



## Review Article

# Juvenile-onset systemic lupus erythematosus: Update on clinical presentation, pathophysiology and treatment options

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## ABSTRACT

Juvenile-onset systemic lupus erythematosus (JSLE) accounts for up to 20% of all SLE patients. Key differences between juvenile- and adult-onset (aSLE) disease include higher disease activity, earlier development of damage, and increased use of immunosuppressive treatment in JSLE suggesting (at least partial) infectivity secondary to variable pathomechanisms. While the exact pathophysiology of JSLE remains unclear, genetic factors, immune complex deposition, complement activation, hormonal factors and immune cell dysregulation are involved to variable extents, promising future patient stratification based on immune phenotypes. Though less effective and potentially toxic, JSLE patients are treated based upon evidence from studies in aSLE cohorts. Here, age-specific clinical features of JSLE, underlying pathomechanisms, treatment options and disease outcomes will be addressed. Future directions to improve the care of JSLE patients, including implementation of the Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) recommendations, biomarkers, treat to target and personalized medicine approaches are discussed.

## 1. Introduction

Juvenile-onset systemic lupus erythematosus (JSLE) is a rare but severe multisystem autoimmune/inflammatory disease with disease-onset before the 18th birthday. It is a highly complex disease with marked heterogeneity between patients, causing anything from mild to life-threatening disease, following a relapsing and remitting course, and

with an unpredictable natural history [1]. Based on its nature with widespread inflammation resulting in damage, the central involvement of self-reactive lymphocytes, and the presence of high-titer auto-antibodies (at least in most patients), SLE (across age groups) is frequently considered the archetypal systemic autoimmune disorder. However, not all children develop “classical” features and may be diagnosed with JSLE in the absence of autoantibodies. Thus,

**Abbreviations:** ACR, American College of Rheumatology; AGS, Aicardi Goutieres Syndrome; ANA, anti-nuclear antibody; dsDNA, anti-double-stranded DNA antibodies; APLS, antiphospholipid syndrome; BLISS, Belimumab in Subjects with Systemic Lupus Erythematosus; BILAG, British Isles Lupus Assessment Group score; BSR, British Society for Rheumatology; CARRA, Childhood Arthritis and Rheumatology Research Alliance; C3, complement factor 3; CCL2, CC Chemokine Ligand 2; CD3, Cluster of Differentiation 3; CD4, Cluster of Differentiation 4; CD8, Cluster of Differentiation 8; CR, complete response; CREM $\alpha$ , cAMP response element modulator.; CTP, consensus treatment plans; DC, dendritic cell; DMARDs, disease modifying anti-rheumatic drugs; DN, double negative; dsDNA, Double stranded Deoxyribonucleic Acid.; ECLAM, European Consensus Lupus Activity Measurement; ENA, extractable nuclear antigens; EULAR, European League Against Rheumatism; HLA, Human Leukocyte Antigen; IFN, interferon; IL-2, Interleukin 2; IL-10, Interleukin 10; IL-17, Interleukin 17; ISN/RPS, International Society of Nephrology/Renal Pathology Society; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; JSLE, juvenile systemic lupus erythematosus; LN, lupus nephritis; MMF, mycophenolate mofetil; NET, Neutrophil Extracellular Trap; PBMC, Peripheral Blood Mononuclear Cell; Ped-ANAM, Pediatric Automated Neuropsychological Assessment Metrics; PLUTO, Pediatric Lupus Trial of Belimumab Plus Background Standard Therapy; PRINTO, Pediatric Rheumatology International Trials Organization; RCT, randomized control trial; SAVI, STING-Associated Vasculopathy, Infantile-Onset; SD-OCT, spectral-domain optical coherence tomography; SLEDAI, SLE disease activity index; SHARE, The Single Hub and Access point for pediatric Rheumatology in Europe; SLE, systemic lupus erythematosus; SRI4, Systemic Lupus Erythematosus Responder Index; SLICC, Systemic Lupus International Collaborating Clinics; SPENCD, Spondyloenchondrodysplasia; TLR, Toll Like Receptor; Th17, T helper 17; TNF $\alpha$ , Tumor Necrosis Factor Alpha; TPMT, Thiopurine S-methyltransferase; T2T, treat to target; US, United States

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**Table 1** Clinical manifestations and laboratory data according to age at onset of juvenile-onset systemic lupus erythematosus (JSLE) patients.

	Abdawni et al. [22]			Pluchinotta et al. [25]			Descoux et al. [23]			Gomes et al. [24]		
	Pre-pubertal (n = 39)	Peri-pubertal (n = 29)	Post-pubertal (n = 35)	Pre-pubertal (n = 13)	Peri-pubertal (n = 11)	Post-pubertal (n = 29)	Pre-pubertal (n = 9)	Peri-pubertal (n = 21)	Post-pubertal (n = 26)	Pre-pubertal (n = 39)	Peri-pubertal (n = 395)	Post-pubertal (n = 413)
Mean age (years)	5.12	10.8	15.3	0.5	6.9	12.5	6.9	12.1	15	4.2	10	13.8
Sex ratio (F:M)	2:1	5:1	11:1	2:1	2:1	3:1	2:1	2:1	3:1	4:1	6:1	8:1
Haematological involvement (%)	28	66	71	-	-	-	99	82	65	14	27	63
Arthritis (%)	77	66	60	-	-	-	-	-	-	71	64	70
Nephritis (%)	51	34	23	92	63	58	11	24	19	53	52	49
Neurological involvement (%)	10	21	14	46	18	20	44	19	4	36	25	24
Skin disease (%)	74	69	74	46	54	65	33	14	4	97	86	83
Low C3 (%)	97	79	77	69	72	72	-	-	-	52	59	67
Anti- SM (%)	7.7	24	40	-	-	-	-	-	-	43	38	34
Anti-SSB (%)	5.1	17	31	-	-	-	-	-	-	43	31	31
Anti-dsDNA (%)	-	-	-	91	72	69	-	-	-	61	70	70

pathomechanisms may vary based on age at disease-onset. In this review, we will provide an up to date account on the epidemiology, clinical manifestations, pathogenesis and treatment of JSLE, highlighting differences between juvenile- and adult-onset SLE. Future directions to improve patient outcomes will be discussed, including evidence-based standards of care, novel treatments and treatment approaches.

