SLE and Immunodeficiency

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Focus on

- Primary antibody immunodeficiency disorders associated with SLE.
- Secondary immunodeficiency in SLE – medications and hypogammaglobulinaemia.

Three primary immunodeficiency disorders prone to develop SLE or lupus-like features

- Homozygous deficiency of the early components of the classical pathway of complement activation(C1q, C1r, C1s, C4, and C2) predisposes to the development of SLE.
- IgA deficiency is also strongly associated with SLE.
- Female carriers of the X-linked chronic granulomatous disease allele are prone to develop discoid lupus, lupus-like manifestations and even SLE.

Primary immunodeficiency disorders (PID) reported in SLE patients

- More commonly associated PID are:
- Selective IgA deficiency (SIgAD)
- Deficiency of early components of the complement cascade (C1q, C2 and C4)
- Common variable immunodeficiency disorders (CVID)
- Selective IgG2 deficiency
- Less commonly associated, mostly case reports and include:
- Autosomal recessive hyper-IgE syndrome
- Chronic granulomatous disease
- CD40 and CD40L deficiency
- IL-12 receptor $\beta 1$ deficiency

Complement and antibody primary immunodeficiency in juvenile systemic lupus erythematosus patients

Lupus (2011) 20, 1275–1284

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- Studied **complements and immunoglobulin** levels.
- **72** patients.

RESULTS

PID identified in 16(22%).

- Complement deficiencies: 3 with C2, 3 with C4, 2 with C1q deficiency.
- Antibody deficiencies: 4 with IgG2 (<20 mg/dl), 3 with IgA (<7 mg/dl), and 3 with IgM (<35 mg/dl) deficiency.
- One patient had IgA, C2 and C4 deficiencies.
- SLICC/ACR-DI was significantly higher in patients with PID compared with those without ($p<0.0033$)

CONCLUSION

- A high frequency of complement and antibody deficiency observed.
- This suggests that these defects may contribute to lupus development.

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High frequency of immunodeficiency-like states in systemic lupus erythematosus: a cross-sectional study in 300 consecutive patients

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Study in adult SLE

Analysed variable	
Gender (F:M)	284:16
Disease duration, mean (s.d.), years	10.74 (8.15)
SLICC-DI, median (IQR)	1 (0–2)
Autoimmune rheumatic diseases, n (%)	32 (10.6)[a]
APS	16 (5.3)
SS	7 (2.3)
SSc	4 (1.3)
RA	4 (1.3)
Polymyositis	2 (0.6)
PsA	1 (0.3)
NRAID, n (%)	20 (6.6)[a]
Hypothyroidism	15 (5)
Psoriasis	3 (1)
Vitiligo	3 (1)
Primary biliary cirrhosis	1 (0.3)
IgA nephropathy	1 (0.3)
Non-autoimmune diseases, n (%)[b]	140 (46.6)
Age, mean (s.d.), years	39.58 (12.54)
Current immunosuppressant, n (%)[c]	204 (68)
Corticosteroids	159 (53)
⩾20 mg (prednisone)	91 (30.3)
<20 mg (prednisone)	67 (22.3)
AZA	66 (22)
MTX	52 (17.3)
CYC	23 (7.6)
Mycophenolate	26 (8.6)
LEF	16 (5.3)
Ciclosporin	8 (2.6)
Tacrolimus	4 (1.3)
Dapsone	3 (1)
Thalidomide	2 (0.6)
Antimalarials, n (%)[d]	206 (68.6)
Previous immunosuppressant, n (%)	198 (66)

TABLE 2 Distribution of SLE patients and controls according to immunodeficiency-like states

