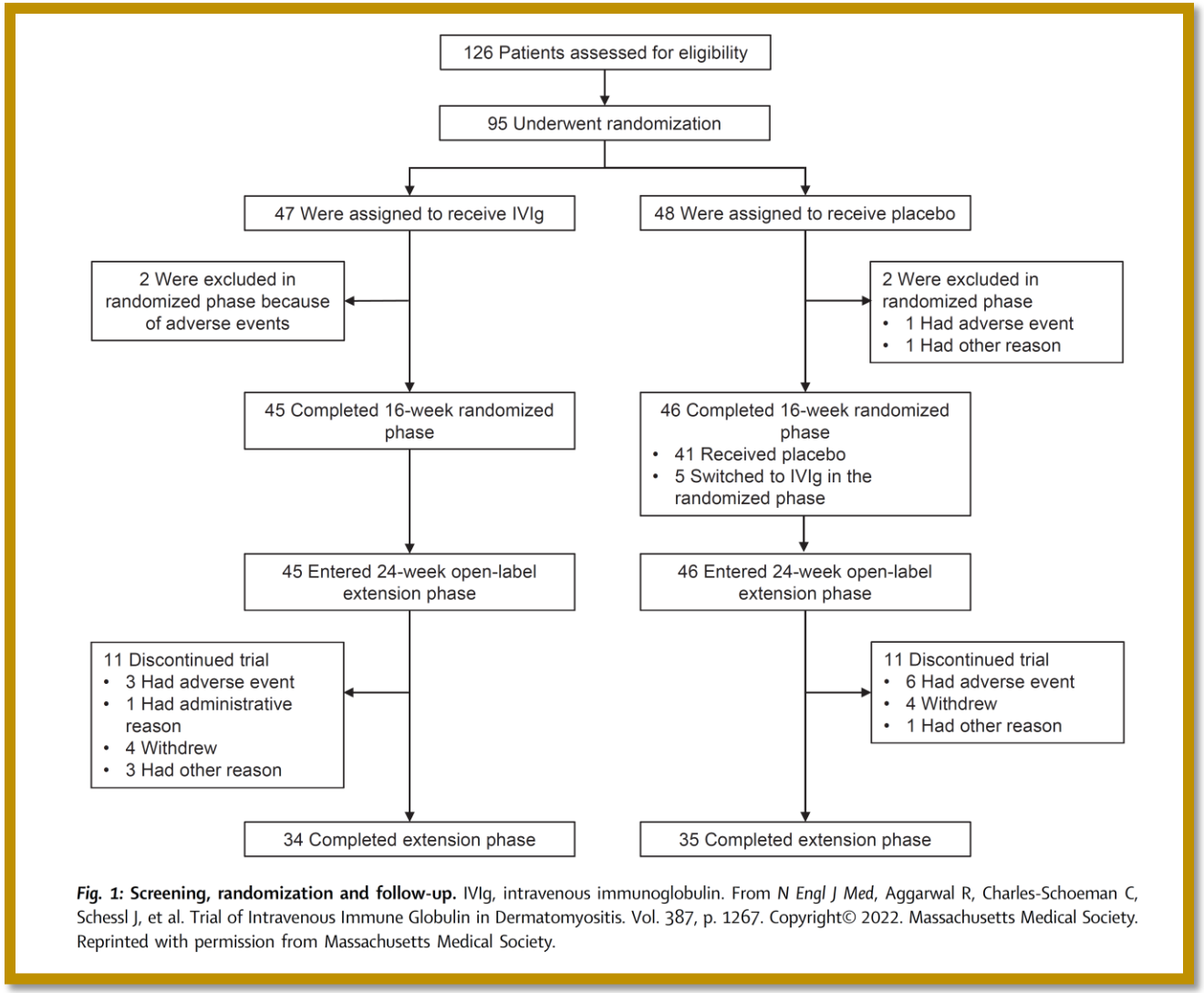


***Fig. 1:* Screening, randomization and follow-up.** IVIg, intravenous immunoglobulin. From *N Engl J Med*, Aggarwal R, Charles-Schoeman C, Schessl J, et al. Trial of Intravenous Immune Globulin in Dermatomyositis. Vol. 387, p. 1267. Copyright© 2022. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Victoria P. Werth et al. eClinical Medicine 2023

Efficacy of intravenous immunoglobulins (IVIg) in improving skin symptoms in patients with dermatomyositis: a post-hoc analysis of the ProDERM study

IDIOPATHIC INFLAMMATORY MYOPATHY

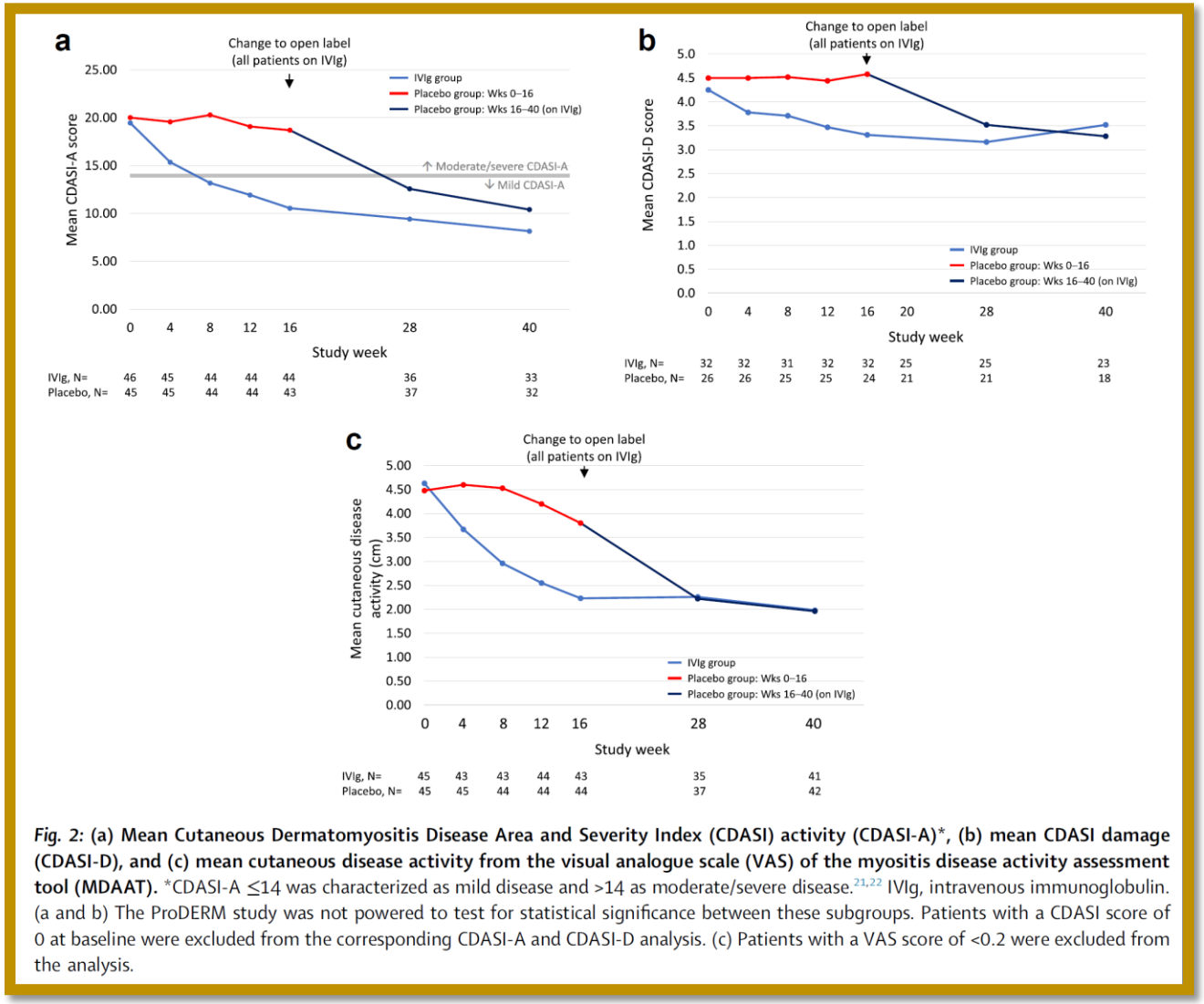


Fig. 2: **(a) Mean Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity (CDASI-A)*, (b) mean CDASI damage (CDASI-D), and (c) mean cutaneous disease activity from the visual analogue scale (VAS) of the myositis disease activity assessment tool (MDAAT).** *CDASI-A ≤14 was characterized as mild disease and >14 as moderate/severe disease.[21,22] IVIg, intravenous immunoglobulin. (a and b) The ProDERM study was not powered to test for statistical significance between these subgroups. Patients with a CDASI score of 0 at baseline were excluded from the corresponding CDASI-A and CDASI-D analysis. (c) Patients with a VAS score of <0.2 were excluded from the analysis.