## 2. Epidemiology and demographics

Estimated incidences of JSLE range between 0.36 and 2.5 per 100,000 children, with a prevalence of 1.89–34.1 per 100,000 children [2–6]. Peak age of onset is approximately 12.6 years [7], and disease is more common in girls and young women (4.7–5.6:1) although the female predominance is less marked in children when compared to adults [7,8]. Of note, even within the pediatric population, gender distribution varies and is approximately equal in children < 5 year-of-age [9] (Table 1 and unpublished data from UK JSLE Cohort Study). Similar to adult-onset SLE (aSLE), JSLE more frequently affects individuals of non-Caucasian heritage [7,10]. Lupus patients have higher mortality rates when compared to the general population and they are highest in young people [11]. A study of 924 patients (413 with JSLE) demonstrated the standardized mortality ratio to be 18.3 in juvenile-onset disease compared to 3.1 in those with adult-onset disease [8]. Most common causes of death include infection, renal disease, malignancy and vascular disease and vary with disease duration. There is an increasing recognition of premature atherosclerosis contributing to mortality in JSLE, with more patients surviving the early course of their disease [12,13].

## 3. Clinical presentation

Juvenile-onset SLE is a multi-system inflammatory disease characterized by extremely variable presentation and clinical courses even as compared to a SLE (Tables 1 & 2). Thus, diagnosis can prove challenging. It covers a spectrum from sometimes relatively mild disease to severe, life-threatening presentations. Many features such as oral ulceration, fever, arthralgia, headaches and weight loss are non-specific and frequently occur in children for other reasons. Major organ involvement is common and includes renal inflammation occurring most frequently. Lupus nephritis (LN) affects up to 80% of patients and as many as 19% may develop end stage renal failure [7,14–17]. Also, neuropsychiatric involvement is more frequent in JSLE when compared to adult-onset disease and can cause significant morbidity [8,18–20]. Features of neuropsychiatric disease are highly variable and may include headaches, psychosis, cognitive dysfunction and cerebrovascular disease [21]. Of note, the incidence of arthritis, nephritis, neurological involvement in JSLE appears to negatively correlate with age at disease-onset (Tables 1 & 2) [22–25]. Hematological involvement, in particular hemolytic anemia, lymphopenia and thrombocytopenia, is also quite common [7,26]. Mucocutaneous disease is frequently observed and includes malar rash, photosensitivity, oral ulceration and vasculitis lesions [27,28].

## 4. Classification criteria

The heterogeneity of SLE causes difficulty developing diagnostic criteria, and indeed none are currently in routine use. Classification criteria have been developed for aSLE to define relatively homogenous patient populations for inclusion in clinical trials (Table 3). The American College of Rheumatology (ACR-1997) first developed classification criteria in 1982 which were updated in 1997 [29]. Because of concerns regarding sensitivity the Systemic Lupus International Collaborating Clinics (SLICC-2012) group established classification criteria in 2012 which include 11 clinical criteria and 6 immunological criteria and also allowed classification of patients with LN on renal biopsy and the presence of anti-nuclear antibody (ANA) or anti-double-stranded

**Table 2**  
Variation in clinical and immunological presentation between juvenile-onset and adult-onset disease.

	Ambrose et al. 2016, UK [8]		Artim-Esen et al. 2017, Turkey [20]		Mohamed et al. 2017, Egypt [19]		Sousa et al. 2016, Portugal [190]		Webb et al. 2011, USA [43]	
	jSLE	aSLE	jSLE	aSLE	jSLE	aSLE	jSLE	aSLE	jSLE	aSLE
Female (%)	<b>83</b>	<b>92</b>	87	86	78	74	<b>87</b>	<b>96</b>	<b>82</b>	<b>91</b>
Caucasian (%)	50	60	100	100	–	–	78	72	–	–
Malar rash (%)	–	–	<b>74</b>	<b>46</b>	<b>56</b>	<b>75</b>	<b>62</b>	<b>36</b>	(OR) 2.25	
Photosensitivity (%)	34	41	<b>72</b>	<b>57</b>	53	46	46	60	(OR) 1.19	
Arthritis (%)	<b>72</b>	<b>93</b>	70	71	71	63	<b>70</b>	<b>89</b>	(OR) 1.62	
Serositis (%)	<b>23</b>	<b>41</b>	<b>12</b>	<b>18</b>	8	13	26	19	–	
Renal involvement (%)	<b>44</b>	<b>33</b>	<b>53</b>	<b>39</b>	<b>73</b>	<b>36</b>	<b>58</b>	<b>31</b>	(OR) 3.34 <sup>a</sup> (OR) 2.04 <sup>b</sup>	
Neurological involvement (%)	24*	21*	12	8	<b>23</b>	<b>8</b>	<b>11</b>	<b>6</b>	(OR) 1.45	
ANA positive (%)	97	94	98	97	100	100	97	99	Anti-RNP (OR) 0.53	
Anti-dsDNA + ive (%)	<b>71</b>	<b>63</b>	<b>79</b>	<b>70</b>	<b>84</b>	<b>70</b>	–	–	(OR) 1.95	
Low C3 (%)	<b>62</b>	<b>46</b>	–	–	<b>61</b>	<b>50</b>	<b>83**</b>	<b>67**</b>	–	

Significant results ( $P < 0.05$ ) noted in bold. \*Approximated from figure \*\*Low complement rather than low C3. OR = Odds ratio. JSLE: juvenile-onset SLE, aSLE: adult-onset SLE.

<sup>a</sup> Proteinuria.

<sup>b</sup> Cellular casts.

DNA antibodies (dsDNA) in the absence of other clinical criteria [30]. Studies in adult and juvenile-onset disease demonstrated higher sensitivity but lower specificity using the SLICC when compared to ACR classification criteria [31–33]. SLICC criteria are currently recommended to be used as guides for diagnosing jSLE in the European SHARE recommendations (Single Hub and Access point for pediatric Rheumatology in Europe) [34]. Recently, the ACR and European League Against Rheumatism (EULAR) have jointly developed new classification criteria, which include ANA positivity as an entry criterion, but these have not yet been validated in JSLE [35,36]. This will likely bring benefits homogenizing patient cohorts for clinical trials, but holds risks if colleagues use criteria for diagnosing SLE patients, as ANA negative individuals (likely more prevalent in jSLE) may be missed and not referred to Rheumatology services.