Immunodeficiency-like states	Controls, n (%) n = 301	SLE, n (%) n = 300	P-value
IgM	5 (1.6)	24 (8)	<0.001
IgA	1 (0.3)	3 (1)	0.372
IgG	2 (0.6)	1 (0.3)	1.000
IgG subclasses	2 (0.6)	59[a] (19.7)	<0.001
IgG_1	1 (0.3)	5 (1.6)	0.122
IgG_2	1 (0.3)	40 (13.3)	<0.001
IgG_3	0	24 (8)	<0.001
IgG_4	0	11 (3.6)	<0.001
CVID	0	0	1.000
Hyper-IgM syndrome	0	0	1.000
Hyper-IgE syndrome	0	0	1.000
CGD	0	0	1.000
CGD gene carrier	0	1 (0.3)	0.499
C1q	0	0	1.000
C2	0	2 (0.6)	0.248
C3	0	0	1.000
C4	0	0	1.000
Any immunodeficiency-like state	10 (3.3)	86[a] (28.7)	<0.001

- Eighty-six (28.7%) of 300 SLE patients exhibited an immunodeficiency-like state, with no association with immunosuppressant therapy.
- Immunodeficiency-like states in SLE were not associated with increased susceptibility to or severity of infections.
- Low serum immunoglobulin was the most frequent abnormality; IgG3/IgG4 deficiency was associated with lupus nephritis.

Comments on results:

Interesting finding of high frequency of IgG subclass deficiency.

Studies from lupus cohorts from other countries and with larger numbers needed.

Selective IgA deficiency

- Defined as serum IgA levels ≤0.07g/L with normal IgM and IgG levels in individuals ≥4 years old.
- Most common primary immunodeficiency in Western world; prevalence of about 1 : 600 in the general population.
- A polygenic disorder with involvement of genes associated with autoimmunity.
- Most are clinically asymptomatic
- Recurrent respiratory and gastrointestinal tract infections (especially if concomitant IgG subclass deficiency), allergies and autoimmunity have often been reported.
- Autoimmune diseases often reported: Graves' disease, SLE, type I DM, Coeliac disease, JRA.
- An increased frequency of IgA deficiency among SLE patients of different ethnical backgrounds.
- Prevalence among SLE patients: 5.2% in juvenile and 2.6% in adult SLE patients.

Wang N and Hammarstrom L. Curr Opin Allergy Clin Immunol 2012, 12:602–608

Prevalence of selective IgA deficiency in SLE

- Serum IgA levels measured in 3,388 SLE patients in Sweden, UK, USA and China.
- IgA deficiency identified in 44 patients; a total frequency of 1:67 in Caucasians and 1:121 in Chinese .
- Interestingly, prevalence of IgA deficiency among Chinese SLE patients was >30-fold higher than in the general Chinese population (1:4,146), indicating a strong association between these two diseases.

Table 2. Prevalence of IgAD among SLE patients.

Year	Reference	Country	Age (years)	Sample size	IgAD (prevalence)	Criteria (g/L)
1969	53	USA	NM	87	4 (1:22)	Undetectable
1972	54	Mexico	NM	106	1 (1:106)	Traces
1976	55	USA	NM	114	3 (1:38)	<0.10
1983	56	UK	NM	138	4 (1:35)	<0.05
1985	57	Turkey	9–66	96	3 (1:32)	<0.05
1988	58	France	NM	72	3 (1:24)	<0.10
1990	59	Spain	NM	130	1 (1:130)	<0.05
1991	60	USA	NM	75	3 (1:25)	NM
1997	61	UK	NM	96	5 (1:19)	<0.5
2007	62	USA	Children	77	4 (1:19)	<0.01
			Adults	152	8 (1:19)	Absent
2010	63	Brazil	Adults	189	11 (1:17)	<0.05
Total				1,332	50 (1:27)	
			Present study			
		Sweden	Adults	706	11 (1:64)	<0.07
		UK	Adults	844	5 (1:111)	<0.07
		USA	Adults	874	20 (1:41)	<0.07
		China	Adults	964	8 (1:121)	<0.07
Total				3,388	44 (1:77)	

NM, not mentioned.

