Juvenile-onset systemic lupus erythematosus (jSLE) – Pathophysiological concepts and treatment options

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Abstract

The systemic autoimmune/inflammatory condition systemic lupus erythematosus (SLE) manifests before the age of 16 years in 10–20% of all cases. Clinical courses are more severe, and organ complications are more common in patients with juvenile SLE. Varying gender distribution in different age groups and increasing severity with younger age and the presence of monogenic disease in early childhood indicate distinct differences in the pathophysiology of juvenile versus adult-onset SLE. Regardless of these differences, classification criteria and treatment options are identical. In this article, we discuss age-specific pathomechanisms of juvenile-onset SLE, which are currently available and as future treatment options, and propose reclassification of different forms of SLE along the inflammatory spectrum from autoinflammation to autoimmunity.

Keywords: Juvenile-onset systemic lupus erythematosus; Early-onset SLE; SLE; Tissue damage; Autoinflammation; Autoimmune; Inflammation; Tissue damage; Treatment; Individualised; Target-directed

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune/inflammatory disorder that can affect any organ system. The disease presentation, clinical course and outcome vary significantly between individuals, ethnicities and age groups. Variable presentations are reflected by the 11 American College of Rheumatology (ACR) classification criteria for SLE, four of which need to be fulfilled for a patient to be classified as having SLE [1,2].

The pathophysiology of SLE is not fully understood. Familial clusters, the relatively high prevalence of disease concordant monozygotic twins and poor prognosis of individuals of African or Asian descent independent of their current location indicate a key contribution of heritable genetic predisposition to disease expression [2–6]. The observation that gender distribution varies between age groups with almost equal risk for boys and girls under 5 years of age, a 4- to 5-fold higher prevalence in girls under the age of 16 years and a female-to-male ratio of 10:1 in the adult age group are a strong demographic indicator that hormonal factors are a central contributor to disease expression in SLE [2,7]. Finally, environmental factors including infections, medication and UV irradiation play a role in the pathophysiology of SLE in genetically predisposed individuals, where they appear to contribute to the breach of self-tolerance, enhancement of pre-existing but sub-clinical inflammation and the development of tissue damage [2,3] (Fig. 1).

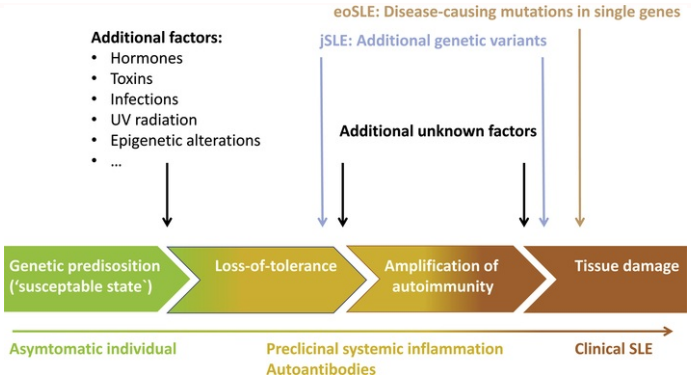

Fig. 1 Model of SLE pathogenesis and disease progression. The clinical picture of SLE is the net result of diverse, inter-individually variable molecular mechanisms. Genetic predisposition is a key factor in SLE pathology. However, in most individuals, individual genetic factors are not strong enough to confer disease. An exception to this may be eoSLE. Most likely, the majority of patients with eoSLE carry disease-causing mutations in single genes that mediate early-onset tissue damage and disease expression. Patients with juvenile-onset SLE carry an increased number of risk alleles compared to those with aSLE. This increased genetic risk may centrally contribute to disease onset in childhood or adolescence. Most patients with SLE (>80%) develop disease in adulthood. In most of these patients with 'classical' aSLE, genetic predisposition results in a 'susceptible' state and additional factors trigger loss of tolerance, chronic immune activation, and initially 'subclinical' systemic inflammation. For this, environmental (e.g. toxins, UV light, etc.) and additional endogenous (e.g. hormones) factors may need to accumulate to trigger loss of self-tolerance. Furthermore, additional currently unknown factors may be necessary to amplify inflammation and autoimmune processes that finally result in tissue damage and in the diagnosis of SLE.