## 5. Pathogenesis of jSLE

Genetic factors are centrally involved in the pathophysiology of jSLE. However, single gene mutations are causing SLE or “lupus-like” disease in only 1–4% of patients. Thus, in most jSLE/SLE patients, the onset of disease depends upon environmental triggers, including exposure to ultra violet light, certain medications, infectious stimuli, and others [37]. Dysregulated immune responses leads to (variable) activation of innate and adaptive immune mechanisms subsequently resulting in the release of inflammatory cytokines, aberrant activation of effector T cells, autoantibody production and immune complex

deposition, which contribute to tissue inflammation and organ damage [38] (Fig. 1). Indeed, the exact contribution of innate vs adaptive immune mechanisms in the pathophysiology of SLE may vary between individuals and age groups. We recently demonstrated that ANA (and other autoantibody) positivity varies significantly between age groups with more autoantibody negative individuals in younger patients (< 7 years) (unpublished data, currently under review). Furthermore, the observation that the female:male sex distribution ranges around 5:1 in children and young adults and even close to 1:1 before the 5th birthday (while the predominance in females rises to 9–10:1 in aSLE) indicates that hormonal factors are centrally involved in the pathogenesis of “classical” SLE [7,14,39,40].

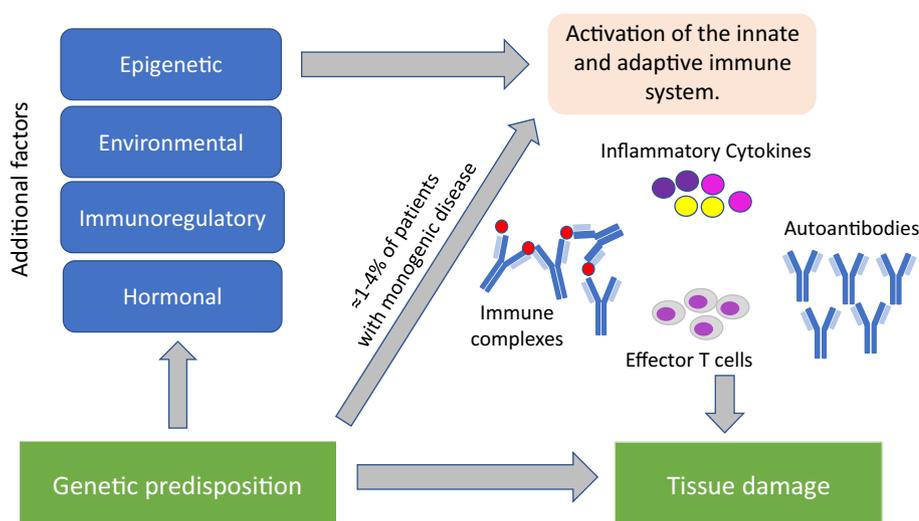
### 5.1. Genetic factors

Familial clusters of SLE, genetic associations with multiple common variants and rare disease-causing mutations resulting in SLE or SLE-like disease underscore the central involvement of genetic variants in the pathophysiology of SLE [1]. The strongest indicator of genetic factors in SLE is so-called “monogenic” SLE-like conditions. Over recent years, a number of mutations affecting genes involved in the cytoplasmic nucleic acid sensing machinery have been identified to result in increased type I interferon expression and systemic inflammation (Table 4). Furthermore, complement deficiencies can result in immune complex deposition and “secondary” type I interferon responses [1]. Though monogenic lupus-like disorders delivered valuable insights into the

**Table 3**  
Classification criteria used in SLE.

	ACR-1997 criteria	SLICC-2012 criteria	EULAR/ACR-2017 criteria
Entry criterion	None	None	ANA positivity
Number of criteria	11 criteria	17 criteria: 11 clinical criteria 6 immunological criteria	10 domains with criteria within: 7 clinical domains 3 immunological domains
Scoring	Each criteria present scores one point	Each criteria present scores one point	Weighted criteria within each domain – highest weighted criterion scored towards total
Classification of lupus	≥4 criteria	≥4 criteria (including at least one clinical and one immunological criteria) OR Lupus nephritis AND ANA or dsDNA positivity	ANA positivity AND ≥10 points AND presence of at least one clinical criteria

ACR-1997: American College of Rheumatology classification criteria, updated 1997; SLICC-2012: Systemic Lupus International Collaborating Clinics classification criteria, developed 2012; EULAR/ACR-2017: European League against Rheumatism and American College of Rheumatology classification criteria, developed 2017.



**Fig. 1. The pathophysiology of Systemic Lupus Erythematosus (SLE).** The complex pathophysiology of "classical" SLE involves genetic predisposition in the context of additional factors, including hormones, immunoregulatory and/or environmental events, and epigenetic factors (that can be affected by all the aforementioned). Together, pathophysiologic factors result in inappropriate activation of innate and adaptive immune responses, including altered cytokine expression, antibody production, immune complex generation, and effector lymphocyte generation and activation. The end result of these events is tissue inflammation and organ damage, defining the clinical picture of SLE.

pathophysiology of SLE, mutations in single genes only occur in a minority of patients [1,41]. Indeed, the observation that SLE disease concordance in genetically identical monozygotic twins only ranges between 25 and 40% strongly indicates that genetic factors are involved in the pathophysiology, but additional factors are necessary for disease expression at least in most patients [42]. Over the past decade, a constantly growing number of genes and genomic regions involved in SLE susceptibility have been revealed through linkage analysis and candidate gene studies [43,44]. So-called risk alleles are involved in many immune cells processes (Table 5) including B and T cell activation, neutrophil and monocyte signaling, Toll like receptor (TLR) and interferon signaling, inflammation and immune complex processing and clearance [1,45,46]. However, a significant proportion of risk alleles are also present in other autoimmune diseases (such as Rheumatoid Arthritis and Juvenile Idiopathic Arthritis), implying that common molecular pathways may exist among various autoimmune disorders [44].

Generally, higher genetic risk has been suggested in jSLE as compared to adult-onset SLE in American populations of African ancestry [47]. An association between the age at disease onset and genetic risk in patients of European descent was not observed, which may reflect more severe disease phenotypes in non-Caucasian individuals and/or limited numbers of patient samples and risk alleles included in the study [47]. A recent study involving two larger multi-ethnic cohorts of both adult-onset and jSLE patients observed an association between genetic burden, as estimated by Human Leukocyte Antigen (HLA) and non-HLA SLE genetic risk scores, and Lupus Nephritis (LN) risk. Results suggest a

stronger association between genetic susceptibility and juvenile LN, particularly in patients of European ancestry [48].