Victoria P. Werth et al. eClinical Medicine 2023

Role of Intravenous Immunoglobulin in Necrotizing Autoimmune Myopathy

Amanda Kocoloski, DO, MMEL, Silvia Martinez, MD,* Siamak Moghadam-Kia, MD, MPH,* David Lacomis, MD,† Chester V. Oddis, MD,* Dana P. Ascherman, MD,* and Rohit Aggarwal, MD, MSc**

IDIOPATHIC INFLAMMATORY MYOPATHY

TABLE 1. Frequency of Myositis-Specific and Myositis-Associated Autoantibodies in Patients With Necrotizing Myopathy

Autoantibodies Positive	All (n = 20)
Myositis-specific autoantibodies (any)	19 (95%)
Anti-HMGCR	14 (70%)
Anti-SRP	4 (20%)
ANA	4 (20%)
Ro-52	2 (10%)

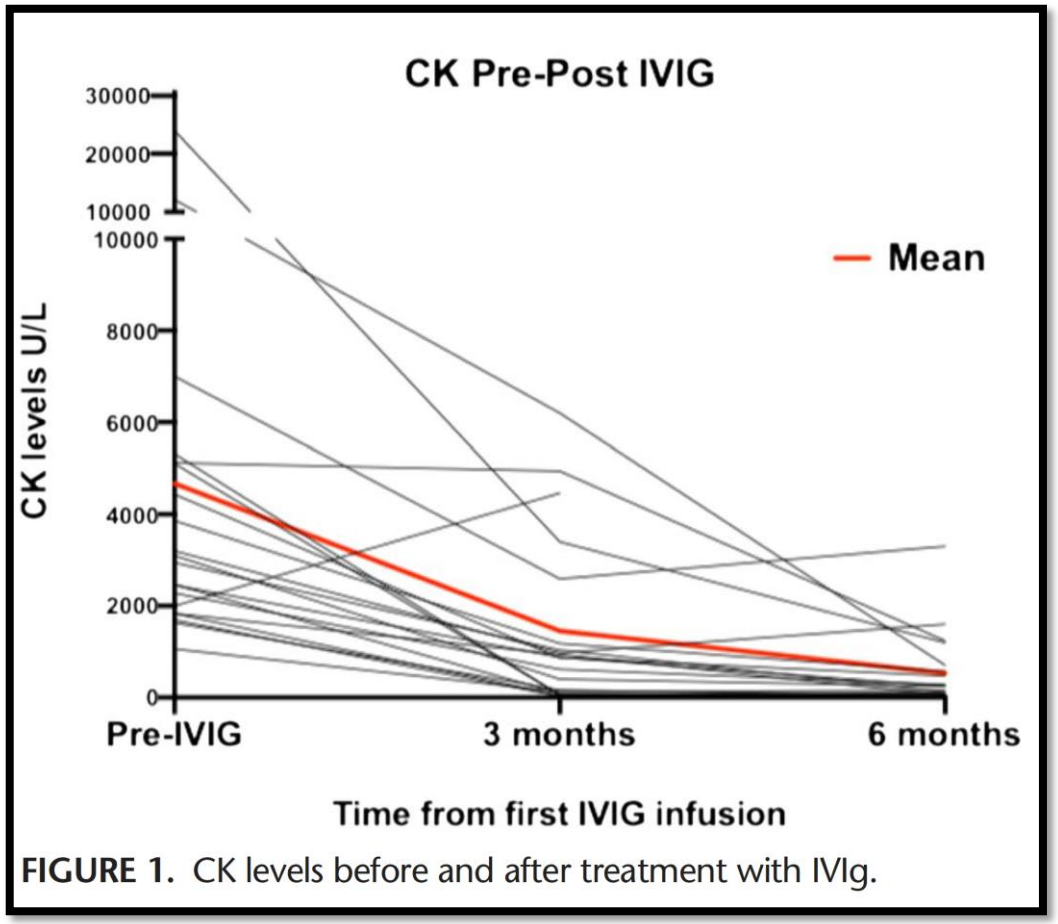


FIGURE 1. CK levels before and after treatment with IVIg.

Role of Intravenous Immunoglobulin in Necrotizing Autoimmune Myopathy

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IDIOPATHIC INFLAMMATORY MYOPATHY

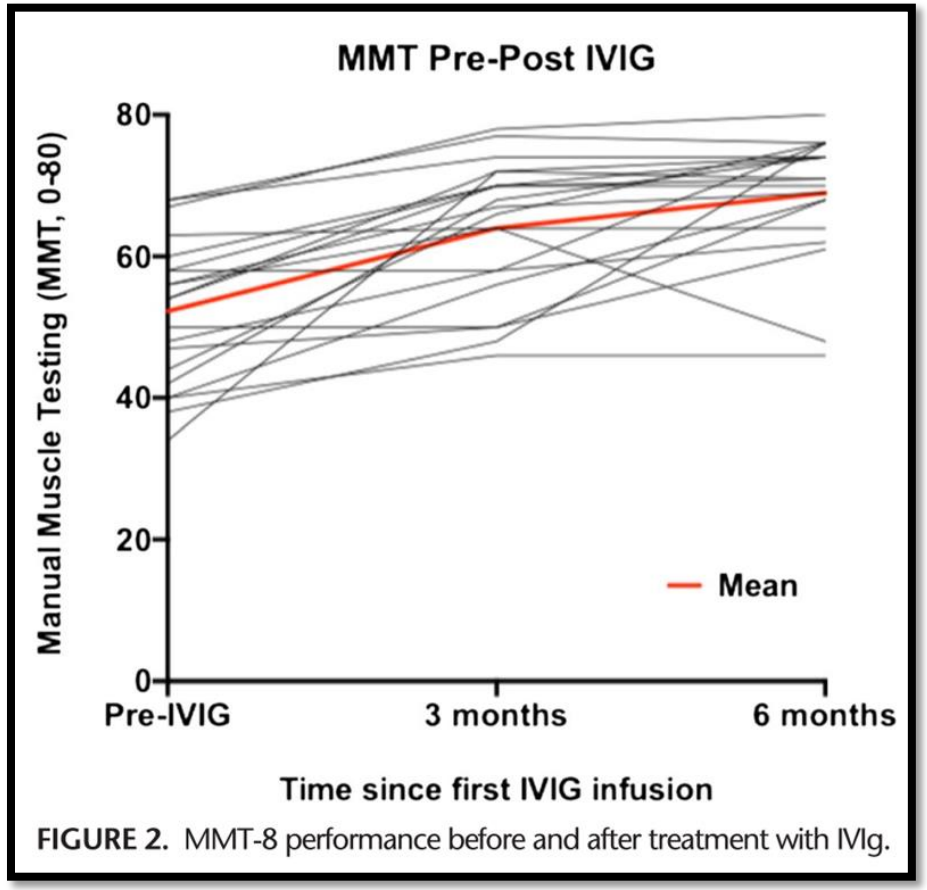


FIGURE 2. MMT-8 performance before and after treatment with IVIg.

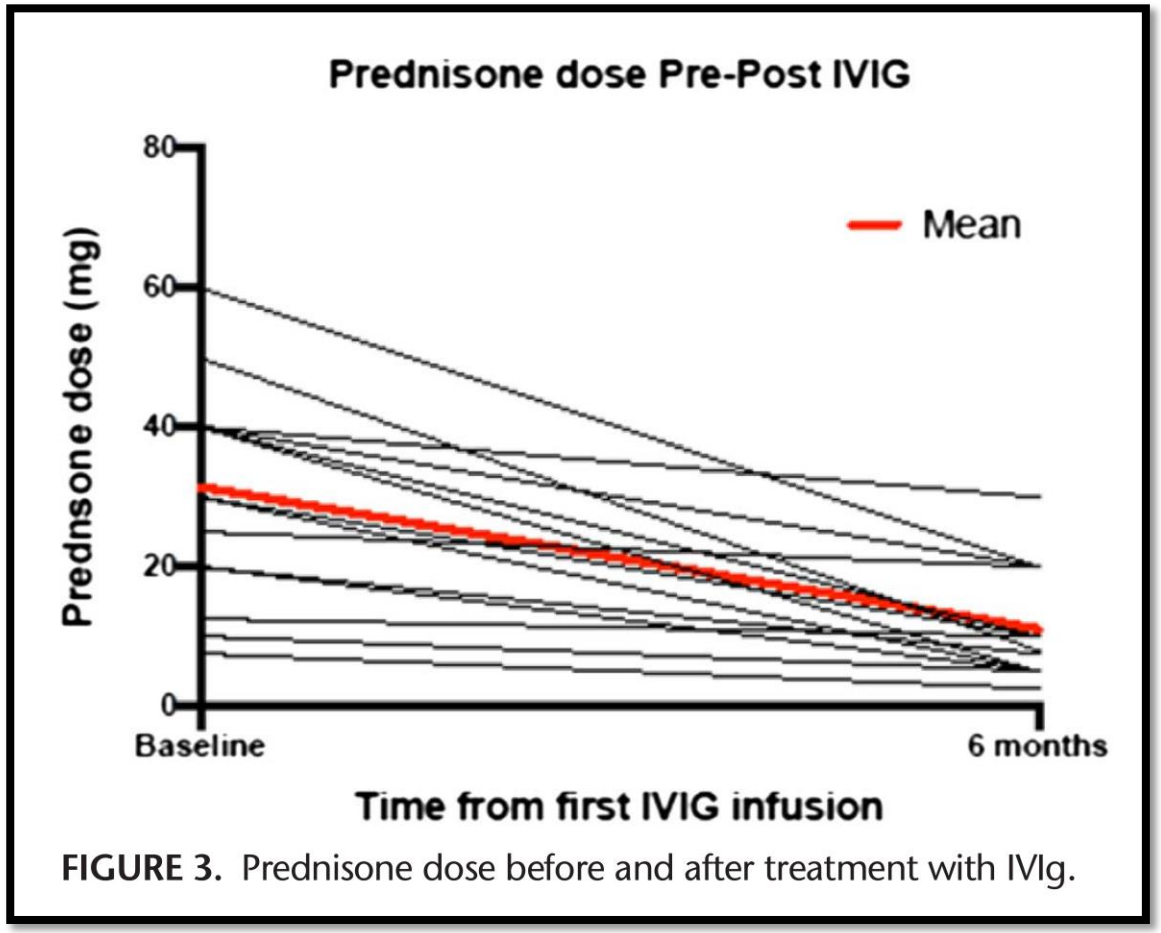


FIGURE 3. Prednisone dose before and after treatment with IVIg.