Wang N, et al. Selective IgA deficiency in autoimmune diseases. Mol Med 2011:17:

BRIEF REPORT

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IFIH1 Mutation Causes Systemic Lupus Erythematosus With Selective IgA Deficiency

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- Identified a de novo IFIH1(interferon-induced helicase C domain-containing protein 1) mutation in a patient with elevated serum IFNα, severe early onset SLE, selective IgA deficiency(SIgAD), and mild lower limb spasticity.
- Association between SIgAD and SLE, as well as the common IFIH1 polymorphism conferring risk in both diseases, indicates a shared genetic predisposition through IFIH1.
- SIgAD leads to defective host defence against viral infections and n abnormal presentation of viral antigens.
- Low or absent IgA may favour autoantibody production and development of autoimmunity.
- SIgAD may be the modifying factor that drove the interferonopathy toward the SLE phenotype in this patient.

Other studies on IFIH1 in SLE and in IgA deficiency:

- Cunninghame Graham DS, et al. Association of NCF2, IKZF1, IRF8, IFIH1, and TYK2 with systemic lupus erythematosus. PLoS Genet 2011;7:e1002341.

- Ferreira RC, et al. Association of IFIH1 and other autoimmunity risk alleles with selective IgA deficiency. Nat Genet 2010;42:777–80.

Common Variable Immunodeficiency Disorders (CVID)

- A group of heterogeneous primary antibody failure syndromes characterized by hypogammaglobulinemia.
- Polygenic inheritance in most cases; monogenic forms described.
- Diagnosis is one of exclusion.
- Onset of the varied clinical manifestations and laboratory abnormalities do not necessarily coincide; may occur from early childhood to old age.
- Phenotype ranges from only bacterial infections, to progression from a CVID-like condition to disease similar to a combined immunodeficiency.
- Some patients may have distinct initial presentations, such as autoimmune disease, granulomatous disease, or enteropathy without recurrent infections.

- Chapel H, et al. Confirmation and improvement of criteria for clinical phenotyping in common variable immunodeficiency disorders in replicate cohorts. J Allergy Clin Immunol. 2012; 130:1197-
- Malphettes M, et al. Late-onset combined immune deficiency: a subset of common variable immunodeficiency with severe T cell defect. Clin Infect Dis. 2009; 49:132-
- Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Curr Allergy Asthma Rep. 2009; 9:347-
- Quinti I, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol. 2007; 27:308 -

Autoimmunity in CVID

- Occurs in approximately 25% to 30% of CVID.
- Most common autoimmune disorders: ITP, AIHA, or both.
- Other autoimmune disorders include: seronegative arthritis, Sjogren's syndrome, SLE, vasculitis, uveitis, inflammatory bowel disease, pernicious anemia, hepatitis, primary biliary cirrhosis, thyroiditis, alopecia, vitiligo.
- In one study, 17% of 224 patients had autoimmunity as one of the presenting manifestations of CVID.
- Autoimmune manifestations may precede the appearance of hypogammaglobulinemia.

- Gathmann B, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014; 134.
- Podjasek JC, Abraham RS. Autoimmune cytopenias in common variable immunodeficiency. Front Immunol. 2012; 3.
- Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Curr Allergy Asthma Rep. 2009; 9.
- Quinti I, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol. 2007; 27.

CVID and SLE

- CVID is defined by a severe lack of immunoglobulins and variable T-cell dysfunction.
- SLE is characterized by high levels of immunoglobulins and autoreactive antibodies.
- Literature findings suggest CVID in SLE patients may be caused by an intrinsic B-cell defect or by an extrinsic factor with an effect on B-cell maturation.
- SLE-associated CVID is uncommon.
- However, CVID should be considered in SLE when hypogammaglobulinemia is present as it has potentially fatal outcome.
- Recurrent infections in SLE, apart from SLE activity and/or immunosuppressive treatment, must also alert the physician to possible CVID.