An estimated 10–20% of all patients with SLE develop clinical disease before the age of 16 years and are therefore classified as childhood-onset or juvenile-onset SLE (jSLE) [7,8]. Peak disease onset in the jSLE cohort is between 12 and 14 years. Patients with disease onset before 5 years of age are very uncommon and may be referred to as early-onset SLE (eoSLE) [9,10]. Of note, jSLE, particularly eoSLE cases, is characterised by more severe clinical phenotypes, a high prevalence of pre-existing organ damage at diagnoses, more complications and less favourable outcomes compared to adult-onset SLE (aSLE) [7–13] (Table 1). The observations that gender distribution varies between age groups and that more severe phenotypes occur in patients with jSLE, particularly those with eoSLE, suggest that genetic causes or risk alleles may play a more pronounced role in jSLE. In patients with aSLE, although molecular alterations, e.g. due to environmental factors, may accumulate over time and finally cause disease expression, disease-causing mutations or a combination of risk alleles may be sufficient to cause disease in the paediatric age group (Fig. 1).

Table 1 Monogenic forms of SLE or 'SLE-like' disease (alphabetical listing, may be incomplete).

Gene	Protein product	Affected pathway	Disease phenotype	Inheritance	Ref.
C1Q	C1q	Complement activation (classical pathway), immune clearance	SLE-like disease with skin inflammation, glomerulonephritis, CNS disease, sometimes recurrent infections	AR	[38]
C1R	C1r	Complement activation (classical pathway), immune clearance	SLE-like disease with skin inflammation, glomerulonephritis, sometimes recurrent infections	AR	[39]
C1S	C1s	Complement activation (classical pathway), immune clearance		AR	[40]
C2	C2	Complement activation (classical pathway), immune clearance	SLE-like disease with arthritis, skin inflammation, pulmonary disease, sometimes recurrent infections	AR	[41,42]
C4	C4	Complement activation (classical pathway), immune clearance	SLE-like disease with variable phenotypes, skin inflammation, glomerulonephritis, sometimes recurrent infections	AR	[43]

DNASE1 *DNASE1L3*	DNAse1 DNAse1L3 (homologous to DNAse1)	Reduced clearance of chromatin	SLE with high-titre anti-DNA antibodies	AD AR	[23,26]
FASLG (Fas ligand)	FasL (Fas ligand)	Apoptosis	Autoimmune lymphoproliferative syndrome (ALPS)	AD	[19,21]
PRKCD (Protein kinase C delta)	PKCδ	Lymphoproliferation, spontaneous cell death	SLE with ALPS-like phenotype	AR	[35–37]
SAMHD1 (SAM domain and HD domain-containing protein 1)		Reduced metabolisation of dNTPs may result in increased retrotranscription of endogenous retroelements and subsequent accumulation of cytoplasmic DNA and type I interferon production	SLE, Aicardi-Goutieres syndrome	AR	[44,45]
TNFRSF6 (Tumour necrosis factor receptor super family member 6)	Fas (CD95)	Apoptosis	Autoimmune lymphoproliferative syndrome (ALPS), autoimmune cytopenia	AD	[20]
TREX1	Trex1	Reduced clearance of chromatin (ssDNA), activation of type I interferon expression	Familial chilblain lupus in approximately 20% progression to SLE	AR or AD	[28–31,34,46]

AR: autosomal recessive; AD: autosomal dominant.

In the following, we discuss the current understanding of jSLE pathology and currently available and future therapeutic options and we propose classification of ‘SLE sub-groups’ based on genetic risk. We focus on key concepts and recent publications rather than providing an all-inclusive collection of published reports.

Monogenic SLE and ‘SLE-like’ disease

Very few patients suffer from SLE caused by mutations in single genes. These forms are referred to as monogenic or Mendelian forms [2,3,14,15]. While rare mutations in single genes do not contribute significantly to the overall population heritability, effects can be devastating in affected individuals. Monogenic SLE has also provided valuable insights into disease pathophysiology of ‘classical’ SLE (Table 1). Interestingly, most patients presenting with monogenic forms of SLE will (at least initially) not present with high titres of autoantibodies and may not exhibit autoreactive lymphocyte populations. Thus, at least some forms of monogenic SLE meet the definition of autoinflammatory disorders that are caused by dysregulation of innate immune responses [16,17] (Fig. 2).