Intravenous immunoglobulin for interstitial lung diseases of anti-melanoma differentiation-associated gene 5-positive dermatomyositis

Li-Mei Wang [1], Qi-Hua Yang, Lei Zhang [1], Sheng-Yun Liu[1], Pan-Pan Zhang [1], Xin Zhang[1], Xiao-Jun Liu[1], Li-Shuai Han[1] and Tian-Fang Li[1]

IDIOPATHIC INFLAMMATORY MYOPATHY

TABLE 2 Number of IVIG courses of the patients in the IVIG used group

Courses of IVIG	Number of patients, *n* (%)
One	13 (41.9)
Two	11 (35.5)
Three or more	7 (22.6)

IVIG: intravenous immunoglobulin.

	IVIG used (*n* = 31)	IVIG no-used (*n* = 17)	*P*
Infection in 3 months, *n* (%)	8 (25.8)	3 (17.6)	0.776
Infection in 6 months, *n* (%)	8 (25.8)	3 (17.6)	0.776
Remission at 3 months, *n* (%)	22 (71.0)	7 (41.2)	0.044
Remission at 6 months, *n* (%)	20 (64.5)	8 (47.1)	0.241
GCs dosages at 3 months, mg/day	30 (22.5–55)	30 (20–50)	0.427
GCs dosages at 6 months, mg/day	15 (10–60)	20 (15–20)	0.800
Mortality			
Within 3 months, *n* (%)	6 (19.4)	9 (52.9)	0.016
Within 6 months, *n* (%)	7 (22.6)	9 (52.9)	0.033

GCs: glucocorticoids; IVIG: intravenous immunoglobulin.

Maintenance treatment with subcutaneous immunoglobulins in the long-term management of anti-HMCGR myopathy

Angela Zuppa[a], Chiara De Michelis[a], Giuseppe Meo[a], Valeria Prada[a,b], Chiara Gemelli[a],

IDIOPATHIC INFLAMMATORY MYOPATHY

Table 1
Characteristics of the three patients at baseline and in the follow-up.

Patient n°	Pt 1	Pt 2	Pt 3
Sex, Age	M, 59	F, 77	M, 63
Statin, Duration of treatment (months)	Atorvastatin 20 mg, 13	Atorvastatin 20 mg, 11	Atorvastatin 20 mg, 85,5
Onset, Duration of disease (months)	Dec-2018, 17	Sept-2018, 20	Feb-2018, 26
Co-morbidity	Dyslipidemia, Hypertension, Psoriasis, DM2	Dyslipidemia, Hypertension, Latent tuberculosis	Dyslipidemia DM2,
MRC-SS at onset	48	56	54
MRC-SS SCIg onset	58	58	60
MRC-SS after 12 months	60	60	60
CK at onset	11.649 U/L	7.000 U/L	8.900 U/L
CK after 12 months	81 U/L	32 U/L	363 U/L
Anti-HMGCR Ab Titres at onset	370 CU/ml	126,2 CU/ml	160,8 CU/ml
Anti-HMGCR Ab Titres after 12 months	56 CU/ml	<20 CU/ml	127.6 CU/ml
Induction therapy	Prednisone 1 mg/kg/day, IVIg 2 g/kg	Prednisone 1 mg/kg/day, IVIg 2 g/Kg	Methylprednisolone 1000 mg/day/5 days, IVIg 2 g/kg
Maintenance therapy before SCIg	Prednisone (tapered), Methotrexate 7,5 mg/weekly, IVIg 2 g/kg/month (4 cycles)	Prednisone (tapered), IVIg 2 g/kg/month (5 cycles)	Prednisone (tapered), Methotrexate 7,5 mg/weekly, IVIg 2 g/kg/month (6 cycles)

Legend: Pt, patient; M, male; F, female; Dec, December; Sept, September; Feb, February; DM2, diabetes type 2; MRC-SS, Medical Research Council sum score; CK, creatine kinase; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; Ab, Antibodies; IVIg, intravenous immunoglobulins; SCIg, subcutaneous immunoglobulins.

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

ANCA-ASSOCIATED VASCULITIS

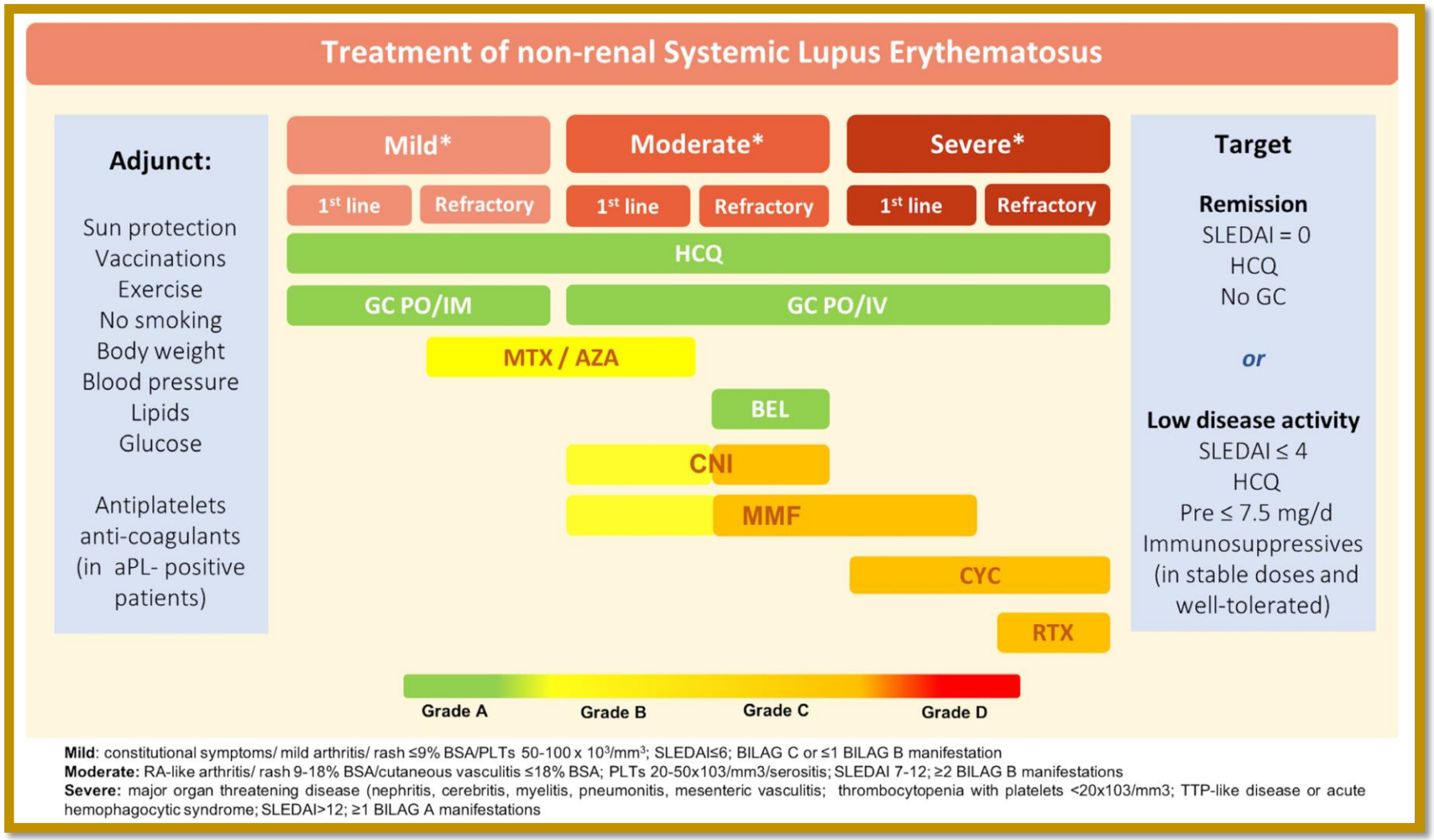
Treatment of refractory disease Recommendation:		
For patients with severe GPA/MPA that is refractory to treatment with rituximab or cyclophosphamide for remission induction, we conditionally recommend switching treatment to the other therapy over combining the 2 therapies.	30	Very low
For patients with GPA/MPA that is refractory to remission induction therapy, we conditionally recommend adding IVIG to current therapy.	31	Low to moderate

Other considerations		
For patients with active GPA/MPA who are **unable to receive other immunomodulatory therapy**, we conditionally recommend administering IVIG.	32	Low

Chung SA, ve ark. Arthritis Rheumatol 2021

2019 update of the EULAR recommendations for the management of systemic lupus erythematosus

SLE



Fanouriakis A, et al. Ann Rheum Dis 2019

2019 update of the EULAR recommendations for the management of systemic lupus erythematosus

SLE

Haematological disease

Thrombocytopaenia / autoimmune haemolytic anaemia (AIHA).	First-line treatment of significant lupus thrombocytopaenia (platelet count below 30 000/mm3) consists of moderate/high doses of GC in combination with IS agent (AZA, MMF or cyclosporine; the latter having the least potential for myelotoxicity) to facilitate GC-sparing.	Initial therapy with pulses of intravenous MP (1–3 days) is encouraged.	Intravenous immunoglobulin **(IVIG)** may be considered in the acute phase, in cases of inadequate response to high-dose GC or to avoid GC-related infectious complications.