### 5.2. Innate immunity in jSLE

Innate immune cell-derived type I interferon (IFN) (IFN- $\alpha$  and - $\beta$ ) has a driving role in a number of systemic autoimmune/inflammatory diseases [49]. Oligonucleotide microarray analysis on peripheral blood mononuclear cells (PBMC) from jSLE patients have shown that > 95% of children with SLE display a type I IFN signature [50]. While Type I IFNs can activate the adaptive immune system, in turn, B cell-derived autoantibodies and/or immune complexes can also stimulate plasmacytoid dendritic cells (pDCs) to produce type I IFN [18]. Thus, an inflammatory feedback loop is produced that involves both the innate and adaptive immune system.

Dendritic cells are professional antigen-presenting cells (APCs) and key regulators of the immune system. Monocytes are precursors to DC, have limited antigen-presenting capacity, and are unable to initiate primary immune responses unless they are triggered to differentiate into myeloid DCs. Increased type I IFN expression may break peripheral tolerance through the differentiation of monocytes into myeloid DC and the subsequent activation of these myeloid DC by jSLE serum-associated factors [51]. In the context of SLE, where apoptotic and necrotic cells and nucleosomes are present in patients' blood, DCs present autoantigens to CD4<sup>+</sup> T cells initiating the expansion of autoreactive T cells and differentiation of autoantibody-producing B cells. Lastly, type I IFN- $\alpha$  production may be sustained by the formation of immune complexes by

**Table 4**  
Known genes causing monogenic SLE and/or SLE like diseases.

Gene	Pathway involved	Disease association	Ref
ACPS5	Nucleic acid metabolism and processing	Spondyloenchondrodysplasia (SPENCD)	[191]
ADAR	Nucleic acid metabolism and processing	Aicardi Goutieres Syndrome (AGS)	[192]
C1Q, C1R, C1S, C2, C3, C4	Complement activation Immune clearance	SLE like disease	[193–198]
DNASE1	Nucleic acid metabolism and processing	Aicardi Goutieres Syndrome (AGS)	[199–201]
DNASE1L3 RNASEH2A, B & C SAMHD1		Chilblain Lupus	
FAS FASLG	Apoptosis	Autoimmune lymphoproliferative syndrome (ALPS)	[202–204]
IFIH1	Nucleic acid metabolism and processing	Aicardi Goutieres Syndrome (AGS)	[205]
PEPD	Immune clearance	SLE like disease	[206]
TREX1	Reduced clearance of chromatin (ssDNA), activation of type I interferon expression	Familial chilblain lupus. Approximately 20% progress to SLE.	[207–211]
TMEM173	Nucleic acid metabolism and processing	STING-Associated Vasculopathy, Infantile-Onset (SAVI)	[212]

**Table 5**  
Selection of susceptibility genes and risk alleles in SLE.  
Adapted from [213].

Immune cell process	Genes associated with SLE	Ancestry <sup>a</sup>	References
B and T cell activation	<i>LYN</i>	EUR	[214]
	<i>HLA-DR3, HLA-DR2, RASGRP3</i>	AFR, EAS, EUR, HIS	[43,215,216]
	<i>MSH5</i>	EUR, EAS	[217]
	<i>AFF1</i>	EAS	
Immune complex clearance	<i>ITGAM, FCGR2A</i>	AFR, EAS, EUR, HIS	[216]
Immune complex processing	<i>MECP2</i>	EUR	[218]
	<i>PTPN22, TNFSF4, IL-10, STAT4</i>	AFR, EAS, EUR, HIS	[43,219]
	<i>BANK1, BLK, ETS1</i>	AFR, EAS, EUR, HIS	[43]
	<i>PXK, IL-21</i>	EUR, HIS	[43]
	<i>IKZF2</i>	AFR, EUR, HIS, EAS, EUR	
Inflammation	<i>PRKCB, SLC15A4</i>	EAS	[43]
	<i>UBE2L3, TNFAIP3, TNIP1</i>	AFR, EAS, EUR, HIS	[43]
TLR/IFN signaling	<i>IRAK1</i>	EAS, EUR, HIS	[43]
	<i>IRF8, TYK2, IRF7, IRF5, IFIH1, PRDM1</i>	AFR, EAS, EUR, HIS	[43]
	<i>TNPO3</i>	AFR, EAS, EUR, HIS	[215]
	<i>JAK2</i>	EUR, HIS, EAS, EUR	

<sup>a</sup> Ancestry indicates the populations in which associations to SLE have been described. AFR, African American, EAS, East Asian, EUR, European, HIS, Hispanic.

autoantibodies and circulating nucleosomes thereby (auto-)amplifying inflammation [18].

Dendritic cells also have a role in the sensing and clearance of extracellular nucleic acids and immune complexes, both well-established autoantigens in SLE. Major sources of these antigens are aforementioned cell death [52] and the generation of neutrophil extracellular traps (NETs; see below) [53,54]. Neutrophils, critical components of the innate immune system, are one of the first cell types to be recruited to inflammatory sites during infection. Various cytokines, immune complexes and auto-antibodies abundant in SLE enhance mobilization of neutrophil precursors from the bone marrow or interfere with their differentiation capacity [55]. Early neutrophils may also enter the blood due to the accelerated death of mature neutrophils. We have shown that jSLE neutrophils undergo accelerated spontaneous apoptosis in vitro, and that serum from jSLE patients induces apoptosis in neutrophils from healthy controls, both of which correlate with disease activity [56].

An important antimicrobial mechanism of neutrophils involves the release of so-called neutrophil extracellular traps (NETs) into the local environment to bind and immobilize pathogens [57]. They are composed of chromatin, with specific proteins from the neutrophilic granules attached [57]. Excess and impaired degradation of NETs are associated with SLE disease severity, LN, anti-dsDNA antibodies and complement consumption [58]. Thus, NETs may be involved in disease expression in genetically predisposed individuals e.g. as a response to infections and/or tissue damage, and may feed into (self-)perpetuation of inflammation in SLE.

Monocytes and macrophages are involved in the engulfment and internalization of microorganisms, apoptotic cells and environmental debris among others. Impaired phagocytosis results in prolonged exposure of cellular debris to the immune system contributing to the production of autoantibodies directed against intracellular nuclear components as seen in SLE. Intrinsic monocyte and macrophage phagocyte dysfunction [59] and SLE serum itself contribute to impaired phagocytosis in adult-onset SLE [60,61]. Patients with jSLE exhibit impaired phagocytosis of bacteria, dysregulated phagocytosis receptor

expression and soluble phagocytic decoy receptors in the serum [62]. Furthermore, monocytes from patients with SLE express increased amounts of pro-inflammatory CC chemokine ligand 2 (CCL2), which is regulated by type I interferons [63]. Epigenetic patterns such as acetylation in monocytes from jSLE patients contribute to increased expression of tumor necrosis factor (TNF)- $\alpha$  [64], priming early maturation and downstream pro-inflammatory cytokine and chemokine expression [63]. Patients with lupus nephritis exhibit increased numbers of circulating monocytes in comparison to controls [65], and infiltration of monocytes to the kidneys mirrors inflammation and tissue damage [66].