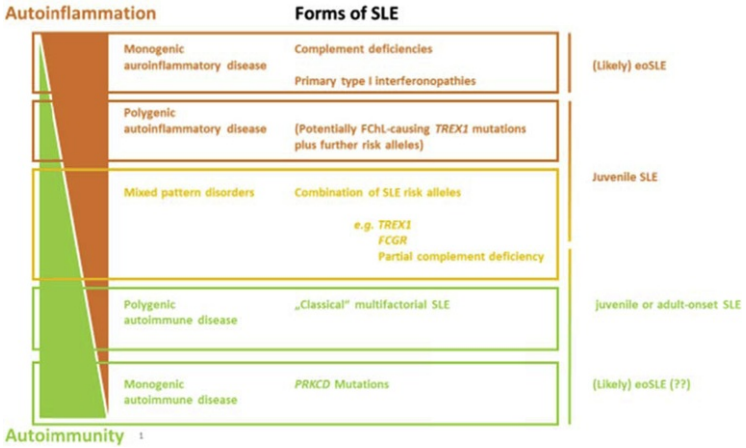

Fig. 2 Stratification of SLE along the inflammatory spectrum. Forms of SLE can be stratified along the inflammatory spectrum proposed by McGonagle and McDermott [17]. Rare monogenic forms of SLE may occur at either end. Mendelian disease likely manifests early in life (eoSLE), while multi-factorial disease that relies on genetic predisposition and the accumulation of other factors usually manifests later in life (jSLE or aSLE).

Autosomal recessive loss-of-function mutations in upstream components of the classical **complement** pathway, namely, C1q, C1r, C1s, C2, C4A and C4B, result in lupus-like phenotypes in a large subset of affected individuals [2,3,14,18]. Deficiencies of complement components may promote autoimmune reactions and inflammation through several, incompletely understood mechanisms. Defective clearance and resulting tissue deposition of immune complexes (C1 deficiency) and altered negative selection of self-reactive B lymphocytes (C4 deficiency) are two possible explanations for systemic inflammation in affected individuals. Aberrant clearance of cellular debris (as a result of apoptosis or necrosis), which is also dependent on complement activation, has emerged as a central mechanism not only in primary complement deficiencies but also in classical SLE [2,3,14,18].

Disturbed **apoptosis** has been proposed to be involved in SLE and other autoimmune/inflammatory conditions. Indeed, mutations in the *FAS* or *FASL* genes, which are key regulators of activation-induced cell death, result in autoimmune lymphoproliferative syndrome (ALPS) [2,19,20]. Furthermore, animals deficient of Fas (MRL.*lpr* mice) develop lupus-like disease with generalised lymphoproliferation. In both humans and mice, ineffective elimination of autoreactive T lymphocytes results in lupus-like systemic inflammation, tissue and organ damage [21,22].

Aberrant clearance of cytosolic and/or extracellular **nucleic acid** can result in a lupus-like pattern. Mutations in several genes involved in sensing or degradation of nucleic acids have been reported to cause monogenic forms of SLE or related disease [3,14]. Impaired degradation and removal of chromatin components (including DNA) contribute to autoantibody production and tissue damage. Humans and mice deficient in DNAse1 exhibit accumulation of extracellular chromatin, autoantibody production and subsequently lupus-like disease [14,23–26]. Recently, rare familial cases of SLE were associated with autosomal recessive mutations in *DNASE1L3* (a homologue of DNAse1), resulting in entirely abrogated nuclease activity, extracellular accumulation of DNA, autoantibody production, complement consumption and early-onset SLE [23,27].