Fanouriakis A, et al. Ann Rheum Dis 2019

SLE

Table 1 | Major international recommendations for the treatment of lupus nephritis

Setting	EULAR–ERA–EDTA 2019[25]	APLAR 2021[26]	KDIGO 2021[27]	ACR 2012[28]
Initial therapy	HCQ for all patients	HCQ for all patients	HCQ for all patients	HCQ for all patients
Class III/IV ± V LN	First line: GC + MMF (2–3 g/day or MPA at an equivalent dose), or low-dose IV CYC	First line: GCs + MMF (2 g/day), or high-dose IV CYC	First line: GCs (lower dose) + MMF (2–3 g/day), or low-dose IV CYC	GCs + MMF (2–3 g/day), or high-dose IV pulse CYC (low-dose for white Europeans)
	Second line: (i) MMF + CNI (Tac) (for nephrotic-range proteinuria); (ii) high-dose IV CYC (for high risk of kidney failure)	Second line: low-dose IV CYC, or Tac	Second line: (i) MMF + CNI (Tac); (ii) high-dose IV CYC, or oral CYC	
Pure V (nephrotic) LN	First line: MMF (2–3 g/day) or MPA	First line: GCs + MMF (2 g/day), or high-dose IV CYC	GCs + MMPA, or CYC, or CNIs, or AZA, or rituximab	GCs + MMF (2–3 g/day)
	Second line: (i) IV CYC; (ii) CNI (Tac); (iii) CNI (Tac) + MMF/MPA (particularly for nephrotic-range proteinuria)	Second line: low-dose IV CYC, or Tac		
Refractory LN	Switching among regimens listed above, or rituximab, or IVIG (when contraindicated to increase immunosuppression, such as with risk of infection)	Switching among regimens, or MMF + Tac, or rituximab, or belimumab	Switching among regimens, or rituximab, or CNI-based regimens; options to be reassessed in future: MMF + voclosporin, belimumab, anti-CD20 agents	Switching between MMF and CYC, or rituximab, or CNIs
Maintenance after a clinical response	MMF (1–2 g/day) or MPA, or AZA (2 mg/kg/day) + prednisone (2.5–5.0 mg/day) for 3–5 years	First line: MMF or AZA for 5 years	First line: MMPA for at least 3 years	MMF (1–2 g/day), or AZA (2 mg/kg/day) ± low-dose GCs
		Second line: low-dose CNI (Tac)	Second line: AZA, or CNI (Tac)	
Rapidly progressive LN	Consider high-dose IV CYC	NS	NS	NS

APLAR, Asia Pacific League of Associations for Rheumatology; AZA, azathioprine; CNI, calcineurin inhibitor; CYC, cyclophosphamide; EDTA, European Dialysis and Transplant Association; ERA, European Renal Association; GC, glucocorticoid; HCQ, hydroxychloroquine; IV, intravenous; IVIG, intravenous immunoglobulin; KDIGO, Kidney Disease: Improving Global Outcomes; LN, lupus nephritis; MMF, mycophenolic mofetil; MMPA, mycophenolic acid analogue (MMF or MPA); MPA, mycophenolic acid; NS, not specified; Tac, tacrolimus.

2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis

SLE

Non-responding/refractory disease

- High-dose intravenous immunoglobulin (2 g/kg) could be considered when there are **contraindications to increasing glucocorticoids or immunosuppressive drugs**, such as infection, while plasma exchange is rarely indicated.

Fanouriakis A, et al. Ann Rheum Dis 2020

Efficacy and safety of intravenous immunoglobulin in patients with lupus nephritis: A systematic review of the literature

SLE

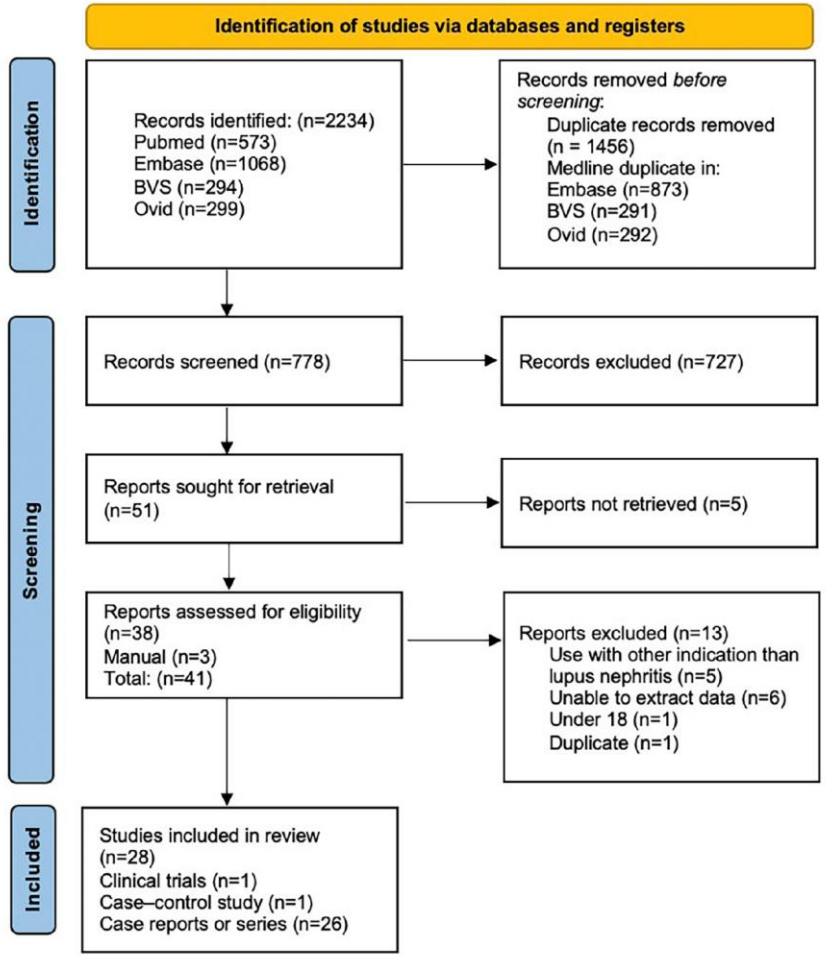


Fig. 1. Flowchart of the studies included using the PRISMA methodology.

Table 2
Percentage of responses achieved in different scenarios of Lupus Nephritis under treatment with Intravenous Immunoglobulin.

Scenario	Overall response	Complete response	Partial response
Case reports + case series	64.3	30.4	33.9
Class III + IV	70.4	38.6	31.8
Rescue	68	29.5	38.5
Induction	70	35	35
Monova 2002	69	20.7	48.3
Monova 2006	59.1	27.9	31.2