The central involvement of innate immune mechanisms in SLE has furthermore been supported by animal studies. Systemic inflammation in lupus-prone mice can be reversed by deletion of TLRs, and auto-antibody profiles are altered in MRL/*lpr* mice based on the deletion of either TLR7 or TLR9 [67]. In humans, the *TLR7* locus is located on the X chromosome [68]. This is of particular interest due to SLE being more prominent in females to males, especially in those who develop the disease after puberty. Not only can TLR-activation drive the terminal differentiation of plasma cells, also SLE autoantigens can be detected by the endosomal TLR compartment [69]. Activation of TLRs in lupus by nuclear antigens may lead to the terminal differentiation of antinuclear B cells, which in turn produce ANA and cause immune complex deposition [67].

### 5.3. Adaptive immunity in jSLE

#### 5.3.1. T lymphocytes

T cells play a critical role in the pathophysiology of SLE and during damage accrual [70]. To date, molecular mechanisms contributing to altered T cell phenotypes, characterized by increased effector and reduced regulatory functions, are incompletely understood [1]. Children with LN exhibit profound alterations of the peripheral T cell phenotype, T cell homeostasis, and cytokine milieu during active disease [71], which involves increased frequencies of effector memory and terminal differentiated CD4<sup>+</sup> T cells and reduced naive T cells. T cells from patients with either juvenile- or adult-onset SLE fail to express IL-2 while producing increased amounts of pro-inflammatory IL-17A [72–76]. Reduced IL-2 expression may contribute to impaired activation-induced cell death, reduced cytotoxicity of CD8<sup>+</sup> T cells and an imbalance between effector vs regulatory T cells, as regulatory cell differentiation is dependent on IL-2 [1]. Indeed, an imbalance between IL-17A expressing effector vs regulatory T cells has been observed in SLE creating a pro-inflammatory profile [57] where uncontrolled IL-17A production contributes to immune cell activation and infiltration of inflamed tissues [77,78].

Repression of IL-2 is caused by several molecular disturbances orchestrated by the transcription factor cAMP response element modulator (CREM) $\alpha$  [75,79]. CREM $\alpha$  is expressed at increased levels in patients with SLE and adolescent jSLE patients [40]. It alters IL-2 expression through *trans*-repression of the *IL2* proximal promoter and induction of epigenetic remodeling through DNA methylation and histone deacetylation [75,79].

Effector T cells in the CD4<sup>+</sup> and TCR/CD3<sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup> ‘double negative’ (DN) T cell compartment of SLE patients are characterized by the increased expression of IL-17A [80,81]. Furthermore, numbers of DN T cells are increased in the peripheral blood of both adult-onset SLE and jSLE patients. They are a contributor to tissue damage in LN due to infiltration of the kidneys where they produce pro-inflammatory IL-17A [82,83]. The transcription factor CREM $\alpha$  induces IL-17A expression through *trans*-activation and the induction of DNA demethylation and histone acetylation in a yet to be determined fashion [75,79]. Recently, we demonstrated that CD4<sup>+</sup> T cells from patients with jSLE share phenotypical features with CREM $\alpha$  overexpressing Jurkat CD4<sup>+</sup> T cells, in which interactions between CREM $\alpha$  and the transcriptional co-activator p300 result in histone acetylation and increased expression of the

dual specificity phosphatase (DUSP)4. DUSP4 impacts the balance between phosphorylated STAT3 and STAT5, thereby likely altering the balance between IL-17A and IL-2 production [84].

### 5.3.2. B lymphocytes

In addition to the production of autoantibodies, B cells can contribute to the development of SLE through the presentation of autoantigens to autoreactive T cells and the secretion of pro-inflammatory cytokines and chemokines which further contribute to uncontrolled inflammation [67].

Anti-nuclear antibody (ANA) positivity is a critical characteristic used to define the development of SLE and is observed in over 95% of cases. Both adult-onset and jSLE display positivity for a variety of ANAs including those directed against double-stranded DNA (dsDNA) and other extractable nuclear antigens (ENA), such as anti-Sm/RNP and anti-SSA/SSB [85]. There is a higher prevalence of anti-dsDNA, anti-Sm/RNP and a decrease in anti SSA/SSB antibodies in jSLE patients as compared to adult SLE populations [39].

Studies in cohorts including both adult-onset and jSLE patients have observed regulatory B cells to be abnormal [86], with an inability of CD24<sup>hi</sup>CD38<sup>hi</sup> B cells to produce immune regulatory IL-10 in response to anti-CD40 stimulation and an inability to suppress inflammatory T cell differentiation [86]. Over-production of the type I IFN- $\alpha$  as observed in SLE, skews the differentiation of B cells away from regulatory B cells towards plasma blasts [87]. Furthermore, jSLE patients exhibit increased serum levels of the B cell activating cytokine Bly [88] which correlates with disease severity marking a subset of childhood-onset patients that develop a particularly severe form of disease [89].

## 6. Treatment

### 6.1. The importance of multidisciplinary teams

Due to the complexity of jSLE with multi-organ involvement, patient management often requires multiple specialists, including rheumatologists as case managers, dermatologists, nephrologists, hematologists, neurologists, radiologists, immunologists, gastroenterologists, cardiologists, endocrinologists and infectious disease specialists. Multi-disciplinary teams can be involved with both the initial diagnosis and subsequent management of disease flares and/or complications. Overall, jSLE patient management should be coordinated by a pediatric rheumatologist experienced in the diagnosis and treatment of jSLE, who will identify when additional expertise is required and ensure continuity of care. Nurse specialists play an essential role in providing patient education about the disease and its medications. They also assist in liaising with other specialists, allied healthcare professionals and schools [90].

Psychologists are increasingly becoming integral to pediatric rheumatology teams, specifically assisting with management of debilitating neuropsychiatric manifestations, cognitive and behavioral difficulties, management of fatigue and development of self-management strategies for the patient/family. Formal structured assessment of cognitive performance is frequently performed by psychologists. It is important to identify cognitive dysfunction in view of the known association with poor academic performance [91]. Adjuncts to formal neuropsychiatric assessment include the pediatric Automated Neuropsychological Assessment Metrics (Ped-ANAM) instrument [92], and questionnaire-based assessments of cognitive function and behavioral/emotional symptoms [93]. Physiotherapists, occupational therapists and play specialists are also extremely important, assessing function in the home and school, providing rehabilitation following disease flares, and helping patients to cope with procedures and limitations related to their diseases and its management [94–96].