Common Variable Immunodeficiency in Systemic Lupus Erythematosus

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María Jesús Citores, PhD,† Pilar Muñoz, MD,* Pablo Tutor-Ureta, PhD,†
Lucia Silva, MD,* Juan Antonio Vargas, PhD,†
Miguel Yebra-Bango, PhD,† and José Luis Andreu, PhD*

Fernández-Castro M, et al. Semin Arthritis Rheum 2007; 36:238-245

- Described 2 patients with SLE and CVID and reviewed cases published in English literature.
- Detailed descriptions available for 18 patients; 89% females
- Mean age at onset of SLE of 23.8 years (range 7 to 44 years).
- In 50% of patients, CVID developed within first 5 years after diagnosis of SLE (range: 1 to 22 years).
- All patients had been treated with corticosteroids.
- 72% also had immunosuppressive therapy; 7(38%) azathioprine, 5(28%) cyclophosphamide, and 1 with chorambucil.
- 3(17%) were on carbamazapine, 3(17%) phenytoin, and 2(11%) phenobarbital.
- Sinopulmonary infections were the most frequent symptoms.
- In 67% of patients, SLE disease activity decreased after development of CVID.
- 4(33%) had exacerbations of lupus nephritis and other symptoms of SLE and anti-DNA antibody levels remained high after diagnosis of CVID.
- After diagnosis of CVID, ANAs were present in 11/17(65%) and anti-DNA in 8/17(47%).

Reasons for hypogammaglobulinaemia in SLE patients other than PID

Drugs used to treat SLE:

- Corticosteroids, azathioprine, cyclophosphamide, rituximab

SLE disease manifestations:

- Protein-loosing enteropathy, lupus nephritis with nephrotic state

Corticosteroids and hypogammaglobulinaemia

- Suppressive activity of corticosteroids is predominantly on cell-mediated immunity; marginal inhibitory effect on humoral immunity.

- Studies on suppression of humoral arm were carried out mainly in asthmatic patients:

• Inhaled corticosteroids have no effect on B-cell function.

• Oral corticosteroids may suppress humoral immune responses.

• Low serum immunoglobulin levels, especially IgG and to a lesser extent IgA and IgM noted in patients on oral corticosteroids.

• Corticosteroids >20 mg daily for 14 days or lower doses over longer periods (months to years) may lead to hypogammaglobulinemia.

• However, hypogammaglobulinaemia is rarely associated with functional antibody defects.

- Lee RJE, Fay AC. Hypogammaglobulinemia associated with long term, low dose steroid therapy. Postgrad Med J. 1985;61.
- Hamilos DL, et al. Hypogammaglobulinemia in asthmatic patients. Ann Allergy 1992; 68.
- Lack G, et al. Humoral immunity in steroid-dependent children with asthma and hypogammaglobulinemia. J Pediatr 1996; 129.
- Kawano T, et al. Hypogammaglobulinemia in steroid-dependent asthmatics correlates with the daily dose of oral prednisolone. Int Arch Allergy Immunol. 2002;128.
- Fedor ME, Rubinstein A. Effects of long-term low-dose corticosteroid therapy on humoral immunity. Ann Allergy Asthma Immunol. 2006; 97:113–116.

Case report

Effects of long-term low-dose corticosteroid therapy on humoral immunity

Mary E. Fedor, MD, and Arye Rubinstein, MD

Ann Allergy Asthma Immunol. 2006;97:113–116.

Table 1. Immunologic Variables During Corticosteroid (Methylprednisolone) Taper

Month/ year	Corticosteroid, mg/d	IgG, mg/dL	IgG1, mg/dL	IgG2, mg/dL	IgG3, mg/dL	IgG4, mg/dL	IgA, mg/dL	IgM, mg/dL	CD19⁺, %	CD19⁺, /mm³	CD4⁺, %	CD4⁺, /mm³	Pneumococcal antibodies, x/12 serotypes
7/1999	4	748	373*	310	44	40	83	100	4*	30*	48	368*	0/12*†
11/1999	4/2, alt	651	294*	339	42	45	89	103	4*	65*	52	845	0/12*†
5/2000	4/0, alt	756	379*	344	40	28	82	102	4*	57*	51	726	Not done
9/2000	2/0, alt	758	386*	311	43	42	68	106	4*	44*	49	541	1/12*†
11/2000	0	798	425*	NA	NA	NA	81	124	10	128	49	625	9/12
2/2001	0	806	427*	383	47	66*	106	126	10	131	49	640	Not done
1/2002	0	985	542	506*	53	77*	123	146	12	118	49	640	9/12
10/2002	0	977	477	464*	41	86*	120	143	19	278	45	659	9/12
5/2003	0	894	459	389	49	58	101	121	14	188	46	619	11/12
Reference range	DNA	596–1,534	456–875	89–459	20–91	7–64	58–366	40–194	6–29	110–660	30–61	490–1,740	DNA

Abbreviations: alt, alternating days; DNA, does not apply; NA, not available.
* Abnormal values.
† Pneumococcal vaccine administered.