J. Cajamarca-Bar´on ve ark. *Autoimmunity Reviews 2022*

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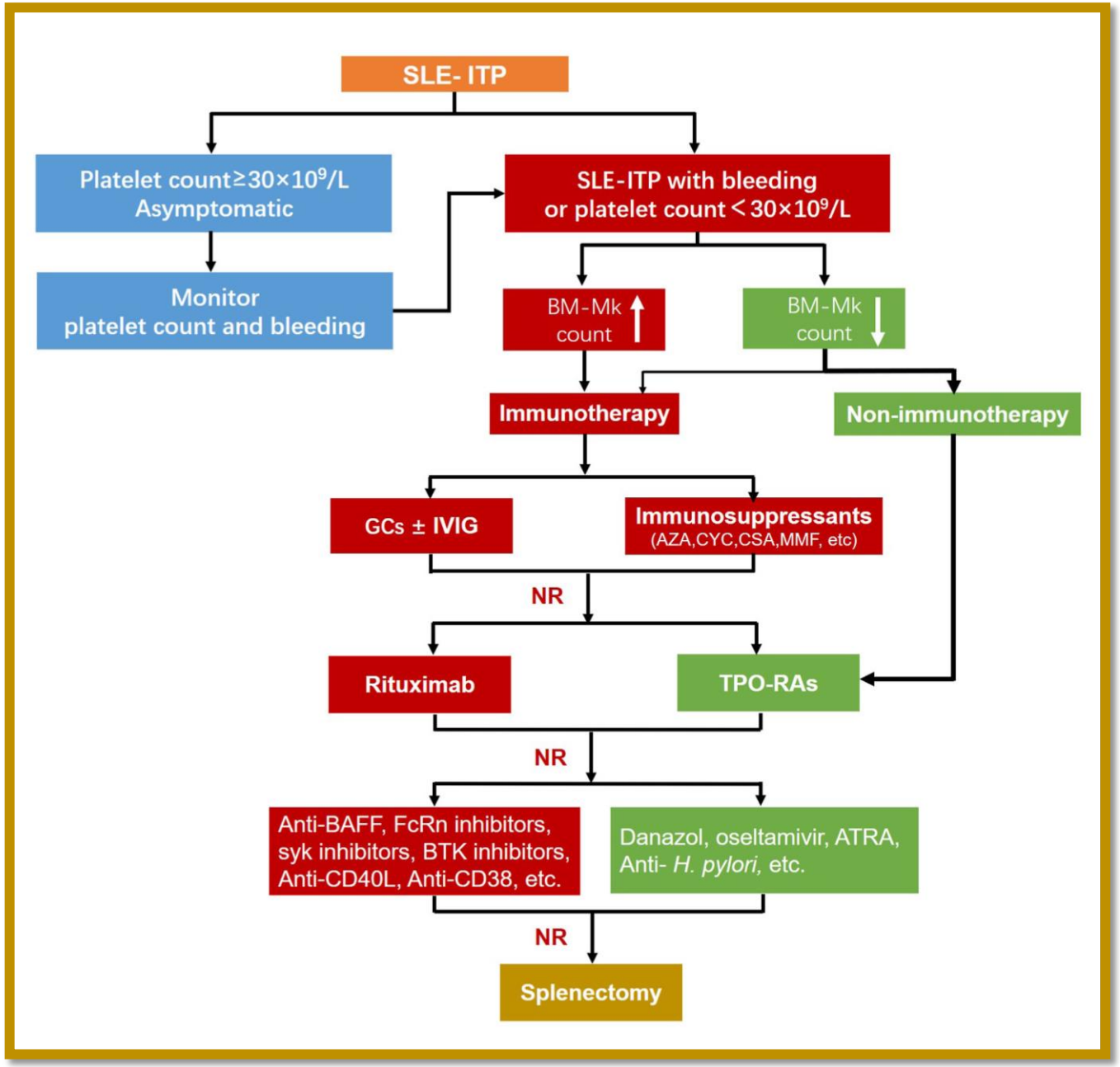


Fig. 5. A simplified strategy for management of SLEITP. These factors should be considered when tailoring an individual treatment regimen, including age, SLE disease status, comorbidity & complication, lifestyle, combined medications, and patient willingness. TPO-RAs, thrombopoietin receptor agonists.

Y. Jiang et al. *Journal of Autoimmunity 2022*

Lupus acute cardiomyopathy is highly responsive to intravenous immunoglobulin treatment

Case series and literature review

Katya Meridor, MD[a,d,*], Yehuda Shoenfeld, MD[b,d], Oshrat Tayer-Shifman[c,d], Yair Levy, MD[a,d]

SLE

Patient concerns: We report 5 female patients with SLE, who presented with signs of acute heart failure including pulmonary congestion and arrhythmias.

Diagnosis: Echocardiography demonstrated new reduced left ventricular ejection fraction of 20% to 30%. Two patients underwent coronary artery angiography, which demonstrated normal coronary arteries, supporting the diagnosis of myocarditis or nonischemic cardiomyopathy.

Interventions: High-dose IVIg treatment was initiated in all 5 patients.

Outcomes: Following the treatment, clinical and echocardiographic improvement in cardiac function occurred within a few days to 1 month. This dramatic improvement persisted for several years.

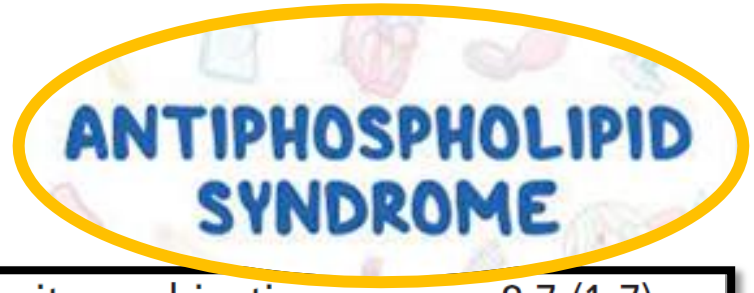
Conclusion: Based on our case series, we believe that IVIg has an important role in the management of lupus acute cardiomyopathy. This safe, well-tolerated optional treatment should be considered, especially in severe cases.

EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors

Myositis may be a severe condition. Immunotherapy withdrawal needs to be discussed. In the presence of life-threatening manifestations (bulbar symptoms (dysphagia, dysarthria, dysphonia), dyspnoea and myocarditis), high dose of glucocorticoids, IVIg and/or plasma exchange should be considered; immunotherapy withdrawal is always necessary.

Kostine M, et al. Ann Rheum Dis 2021

EULAR recommendations for the management of antiphospholipid syndrome in adults



10. In women with 'criteria' obstetric APS with recurrent pregnancy complications despite combination treatment with LDA and heparin at prophylactic dosage, increasing heparin dose to therapeutic dose (5/D) or addition of HCQ (4/D) or low-dose prednisolone in the first trimester (4/D) may be considered. Use of intravenous immunoglobulin might be considered in highly selected cases (5/D).	8.7 (1.7)

B. For first-line treatment of patients with CAPS, combination therapy with glucocorticoids, heparin and plasma exchange or intravenous immunoglobulins is recommended over single agents or other combinations of therapies. Additionally, any triggering factor (eg, infections, gangrene or malignancy) should be treated accordingly (5/D).	9.7 (0.6)

The cost and availability of suggested treatments are not a barrier to implementation of these recommendations, with the exception of IVIG and plasmapheresis. However, both treatments were recommended as first-line treatment only in CAPS which occurs in less than 1% of patients.

Tektonidou MG, et al. Ann Rheum Dis 2019

Antiphospholipid syndrome management: a 2023 update and practical algorithm-based approach

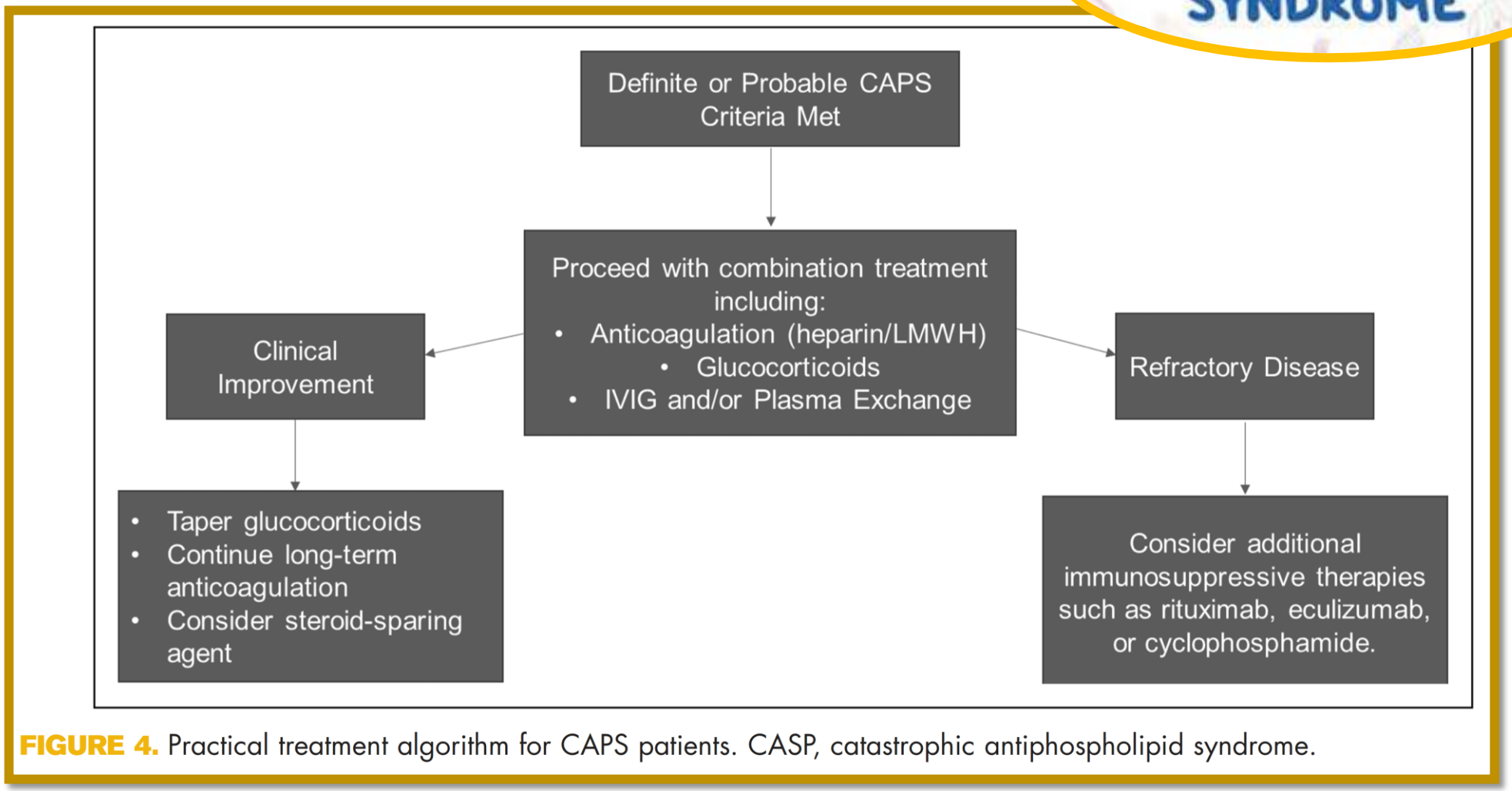


FIGURE 4. Practical treatment algorithm for CAPS patients. CASP, catastrophic antiphospholipid syndrome.