### 6.2. Conventional immunomodulation

#### 6.2.1. Glucocorticoids

Glucocorticoids remain a crucial part of jSLE management in the form of topical and/or low dose oral treatment for mild-to-moderate disease, or high dose oral or intravenous treatment for severe manifestations. This is despite the well-recognized array of significant adverse effects associated with chronic use [97,98], and concerns about serious infections related to high dose induction regimens [99]. Glucocorticoids work through inhibition of prostaglandin and cytokine production, inhibition of cell proliferation, and induction of apoptosis of B and T lymphocytes and macrophages [100,101]. Promising corticosteroid sparing LN induction regimens have been proposed in aSLE, following a prospective observational single-center cohort study of rituximab and mycophenolate mofetil (MMF) without oral steroids for LN (RITUXILUP). This study used two intravenous methylprednisolone (IVMP) pulses (without any oral glucocorticoid) in combination with rituximab and MMF in 50 patients with active International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III, IV, or class V LN, reporting an 86% remission rate at 52 weeks [102]. Unfortunately, the subsequent randomized controlled trial (RCT) testing this regimen was discontinued prematurely due to slow recruitment [103].

Other attempts to use lower doses of glucocorticoid have included the Euro-LN trial which tested low-dose cyclophosphamide in LN, and used lower doses of oral glucocorticoid than previous studies, starting with prednisone 0.5 mg/kg/day in both arms, as opposed to the traditional 1 mg/kg/day [104]. Zehner et al, tested the efficacy of MMF in LN, with two different glucocorticoid regimens (IVMP pulses in both groups followed by standard or lower dose oral glucocorticoid). The two arms did not differ in complete response (CR) rates at 24 weeks (20% vs 19%), although partial response rates were higher in the standard-dose arm [105]. Three other small studies (20–26 patients per study) have compared high versus low dose IVMP in the treatment of adult SLE patients, demonstrating both regimens to be equally effective in controlling disease activity [106–108]. The recent British Society for Rheumatology (BSR) guideline for the management of aSLE, advocate the use of prednisolone  $\leq 0.5$  mg/day or IVMP  $\leq 250$  mg for 1–3 days in patients with moderate disease activity or flares, and prednisolone  $\leq 0.5$  mg/day and/or IVMP 500 mg for 1–3 days for those with severe flares [109]. Defining the appropriate use and dosage of corticosteroids in the management of jSLE remains an important research question.

#### 6.2.2. Hydroxychloroquine

Hydroxychloroquine (HCQ) is recommended in all jSLE patients by both the European SHARE guidelines [90] and the jSLE quality indicators [110]. Our understanding of its mode of action is limited. It is thought to affect phagocytosis, leukocyte migration, and reduce the activation of toll like receptors [111,112]. Hydroxychloroquine has been consistently associated with favorable responses in ‘hard’ disease outcomes, such as prevention of long-term damage in adults with jSLE [113,114] and reducing overall mortality rates [115]. HCQ reduces the number of flares aSLE [116] and prevents renal damage in LN [117]. It has an array of other beneficial effects, including reducing the risk of diabetes mellitus in SLE patients [118], improving lipid profiles [119], reducing common carotid artery intima-media thickness (a surrogate marker of atherosclerosis) [120], and reducing the risk of severe infections [121].

One concern in HCQ treatment is retinal side effects which may be more pronounced in young patients. Sensitive screening techniques are increasingly utilized to detect retinal toxicity (e.g. spectral-domain optical coherence tomography (SD-OCT)), and recent studies indeed demonstrated that the prevalence of HCQ retinopathy is even higher than previously believed (1.6–8.0% vs. 0.4–1.9%) [122]. This is concerning as currently HCQ retinopathy is felt to be irreversible, with the risk of toxicity increasing with the duration of use; < 1% risk for up to 5 years, 2% by 10 years, rapidly increasing to 20% by 20 years. Major

risk factors for hydroxychloroquine retinopathy include dosage of > 5 mg/kg/day and kidney disease [123]. Current recommendations for eye screening advocated by both the European SHARE guidelines and the childhood SLE quality indicators suggest annual screening [90,110]. In aSLE a less intensive screening approach has been suggested, including baseline and yearly optician eye tests for the first 5 years, followed by more detailed ophthalmological screening thereafter [124].

### 6.2.3. Non-biologic disease modifying anti-rheumatic drugs (DMARDs): mild to moderate extra-renal disease

Use of conventional DMARDs for immunomodulation and to allow tapering of glucocorticoids is largely undertaken following 'trial and error' strategies. Azathioprine is a pro-drug that converts to 6-mercaptopurine once activated. It is a purine analogue and inhibits both DNA synthesis and lymphocyte proliferation [125]. It is often used for new mild to moderate disease and as maintenance treatment following severe manifestations. However, there have been no RCTs assessing the efficacy of azathioprine in jSLE specifically [126]. Azathioprine is recommended in adult or older teenagers who are considering pregnancy given its favorable safety profile [109]. Methotrexate is mainly used as an alternative to azathioprine where there is prominent mucocutaneous or musculoskeletal symptoms present [127]. However, the evidence for its use as a monotherapy in jSLE is poor [128].

A fairly recent study has directly compared mycophenolate sodium and azathioprine (with controlled doses of glucocorticoids and antimalarials) in 240 adult Caucasian patients with predominantly musculoskeletal and mucocutaneous involvement, and approximately 30% displaying cardiorespiratory disease. Authors found significantly higher numbers of patients receiving mycophenolate sodium to reach remission at 3 and 24 months, with the mycophenolate sodium arm also demonstrating fewer flares and reduced toxicity [129]. A similar trial in jSLE would be very useful and does currently not exist.

### 6.2.4. Non-biologic DMARDs: severe extra-renal disease and proliferative lupus nephritis

MMF is usually reserved for moderate to severe disease manifestations of jSLE (e.g. hematological, cardiovascular, neuropsychiatric and renal involvement) or where mild to moderate manifestations have proven to be refractory to other treatments. Cyclophosphamide is usually used for major organ involvement and/or life-threatening flares, where rapid disease control is required (e.g. neurological, systemic vasculitis, LN) [21,130–134]. Risks of cyclophosphamide-associated side effects, including infertility, cancer development and/or infections have increasingly led to MMF being used where possible as an alternative. Nowadays, MMF tends to be the most commonly used LN induction and maintenance treatment in jSLE [135,136].