- Describes an asthmatic patient on low dose corticosteroid for 36 years.
- Developed a clinical and immunologic picture suggestive of CVID.
- Suppression of B-cell percentages and absolute counts, levels of serum IgG1, and specific antibody responses to pneumococcal vaccine during long-term low-dose corticosteroid therapy.
-Gradual normalization over 4 years after corticosteroid was tapered and discontinued.

CONCLUSION

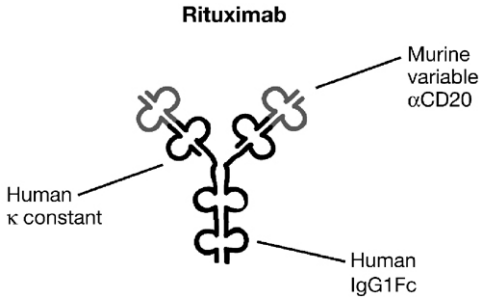
Long-term, low-dose corticosteroid use may reversibly decrease B-cell counts and specific antibody responses.

Hypogammaglobulinaemia and association with Azathioprine and cyclphosphomide

- In SLE, these two drugs have been reported to cause reversible hypogammaglobulinemia.
- Such secondary hypogammaglobulinemic states present as panhypogammaglobulinemia, involving decreased levels of IgG and other immunoglobulin isotypes.

- Yong PF, Aslam L, Karim MY, Khamashta MA. Management of hypogammaglobulinaemia occurring in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2008; 47: 1400–1405.
- Desar IM, Weemaes CM, van Deuren M, van der Meer JW. Reversible hypogammaglobulinaemia. Neth J Med 2007; 65: 381–385.
- Fernandez-Castro M, et al. Common variable immunodeficiency in systemic lupus erythematosus. Semin Arthritis Rheum 2007; 36: 238–245.

Rituximab (RTX)



- A chimeric anti-CD20 mAb, rapidly depletes circulating CD20+ B cells.
- Spares progenitor cells (allows B cell regeneration) and long-lived plasma cells (prevents excessive reduction of normal immunoglobulin levels, at least with initial therapy).
- Half life of 21 days.
- B cells peripherally can remain depleted for 6-9 months.
- Although RTX does not deplete fully mature plasma cells, repeated courses may lead to hypogammaglobulinemia.
- RTX crosses the placenta, manufacturer (Roche) recommends to avoid pregnancy for ≥ 12 months post last drug administration, BSR consensus is 6 months before planned conception.
- Licensed for RA, GPA, MPA but not for SLE; widely used to treat refractory lupus based on strong open-label experience.

Rituximab associated Hypogammaglobulinaemia

- Can be an important adverse outcome.
- May be transient or persistent.
- Transient hypogammaglobulinemia may not require specific therapy.
- Persistent hypogammaglobulinemia with infection would require immunoglobulin replacement.
- Factors that increase risk of persistent hypogammaglobulinemia in ANCA associated vasculitis and other autoimmune diseases:
- Higher cumulative dose or repeated cycles of RTX
- Concomitant or sequential use of immunosuppressants (especially cyclophosphamide)

Makatsori M, et al. Hypogammaglobulinaemia after rituximab treatment-incidence and outcomes. QJM 2014;107.
Besada E, et al. Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 2014;53.
Roberts DM, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015;57.
Marco H, et al. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. BMC Musculoskelet Disord 2014;15.