Yu Zuo et al. Curr Opin Rheumatol 2023

Intravenous immunoglobulins in systemic sclerosis: Data from a French nationwide cohort of 46 patients and review of the literature

Systemic Sclerosis
(Systemic Scleroderma)

Table 3
Characteristics of the study population at first and at last IVIG cycles.

	N	First IVIG Value	Last IVIG Value	*p*
Modified Rodnan skin score				
all SSc patients (mean ± SD)	29	17.6 (±10.9)	17.0 (±12.6)	0.57
lcSSc patients (mean ± SD)	8	8.6 (±5.1)	5.9 (±4.6)	0.13
dcSSc patients (mean ± SD)	20	22.0 (±9.8)	22.3 (±11.5)	0.79
Digital ulcers				
Active DU (n, %)	33	6 (18%)	4 (12%)	0.72
Number of active DU (mean ± SD)	33	0.52 (±1.3)	0.15 (±0.4)	0.19
NYHA score (mean ± SD)	34	1.71 (±0.8)	1.68 (±0.8)	0.96
Class I (n, %)	34	17 (50%)	18 (53%)	0.99
Class II (n, %)	34	10 (29%)	9 (26%)	0.99
Class III (n, %)	34	7 (21%)	7 (21%)	0.99
Class IV (n, %)	0	0 (0%)	0 (0%)	/
6MWD (m, mean ± SD)	6	414 (±89)	393 (±93)	0.40
GERD (n, %)	34	23 (68%)	18 (53%)	0.06
Abnormal bowel motion (n, %)	33	14 (42%)	9 (27%)	0.06
Joint pain (n, %)	32	14 (44%)	6 (19%)	0.02
Muscle pain (n, %)	35	26 (74%)	7 (20%)	<0.0001
Muscle testing <3/5 (n, %)	38	17 (45%)	8 (21%)	0.01
Hemoglobin (g/dL, mean ± SD)	37	12.3 (±1.6)	11.9 (±1.6)	0.31
Platelets (G/L, mean ± SD)	34	320 (±93)	295 (±94)	0.12
Creatinine (μmol/L, mean ± SD)	35	65.7 (±33.8)	70.2 (±36.7)	0.14
Estimated GFR (mL/min/1.73 m^2, mean ± SD)	33	122 (±74)	114 (±61)	0.07
BNP (pg/mL, mean ± SD)	10	180 (±161)	192 (±148)	0.85
Nt-pro-BNP (pg/mL, mean ± SD)	3	674 (±781)	2023 (±3268)	0.75
Elevated BNP or Nt-pro-BNP (n, %)	13	4 (31%)	3 (23%)	0.99
CRP (mg/L, mean ± SD)	37	13.1 (±17.6)	9.2 (±16.6)	0.001
CK (UI, mean ± SD)	35	1069 (±1552)	288 (±449)	<0.0001
FVC				
All SSc patients (% predicted, mean ± SD)	16	73.3 (±18.7)	75.1 (±18.9)	0.91
SSc-ILD patients (% predicted, mean ± SD)	9	67.0 (±16.9)	66.9 (±20.9)	0.99

S. Sanges et al. Autoimmunity Reviews 2017

Corticosteroid-sparing benefit of intravenous immunoglobulin in systemic sclerosis-associated myopathy: A comparative study in 52 patients

Systemic Sclerosis
(Systemic Scleroderma)

Table 2
Muscle involvement in 52 patients with systemic sclerosis associated myopathy.

Patients' characteristics	All (n = 52)	IVIg + (n = 18)	IVIg- (n = 34)	*p value*
Clinical				
Onset, months; median [IQR]	1 [0–15]	4 [0–24]	0 [0 – 13]	*0.24*
Myalgia, n (%)	28 (53.8)	12 (66.7)	16 (47.1)	*0.25*
Muscle weakness, n (%)	34 (65.4)	12 (66.7)	22 (64.7)	*1.00*
Dysphagia, n (%)	24 (46.2)	10 (55.6)	14 (41.2)	*0.98*
Biological				
CK titre IU; median [IQR]	6.6 [3.2–11.4]	6.2 [3.0–12.2]	6.9 [3.4–12.4]	*0.68*
Increased CK, n (%)	50 (96.2)	18 (100)	32 (94.1)	*0.54*
Aldolase titre; median [IQR]	2.7 [1.7–5.5]	2.3 [1.5–11.2]	3.3 [1.7–6.3]	*0.95*
Increased aldolase, n (%)	24 (46.2)	9 (50)	15 (44.1)	*0.77*
EMG, n (%)				
EMG abnormal, n (%)	22/26 (84.6)	10/12 (83.3)	12/14 (85.7)	*1.00*
Myogenic syndrome, n (%)	17/26 (65.4)	10 /12(83.3)	7/14 (50.0)	*0.11*
MRI, n (%)				
MRI with muscle involvement, n (%)	10/12 (83.3)	8/9 (88.8)	2/3 (66.7)	*0.45*
Muscle biopsy, n (%)	50 (96.2)	16 (88.9)	34 (100)	*0.12*
Biopsy with muscle involvement, n (%)	49 (94.2)	16 (88.9)	33 (97.1)	*1.00*
Inflammatory findings, n (%)	32 (61.5)	9 (50)	23 (67.6)	*0.53*
Necrotic findings, n (%)	31 (59.6)	11 (61.1)	20 (58.8)	*0.55*
Regeneration, n (%)	23 (44.2)	7 (38.9)	16 (47.1)	*1.00*
MAC deposition, n (%)	21 (40.4)	8 (44.4)	13 (38.2)	*0.37*
Micro-angiopathy, n (%)	16 (30.8)	4 (22.2)	12 (35.3)	*0.53*
Atrophy, n (%)	16 (30.8)	5 (27.8)	11 (32.3)	*1.00*
Fibrotic findings, n (%)	15 (28.8)	4 (22.2)	11 (32.3)	*0.75*
Vasculitis, n (%)	9 (17.3)	3 (16.7)	6 (17.6)	*1.00*

CK: creatine kinase; EMG: electromyography; IQR: interquartile range; IVIg: intravenous immunoglobulins; IU; MAC: membrane attack complex; MRI: magnetic resonance imaging; n.

B. Chaigne, ve ark. Autoimmunity Reviews 2020

Corticosteroid-sparing benefit of intravenous immunoglobulin in systemic sclerosis-associated myopathy: A comparative study in 52 patients

Systemic Sclerosis
(Systemic Scleroderma)

Table 3
Evolution of 52 patients with systemic sclerosis associated myopathy.

Patients' characteristics	All (n = 52)	IVIg + (n = 18)	IVIg- (n = 34)	*p value*
Follow-up, months; median [IQR]	79 [43–147]	108 [63–156]	69 [41–134]	*0.16*
Clinical or biological remission (data availability)	47 (90.4)	18 (100)	29 (85.3)	*0.15*
Remission, n (%)	46 (88.5)	18 (100)	28 (82.4)	*1.00*
Clinical remission, n (%)	44 (84.6)	16 (88.9)	28 (82.4)	*0.55*
Partial, n (%)	13 (25)	6 (33.3)	7 (20.6)	*0.52*
Complete, n (%)	31 (59.6)	10 (55.6)	21 (61.8)	*0.34*
Biological remission, n (%)	46 (88.5)	18 (100)	28 (82.4)	*1.00*
Partial, n (%)	4 (7.7)	2 (11.1)	2 (5.9)	*0.63*
Complete, n (%)	41 (78.8)	16 (88.9)	25 (73.5)	*1.00*
mRSS (data availibility), n (%)	41 (78.8)	13 (72.2)	28 (82.4)	*0.48*
Change in mRSS; median [IQR]	−0.5 [−7.3–4]	0 [−6.3–0]	0 [−8.5–8.0]	*0.35*
Diminution of mRSS, n (%)	19 (36.5)	5 (27.8)	14 (41.2)	*0.52*
FVC (data availibility), n (%)	22 (42.3)	8 (44.4)	14 (41.2)	*1.00*
Change in FVC; median [IQR]	1 [−10–7.5]	5 [−17–11]	1 [−4.3–7.3]	*0.80*
> /=5% Increase in FVC, n (%)	9 (17.3)	6 (33.3)	6 (17.6)	*0.30*
TLC (data availibility), n (%)	25 (48.1)	7 (38.9)	18 (52.9)	*0.39*
Change in TLC; median [IQR]	2 [−5–6.5]	1 [−29.0–7.0]	2 [−6.5–8]	*0.49*
Increase in TLC, n (%)	8 (15.4)	4 (22.2)	4 (11.8)	*0.16*
DLCO (data availibility), n (%)	19 (36.5)	5 (27.8)	14 (41.2)	*0.38*
Change in DLCO; median [IQR]	−7 [−20−0]	−15 [−26.2–6]	−4 [−17.8–3]	*0.46*
Increase in DLCO, n (%)	5 (9.6)	1 (5.5)	4 (11.8)	
Number of patients with relapse, n (%)	8 (15.4)	4 (22.2)	4 (11.8)	*0.69*
Time before relapse, months; median [IQR]	13 [3.8–52]	23 [3.8–52]	13 [4.3–99.8]	*0.97*

FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusing lung capacity for carbon monoxyde; IQR: interquartile range; IVIg: intravenous immunoglobulins; mRSS: modified Rodnan skin score. N: number.