In adults, evidence for induction treatment of class III and IV LN is based on several large RCTs. MMF is equally effective, but less toxic than cyclophosphamide in the induction phase of LN management [137]. In the MAINTAIN trial, where all patients received Euro Lupus induction treatment [104] with low dose IV cyclophosphamide (six doses) followed by either MMF or azathioprine, no difference was seen in relation to the time to renal flare between the two study arms [138]. In contrast, within the ALMS trial, MMF was shown to be superior to azathioprine as a maintenance treatment, independent of whether MMF or cyclophosphamide was used as induction therapy [139].

In jSLE, there are no RCTs available investigating induction or maintenance treatments for class III/IV LN, but several observational studies. In a recent study from the UK JSLE cohort study, MMF was more frequently used in real world clinical practice than cyclophosphamide for induction therapy, with comparable efficacy demonstrated between the treatments [136]. A pilot study comparing the north American Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans (CTPs), MMF or IV cyclophosphamide, both with high-dose steroids for LN induction therapy in 41 children, demonstrated cyclophosphamide to be used more

commonly used than MMF for patients with ISN/RPS class IV LN (vs. class III). Similarly, no difference in renal response was detected between the two treatments, but these analyses were considered exploratory and further analyses are awaited [140].

A recent study from Nepal comparing low dose MMF (maximum 1.5 g/day) and IV cyclophosphamide in 42 children and adults with SLE, demonstrated equal efficacy between the two treatments, with fewer side effects associated with MMF treatment [141]. In a prospective study from Toronto, MMF was found to be more beneficial than other therapies (mainly azathioprine and cyclophosphamide) in improving/maintaining long-term renal function in 172 juvenile-onset proliferative LN patients followed for up to 7 years [142]. The European SHARE recommendations suggest induction treatment with either MMF or intravenous cyclophosphamide combined with high-dose prednisone (1–2 mg/kg/day, maximum 60 mg/day) for proliferative LN in children. The dosing of intravenous cyclophosphamide is left to the preference of the treating rheumatologist [34].

Recent observational studies in aSLE cohorts (mainly from Asia) suggested that calcineurin inhibitors (cyclosporin A and tacrolimus) may have equal or better efficacy than MMF or cyclophosphamide as induction treatment for proliferative LN, either used alone or as part of a 'multitarget' therapy with MMF [143]. A recent study has looked at addition of cyclosporine or tacrolimus to MMF treatment for 11 pediatric patients with a LN relapse during MMF maintenance therapy. Authors demonstrated complete renal remission to be attained by 45.5%, 45.5%, 40.0%, 44.4%, and 71.4% of patients at 3 months, 6 months, 1 year, 2 years, and 3 years [144].

### 6.2.5. Other treatment options for severe jSLE manifestations

Plasma exchange can be clinically useful during rapidly progressive life threatening SLE flares. Evidence for this is largely based upon case series which are summarized in a review by Pagnoux et al, highlighting the utility of plasma exchange in refractory LN, diffuse alveolar hemorrhage, neuropsychiatric SLE, thrombotic thrombocytopenic purpura, catastrophic antiphospholipid syndrome (APLS), hyperviscosity syndrome and cryoglobulinemia [145]. Intravenous immunoglobulin (IVIG) may also be useful, and is associated with a reduction in SLE disease activity scores (e.g. THE SLE disease activity index, SLEDAI) and improvements in complement factor 3 (C3) levels [146].

## 6.3. Biologic DMARD therapy

### 6.3.1. Rituximab

Rituximab is an anti-CD20 antibody depleting B cells (but not plasma cells) [147]. It is currently the most commonly used biologic DMARD in jSLE and plays a role in disease refractory to first line induction treatment, or in patients experiencing unwanted adverse effects from alternative treatments. To date, no RCTs have been carried out looking at rituximab use in children. However, evidence exists promising patient benefit. Two reports investigated the role of rituximab during the induction phase of treatment for proliferative LN in children. The first included 44 patients and compared rituximab vs MMF vs IV cyclophosphamide, in combination with IV methylprednisolone followed by tapering of prednisolone orally, and introduction of MMF for maintenance treatment in all children. Authors demonstrated higher rates of flare free survival in the rituximab group with more patients in this group reaching complete remission at last follow-up [148]. The second descriptive report included 12 patients who all received rituximab, low dose IV methylprednisolone (500 mg/m<sup>2</sup>) and MMF for induction treatment. At 6 months, 9/12 patients had achieved complete remission and 3/12 partial remission [149].

A recent systematic review [150] identified five retrospective cohort studies [151–155], two case series [156,157] and one pilot study [158], assessing rituximab use in a total of 191 jSLE patients. Rituximab was most commonly used for active disease refractory to corticosteroids and/or non-biologic DMARDs. Six of eight studies reviewed reported

improvement in standardized disease activity measurements (e.g. SLEDAI, British Isles Lupus Assessment Group score (BILAG), European Consensus Lupus Activity Measurement (ECLAM)), following rituximab treatment, lasting  $\geq 12$  months in most studies [151–157], and up to 5 years in one study [158]. Six of eight studies reported significant steroid-sparing effects with the addition of rituximab, ranging from 21 to 100% [151,154–158]. Following rituximab treatment, laboratory measures improved, including hypocomplementemia [151,154–157] and anti-dsDNA titers [151,154,155,157]. One cohort looking specifically at hematological involvement found 96% of patients to achieve normal platelet and/or hemoglobin counts within 48 days (interquartile range 14–103) of rituximab treatment [153]. Five of eight studies demonstrating improvements in serum albumin and creatinine and urinary protein/creatinine ratio in LN patients [151,155–158].

Two meta-analyses have been carried out in aSLE. One examined the utility of rituximab therapy in otherwise treatment refractory patients [159]. It included 31 studies that collectively enrolled 1112 patients. Authors concluded that the overall pooled global response, complete remission, and partial response rates to rituximab therapy were 72%, 46%, and 32%, respectively, and that rituximab treatment significantly decreased SLEDAI and BILAG diseases activity scores. Cumulative prednisone dose was also reduced after rituximab treatment in both SLE and LN groups [159]. The second analysis assessed additional improvements in clinical response can be achieved by adding adjuvant biologic response modifiers (rituximab and belimumab) in moderate to severe SLE [160]. It assessed three RCTs, including a total of 276 patients with extra-renal SLE flares [161–163], and 144 patients with LN [164]. Overall, authors concluded that for moderate to severe extrarenal SLE, evidence was low, but suggested no difference in mortality, clinical response, or harms between immunosuppressive agents plus adjunctive rituximab versus immunosuppressive agents alone. Evidence for rituximab in adults with severe SLE and LN (with an inadequate response to immunosuppressive agents) was also graded as low, and suggested that adjunctive rituximab only increases the rates of partial but not complete renal response [160]. Despite these results, both the pediatric and adult rheumatology communities largely feel that Rituximab is of benefit in clinical practice, and that suboptimal trial designs have contributed to these disappointing results.