Hypogammaglobulinaemia during long term maintenance treatment with RTX in granulomatosis with polyangiitis (GPA)

- 29 GPA patients.
- Received a median total cumulative dose of cyclophosphamide (CYC) of 17g and were treated with 2g RTX followed by re-treatment with either 2g once annually, 1g biannually or a combination of both.
- Hypogammaglobulinaemia defined as levels of total Ig <6 g/L.
- During a median follow-up of 4 years, patients received a cumulative dose of 9g RTX.
- While serum Ig levels decreased during RTX maintenance, the largest decrease occurred after the first infusion.
- Baseline Ig levels and CYC cumulative dose predicted Ig levels, whereas the RTX cumulative dose did not.
- At baseline, low Ig levels were present in 30% of patients, perhaps reflecting the effect of high dose cyclophosphamide.

Besada E. Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. Rheumatology 2014;53

Rituximab and immunoglobulin levels in Rheumatoid Arthritis

- In registry data, patients with low IgG post-therapy was low, 3.5 %.
- In RCTs and LTE studies, 22.4 % of patients developed low IgM, levels lower on 2×1000 mg RTX versus 2×500 mg RTX.
- Low IgM prior to and post-RTX has not been associated with SIE.
- Registry data show that IgG level (<6 g/L) before a cycle of RTX was associated with SIE, particularly in the 3 months following RTX infusion.
- Development of low IgA post-RTX is uncommon (1.1 %) and does not appear to be associated with serious infectious events.

- * SIE = serious infectious event

Gottenberg JE, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010;62(9):2625–32.
Buch MH, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70(6):909–20.
van Vollenhoven RF, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis. 2013;72(9):1496–502

Reddy V et al. Pragmatic treatment of patients with Systemic Lupus Erythematosus with rituximab: long-term effects on serum immunoglobulins. Arthritis Care & Research 2016 'Accepted Article', doi: 10.1002/acr.22993

- Observational study, measured serum immunoglobulin levels.
- 57 consecutive patients with SLE treated with RTX and concomitant or sequential immunosuppressants.
- Serum total IgG, IgM, and IgA and anti-dsDNA Ab measured over a median of 48 months most recent follow-up.
- 12(21%) had persistent IgM hypogammaglobulinemia (<0.4 g/L) and 3/55(5%) had low IgG (<7g/L) at most recent follow-up (range 12-144 months); not associated with serious adverse events.
- Factors predictive of low serum IgM included: baseline serum IgM ≤0.8g/L and subsequent therapy with mycophenolate mofetil (MMF).

Rituximab and infection and vaccine response

- Anti-microbial antibody responses are generally relatively robust.
- However the degree of response to challenge with influenza, pneumococcal and tetanus vaccines after treatment
- may be impaired
- found to relate to the degree and duration of B cell depletion in peripheral blood in patients with RA and SLE.

Eisenberg, R.A., et al. Rituximab-treated patients have a poor response to influenza vaccination. *J Clin Immunol 2013;*33:388-396.
Westra, J., et al. Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clin Exp Immunol 2014;*178:40-47.
Albert, D., et al. Variability in the biological response to anti-CD20 B cell depletion in systemic lupus erythaematosus. *Ann Rheum Dis 2008;*67:1724-1731

Prevention of infections - vaccinations

- Administration of inactivated vaccines, particularly inactivated influenza vaccine and 23-valent polysaccharide pneumococcal vaccine, is strongly encouraged in SLE patients on immunosuppression.
- Vaccines should ideally be given 4 weeks before commencing B-cell depleting therapy such as RTX, or at least 6 months after the start of therapy but 4 weeks before the next course.
- Live attenuated vaccines should be avoided in immunosuppressed patients.

van Assen S, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70(3):414–22.

Summary

- Homozygous deficiency of the early components of the classical pathway of complement predisposes to the development of SLE.
- SIgAD is the most common primary antibody deficiency found in SLE.
- Besides PID, hypogammaglobulinaemia in SLE may be the result of complications of lupus activity as well as drug therapies.
- Evaluation of hypogammaglobulinaemia and diagnosis of associated PID in SLE can be challenging.