B. Chaigne, ve ark. Autoimmunity Reviews 2020

Corticosteroid-sparing benefit of intravenous immunoglobulin in systemic sclerosis-associated myopathy: A comparative study in 52 patients

Systemic Sclerosis
(Systemic Scleroderma)

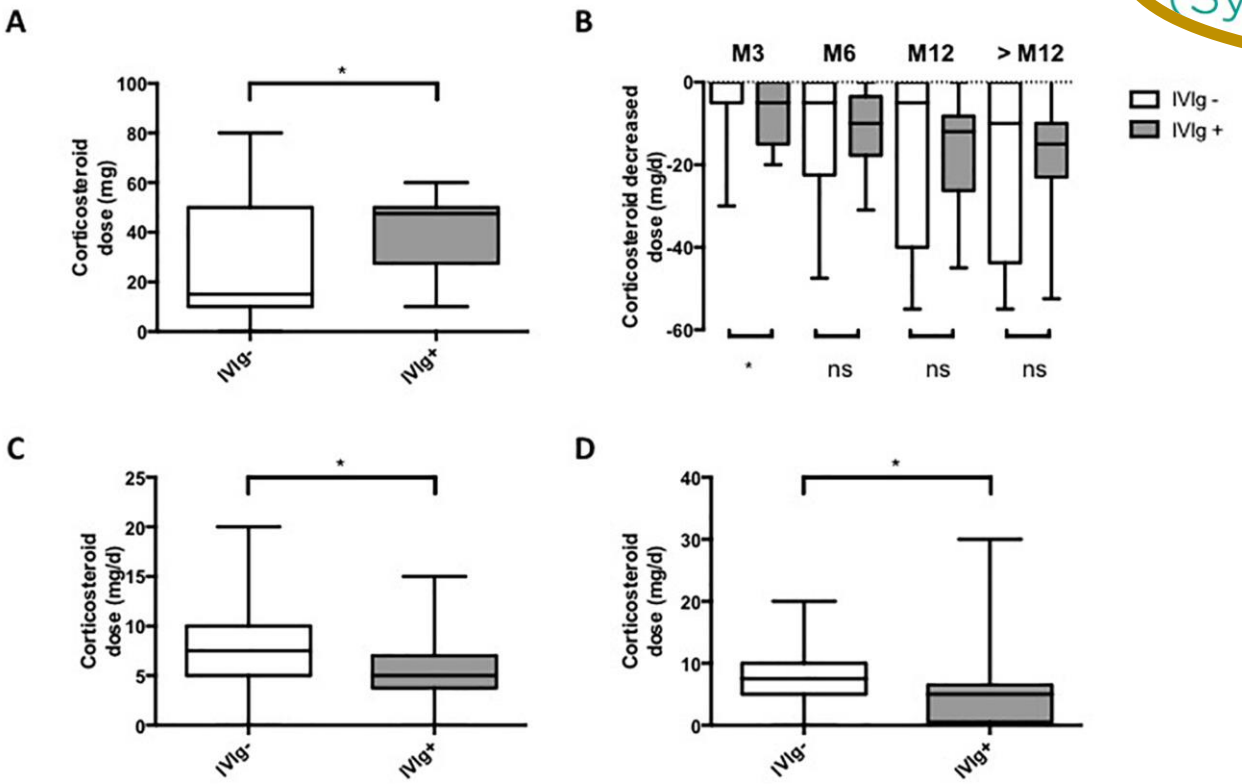


Fig. 1. Corticosteroid sparing effect of intravenous immunoglobulin in patients with systemic sclerosis-associated myopathy.
Panel A. Box and whiskers show the minimum to the maximum median maximal dose of corticosteroid (mg/day) ever received by 18 patients with systemic sclerosis-associated myopathy (SScAM) who were treated with intravenous immunoglobulin (IVIg) and 34 patients with SScAM who were not.
Panel B. Box and whiskers show the minimum to the maximum decreased dose of corticosteroid (mg/day) at 3, 6, 12 months and at the end of the follow-up period (> M12) of 18 patients with SScAM who were treated with IVIg and 34 patients with SScAM who were not.
Panel C. Box and whiskers show the minimum to the maximum median dose of corticosteroids (mg/day) received at 12 months by 18 patients with SScAM who were treated with IVIg and 34 patients with SScAM who were not.
Panel D. Box and whiskers show the minimum to the maximum median dose of corticosteroids (mg/day) received at the end of the follow-up by 18 patients with SScAM who were treated with IVIg and 34 patients with SScAM who were not.
Mann-Whitney test was used for comparisons. * *p*-value < .05.

B. Chaigne, ve ark. Autoimmunity Reviews 2020

Immunoglobulins in systemic sclerosis management. A large multicenter experience

Table 2
Characteristics of IVIG therapy.

	N	Value
Age at IVIG initiation (mean ± SD)	78	55 ± +14,2
First-line therapy for a given organ involvement (n, %)	78	6(8%)
Organ involvement motivating IVIG prescription		
Muscular (n,%)	78	38(49%)
Digestive (n,%)	78	27(35%)
Cutaneous (n,%)	78	17(22%)
Calcinosis (n,%)	78	8(10%)
Articular (n,%)	78	2(3%)
ILD (n,%)	78	1(1%)
Number of cycles (median ± AA)	77	5 ± 8229
Associated treatments		
Glucocorticoids (n,%)	77	54(69%)
Glucocorticoides dosage prednisone mg/d; median (IQR)	56	7,5(10)
Immunosupresors (n,%)	78	52(67%)
Methotrexate (n,%)	78	8(10%)
Cyclophosphamide (n,%)	78	4(5%)
Azathioprine (n,%)	78	12(15%)
Mycophenolate (n,%)	78	29(37%)
Calcineurin inhibitors (n,%)	78	9(12%)
Byological treatment (n,%)	78	14(18%)
Rituximab (n,%)	78	10(13%)
Tocilizumab (n,%)	78	3(4%)
Abatacept (n,%)	78	1(1%)
Immunosupresor treatment and Byological treatment (n,%)	78	9(12%)

Systemic Sclerosis
(Systemic Scleroderma)

Conclusions: this study suggest that IVIG may improve **myositis**, **gastrointestinal** and **skin** involvement in SSc patients treated in routine care and seems to have a good safety profile.

J. Tandaipan et al. *Autoimmunity Reviews 2023*

The additional treatment value of immunoglobulin for the treatment of rheumatoid arthritis complicated with interstitial lung disease: A propensity score-matched pilot study

TABLE 1 Baseline characteristic of included patients.

Characteristic	Control group ($n=40$)	Immunoglobulin group ($n=40$)	p
Age, years	50.6 ± 8.2	51.5 ± 8.4	.84
Gender			
Male	13	12	.81
Female	27	28	

Note: data are presented as mean ± standard deviation or as number.

Patients in the immunoglobulin group were treated with 40 mg/d prednisone for 4 weeks, which was then gradually decreased to 10 mg/d for maintenance, along with the intravenous injection of methotrexate (10 mg/week, once per week). The immunoglobulin (10 g/d) was given for five continuous days before methotrexate injection.

The additional treatment value of immunoglobulin for the treatment of rheumatoid arthritis complicated with interstitial lung disease: A propensity score-matched pilot study

	Immunoglobulin group ($n=40$)	Control group ($n=40$)	p
Upper respiratory infection	2 (5%)	2 (5%)	
Pulmonary infection	4 (10%)	4 (10%)	
Herpes zoster	1 (2.5%)	2 (5%)	
Thrombocytopenia	1 (2.5%)	1 (2.5%)	
Aminotransferase elevation	1 (2.5%)	2 (5%)	
Overall	9 (22.5%)	11 (27.5)	.61

Characteristic	Control group ($n=30$)	Immunoglobulin group ($n=30$)	p
CAT score (mean ± SD)			
Pre-	22.7 ± 2.6	21.8 ± 3.0	.43
Post-	19.1 ± 3.3	17.7 ± 3.4	.03
p	.01	<.001	
Distance of 6MWD (mean ± SD)			
Pre-	265.6 ± 42.4	266.5 ± 46.7	.93
Post-	332.3 ± 55.1	364.4 ± 54.3	.04
p	.02	<.001	
FVC (mean ± SD)			
Pre-	58.7 ± 11.5	57.3 ± 13.1	.85
Post-	66.6 ± 11.2	78.8 ± 12.6	.05
p	.05	.01	
HRCT score (mean ± SD)			
Pre-	9.2 ± 2.5	9.5 ± 1.9	.56
Post-	7.6 ± 1.6	6.0 ± 1.5	.04
p	.04	.01	
ESR (mean ± SD)			
Pre-	39.2 ± 14.6	38.4 ± 13.8	.85
Post-	14.1 ± 6.2	7.4 ± 3.3	.045
p	.01	<.001	

Abbreviations: 6MWD, 6-minute walk test; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HRCT, high-resolution computed tomography; SD, standard deviation.