### 6.3.2. Belimumab

Belimumab, a monoclonal antibody targeting the B-lymphocyte stimulator (BLYS), is the only biologic DNARD approved for active SLE in adults, following the results from the phase II and III BLISS trials (Belimumab in Subjects with Systemic Lupus Erythematosus). Post hoc analysis from these trials initially suggested that patients with serological activity (elevated anti-dsDNA titers and/or low complement levels) show better responses to belimumab [165,166], but real life observational studies have not confirmed robust differences in response between serologically active and in-active SLE patients treated with belimumab [143,167]. Other observational studies have also shown that belimumab is efficacious in reducing disease activity and flare rate, facilitating glucocorticoid tapering, and halting damage accrual [168–170].

The only clinical trial assessing use of Belimumab in jSLE is the PLUTO study (Pediatric Lupus Trial of Belimumab Plus Background Standard Therapy), which was recently presented at the 2019 EULAR meeting, with the full manuscript awaited. This study included 93 jSLE patients and was therefore underpowered to test for differences between belimumab and placebo groups (*p*-values not calculated). Compared to placebo, there were more Systemic Lupus Erythematosus Responder Index (SRI4) responders (study primary endpoint) in the belimumab group. The major secondary endpoints included PRINTO/ACR 30 and 50 response, sustained improvement of SRI and patient well-being (parent global assessment), which again was seen more in the belimumab than placebo group. Severe flares were 62% less frequent with belimumab vs. placebo (hazard ratio 0.38 [95% CI 0.18,

0.82]) [171].

## 7. Co-morbidities and long-term outcomes

In aSLE increasing focus is put on the prevention and management of co-morbidities linked to the SLE disease process itself or its treatment, through attention to cardiovascular risk, smoking status, obesity, hypertension, diabetes mellitus, hyperlipidemia, homocysteine levels, corticosteroid use, antiphospholipid antibody levels, vitamin D deficiency, osteoporosis and malignancy [172]. Atherosclerosis is increasingly recognized as a chronic inflammatory condition which can be influenced by jSLE related factors such as circulating immune complexes, complement activation, anti-phospholipid antibodies, corticosteroid use, lipid abnormalities and endothelial dysfunction [173,174]. Irreversible renal failure is one of the most common long-term consequences of jSLE [175] and increases cardiovascular risk, with shared risk factors which can negatively impact both renal and cardiovascular outcomes. Further research is required to identify and target both sub-clinical and overt co-morbid disease in childhood, in order to reduce and prevent long-term morbidity and mortality.

## 8. Defining standards of care for children with lupus

Despite improvements in the overall survival of SLE patients over the last 50 years, it is of great concern that the survival improvement rate has plateaued over the last 30-years [176] and the standardized mortality ratio is significantly higher in juvenile- as compared to adult-onset SLE [177,178]. To address these concerns, the European Union funded SHARE project was initiated in 2013, with the aim of developing consensus evidence-based international recommendations regarding the diagnosis, monitoring and treatment of pediatric rheumatic diseases. Twenty-five SHARE recommendations for jSLE in general and ten recommendations for neuropsychiatric disease were published in June 2017 [90], with recommendations for LN [34] and antiphospholipid syndrome [179] published separately. These recommendations are of key relevance to tertiary pediatric rheumatologists, but also primary care practitioners and non-rheumatology pediatric specialists who are involved in the management of these patients. Current initiatives are focusing on the implementation of the SHARE recommendations within specialist services, to improve and harmonize patient-centered healthcare across Europe [180].

## 9. Future directions

There is significant and urgent need for research in the field of jSLE focusing on all aspects of disease: pathophysiology, clinical aspects and disease outcomes, as well as treatment including the development of new and approval of existing and future drugs.

A better understanding of molecular pathomechanisms may result in the discovery and establishment of biomarkers that can be used to secure the diagnosis, measure disease activity and/or predict treatment responses and disease outcomes. First steps are indeed being made towards development of personalized approaches. In a fairly recent study, Pascual et al longitudinally profiled the blood transcriptome of 158 jSLE patients and discovered patient genotypes that enabled patient stratification into seven groups which correlate with disease activity, development of active LN and response to treatment in different nephritis sub-types [181]. Such approaches may be translated into clinical trials to improve trial design and provide tailored treatment for complex autoimmune conditions such as jSLE. The development of biomarkers has been prioritized as one of the principle research priorities in jSLE as part of a multidisciplinary research prioritization exercise undertaken by the Lupus Foundation of America and the CARRA [182], with urinary biomarkers for LN currently being one of the most active areas of biomarker research internationally [183–188].

However, also investigation of already existing treatment strategies

is urgently needed, feasible and warranted, particularly in relation to corticosteroid use, with a focus on steroid sparing regimens to minimize comorbidities and drug toxicity. The treat-to-target (T2T) principle has been successfully applied in rheumatoid arthritis and many diseases outside rheumatology (e.g. diabetes and hypertension), which resulted in the identification of appropriate therapeutic targets and systematically pursuing this target has led to improved care for patients, and provided standardized guidance for healthcare providers. An international task force has developed eleven T2T recommendations for aSLE, focusing upon the targeting of remission, preventing damage and improving quality of life [14,18]. Similar approaches should also be considered in jSLE, where higher disease activity at disease onset and throughout the disease course is associated with early accrual of damage [14,18].

## 10. Conclusions

The pathophysiology of jSLE is complex and varies significantly between individuals, sexes and age groups. This results in variable and largely unpredictable disease phenotypes, treatment responses and disease outcomes. Indeed, patients with jSLE exhibit strikingly different sex distribution, more severe disease, insufficient treatment responses and poor outcomes when compared to individuals with aSLE. This underscores likely differences in the pathophysiology and an urgent need for further research to underpin treatment of jSLE. International and multi-disciplinary/multi-professional collaboration are necessary to answer open questions and improve the wellbeing of patients with jSLE.

## Declaration of competing interest

None.

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