Autosomal dominant mutations in *TREX1*, encoding for the 3′-5'exonuclease Trex1, cause familial chilblain lupus (FChL). Clinical characteristics of FChL include Raynaud's phenomenon, painful and sometimes ulcerating chilblain lesions. First symptoms may manifest early in childhood, and up to 20% of patients with FChL progress to full-blown SLE [28–30]. In FChL, loss of function of Trex1 causes cytoplasmic accumulation of nucleic acids (single-stranded DNA), which are sensed by the nucleic acid sensing machinery, resulting in type I interferon production [31–33]. Thus, FChL is a key representative of defects in cytosolic nucleic acid sensing and processing, which are currently referred to as primary type I interferonopathies [34], some of which share clinical characteristics with SLE.

Breach of self-tolerance is a key mechanism in SLE. Though most central for immune homeostasis, to date, few disease-causing mutations have been described, which specifically alter self-tolerance. Homozygous missense mutations in the *PRKCD* gene, encoding the protein kinase C delta (PKCδ), result in abrogated phosphorylation and activation of the enzyme. Peripheral B cells from patients and animals deficient of PKCδ exhibited increased cell death and lymphoproliferation in response to B cell stimulation through the B cell receptor complex, CD40 and Toll-like receptor (TLR) 9 [35–37], culminating in a loss of self-tolerance, lymphoproliferation and systemic inflammation.

Taken together, a relatively small number of currently known gene defects cause monogenic SLE or SLE-like disease. Mendelian forms of SLE are usually characterised by a positive family history, early disease-onset in childhood, relatively equal gender distribution, severe and sometimes not ‘classical’ symptoms and poor response to ‘standard’ treatment.

Risk alleles

‘Classical’ SLE is characterised by the presence of high-titre autoantibodies, usually against nuclear antigens, and autoreactive lymphocyte populations [2,3]. Most patients with jSLE (except those with eoSLE) meet this definition but may also show ‘mixed patterns’ with activation of both innate and adaptive immune responses [16,17] (Fig. 2).

A genetic component to SLE pathophysiology is emphasised by an increased risk for the development of disease with an affected first-degree relative (approximately 30-fold) and high rates of disease concordance in dizygotic (5%) and particularly monozygotic twins (40–60%) [2,4,6,7,15]. More than 40 genes have been associated with SLE through genome-wide association studies (GWAS) and targeted approaches [47]. These associations are established when genetic variants (usually single nucleotide polymorphisms or copy number variants) are more common in patients with SLE compared to matched healthy controls [3]. While very few patients develop the aforementioned monogenic forms of SLE, most individuals carry single nucleotide alterations in coding or non-coding regions or copy number differences of genes that are associated with an increased risk for SLE. These so-called risk alleles are by themselves not ‘strong’ enough to result in the disease without additional factors (Table 2). Of note, some of the disease-associated risk alleles are located in or around genes that can also cause monogenic SLE when carrying loss-of-function mutations (e.g. complement genes, *TREX1*, etc.).

Table 2 Selection of susceptibility genes and risk alleles in SLE (may be incomplete).

Pathway affected	Genomic variants associated with SLE	Ref.
B and T cell activation	*PTPN22, TNFSF4, IL10, SPRED2, STAT4, PXK, AFF1, IL12A, BANK1,*	[3,15,54,60–64]

	TCF7, SKP1, MHC genes, *IKZF1 and IKZF3, BLK, ARID5B, CD44, LYN, ETS1, FLI1, SH2B3, CSK, ELF1, CIITA, ITGAM, TYK2, ITGAM, IKZF2, PPP2CA, SIAE, CREM*	
Neutrophil and monocyte signalling	*ITGAM, ICAM, FCGR2B, FCGR3A, FCGR3B, IL10, IRF8*	
TLRs and interferon signalling	*IFIH1, PRDM1, UHRF1BP1, TNFAIP3, IRF5-TNPO3, IRF7 and IRF8, SOCS1, PRKCB, UBE2L3, IRAK1, TLR7*	[3,15,65]
Inflammation	*TNIP1*	[15]
Immune complex processing and clearance	*FCGR2A, FCGR2B, FCGR3A, FCGR3B, ATG5, CLEC16A, C4, NCF2, LYST*	[3,15,65–67]
Other/unknown	*ABHD6, RAD51B, MECP2, RASGRP3, TMEM39A, PITG1, TNXB, JAZF1, XKR6, FAM167A–AS1, WDFY4, SMG7, DHCR7, NADSYN1, SLC15A4, PLD2, CXorf21,* rs1167796, rs463128, rs7186852, rs7197475	[3,15]