Xiaoxia Shen | Fei Wang *Int J Rheum Dis.* 2023

Summary of guidelines regarding screening and monitoring of immunoglobulin levels*

ANCA vasculitis	2014	BSR BHPR	Measure serum immunoglobulin before each cycle of RTX[69]
ANCA vasculitis	2016	EULAR ERA EUVAS	Measure serum immunoglobulin levels before each course of RTX and in patients with recurrent infection[150]
SLE	2018	BSR	Measure immunoglobulins at time of diagnosis and before starting drugs with the most risk of inducing HG that might increase infection risk (eg, MMF, cyclophosphamide, and RTX). Repeat serum immunoglobulins about 3-6 mo later and then annually[151]
RA	2011	RCEC	Measure baseline IgG levels before the first dose and before each subsequent cycle of RTX. Close monitoring of IgG levels and infections for patients at risk for HG (eg, reduced IgG levels at baseline) or high-risk groups (eg, elderly)[68]
RA	2011	BSR BHPR	Measure immunoglobulin levels before initiating RTX as well as 4-6 mo after infusions and before any re-treatment[70]

Iris M. Otani et Al. J Allergy Clın Immunol 2022

. Summary of guidelines regarding IgG replacement therapy in SHG*

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Recommendation: For patients with GPA/MPA receiving remission maintenance therapy with rituximab who have hypogammaglobulinemia (e.g., IgG <3 gm/liter) and recurrent severe infections, we conditionally recommend immunoglobulin supplementation.	44	Very low

İmmunglobulin takviyesi, tekrarlayan enfeksiyonları olmayan ancak **aşı yanıtları bozuk** olan hipogammaglobulinemili hastalar için de düşünülebilir.

Chung SA, ve ark. Arthritis Rheumatol 2021

Secondary antibody deficiency and immunoglobulin replacement

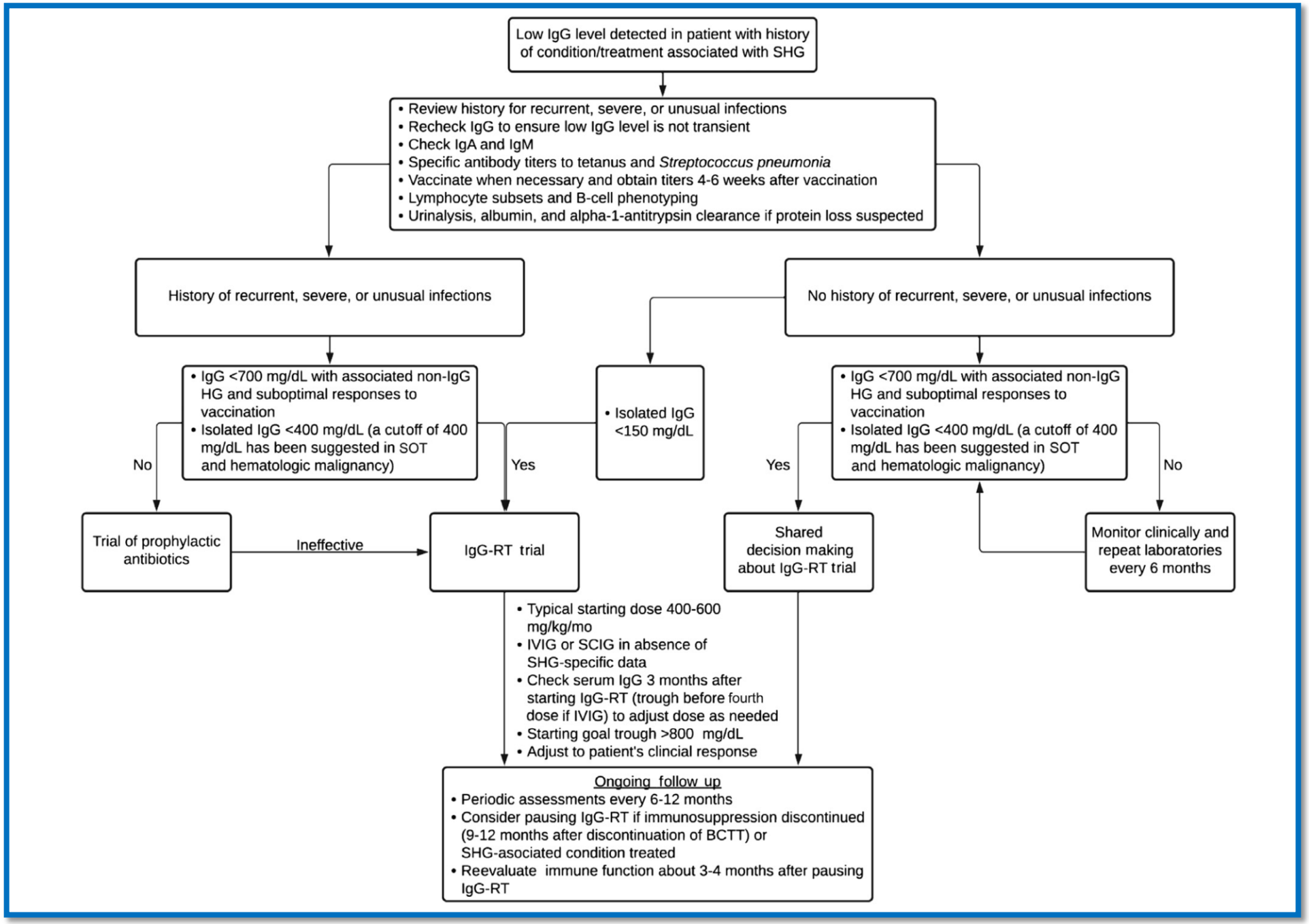
Table 1: Common examples of drug-induced hypogammaglobinemia

Anti-epileptics	Immunosuppressants	Monoclonal antibodies	Others
Carbamazepine	Azathioprine	Belimumab	Antimalarial agents
Lamotrigine	Cyclophosphamide	Ofatumumab	Captopril
Levetiracetam	Cyclosporine	Rituximab	Fenclofenac
Oxcarbazepine	Gold salts	Imatinib	
Phenytoin	Mycophenolate		
Valproate	Penicillamine		
	Steroids		
	Sulphasalazine		

Secondary antibody deficiency and immunoglobulin replacement

- Gerektiğinde;
  - 0.4 g/kg/ay, klinik yanıta ve bireysel hasta faktörlerine göre titre edilmeli
- Hedef IgG seviyesi
  - en az > 4-5 g / l

Philip H. Li*, Chak-Sing Lau Hong Kong Bulletin on Rheumatic Diseases 2017



Iris M. Otani et Al. J Allergy Clın Immunol 2022

Iatrogenic ANA: An emerging source of expensive diagnostic confusion

Lupus
2023, Vol. 32(2) 299–300

DOI: 10.1177/09612033221144600
journals.sagepub.com/home/lup
SAGE

Hammad Ali[1], Connor R. Buechler[2], Oneeb Sanaullah[3], Alexandria Lucas[4] and Kristine L. Lohr[1]

Cureus
Open Access Case Report
DOI: 10.7759/cureus.37008

Inpatient Rheumatology Consultation Prompted by Positive Autoantibodies in Patients Receiving Intravenous Immunoglobulin Therapy: A Case Series and Literature Review

Review began 03/21/2023
Review ended 03/27/2023
Published 04/01/2023

Zarlasht Fnu [1], Asif Uddin [2], Brianne Navetta-Modrov [2], Asha Patnaik [2], Alan Kaell [2, 3, 1]

In the absence of clinical symptoms, we recommended continued monitoring and repeat ANA testing **6 months after** the last dose of IVIg; as any drug needs 5 half-lives to be eliminated from the body.

Sonuç

- Romatolojik hastalıklarda yüksek doz IVIG (2gr/kg 2-5 gün)
- Kesin belirlenmiş doz ve süre yok
- Tedavi kararı organ tutulumuna göre hasta bazlı değerlendirilmeli
- İlk tedavide DM/PM'de (ağır vakalarda) verilebilir
- CAPS'de ilk tedavide üçlü tedavinin bir parçası
  - Glukokortikoid + Heparin + PE veya IVIG
- Sekonder hipogamaglobulinemide
  - IgG <4 g/l ise dikkatli olunmalı beraberinde enfeksiyon mevcutsa IVIG
  - Aşı yanıtı yoksa -- IVIG

Teşekkürler