Currently known risk alleles affect multiple pathways and cell subsets involved in the pathophysiology of SLE. In agreement with the aforementioned reports on monogenic forms of SLE, a large proportion of SLE-associated risk alleles affect lymphocyte activation, TLR and type I interferon pathways, and immune complex processing (Table 2). An all-inclusive discussion of genomic variants in SLE is beyond the scope of this manuscript, but two susceptibility mechanisms should be mentioned.

Partial deficiency of the upstream components of the classical complement cascade (C1, C2 and C4) contributes to SLE pathology, most likely through insufficient clearance of immune complexes and apoptotic material [3,48–51]. Furthermore, reduced levels of C4 may result in increased numbers of autoreactive B cells in the periphery secondary to altered negative selection [52]. Copy number variants (*FCGR3B*) and missense mutations (*FCGR2A*; p.H131R, and *FCGR3A*; F176V) in low-affinity complement receptors are associated with SLE and disease-related tissue damage likely through reduced immune complex clearance and subsequently increased inflammatory responses [53–55].

The aforementioned disease-causing mutations in the DNA repair exonuclease Trex1 result in the clinical picture of FChL. Interestingly, 0.5–3% of patients with SLE in Europe and the USA carry variants in *TREX1* [29,56,57] and are at an increased risk for neurological manifestations, particularly seizures [57]. Most variants associated with SLE are located in regions that are not responsible for exonuclease activity and may affect the ability of Trex1 to associate in the so-called SET complex. The SET complex plays a key role in granzyme A-mediated, caspase-independent cell death, a process that morphologically resembles apoptosis. This granzyme A-mediated cleavage of NDUFS3 results in the release of mitochondrial superoxide. In response to this, the redox-sensitive SET complex translocates to the nucleus. Granzyme A then cleaves the SET complex components SET, HMGB2 and APE2, thereby liberating the endonucleases NM23-H1 and Trex1, resulting in DNA damage and cell death. Through altered association of variant Trex1, autoreactive lymphocytes may survive longer through increased resistance to granzyme-mediated cell death [3,58].

Taken together, defined polymorphisms increase the risk for developing SLE but are usually not strong enough to confer disease. Most affected individuals will develop clinical disease later in life, potentially after the accumulation of additional disease-causing factors (e.g. infections, medication, epigenetic patterns, etc.) [4,6]. Additional contributors to disease expression in SLE are beyond the scope of this manuscript and are discussed elsewhere [2,4–6,15]. One could hypothesise that the combination of multiple risk alleles may result in cumulative effects and early disease onset, namely, jSLE. Indeed, Sawalha et al. (2011) reported a higher prevalence of genetic factors in patients with early disease onset and more severe clinical phenotypes. Thus, the accumulation of individual genetic risk factors may prime individuals to develop disease early in life (jSLE) and develop more severe clinical patterns and complications compared to older patients (aSLE) [59].

Cellular contributors to inflammation and tissue damage in SLE

SLE is characterised by deeply disturbed function and activity of innate and adaptive immune cells. Most of the available data are from adult cohorts. Comparative analyses using cells from patients with eoSLE, other forms of jSLE and aSLE are lacking and urgently needed. However, molecular phenotypes in adolescents and young adults may be comparable and will be summarised in this article.

Neutrophilic granulocytes from patients with SLE exhibit several anomalies and are involved in inflammation and tissue damage. Reduced phagocytic capacities have been reported in patients with SLE, which may contribute to an increased risk for infection and immune complex deposition [15,68]. Furthermore, neutrophils from patients with SLE fail to produce reactive oxygen species (ROS) when compared to cells from healthy controls [69].

This may alter apoptosis and immune complex clearance in SLE. As neutrophils are short lived and exist in rather large numbers, minor changes to their apoptotic behaviour may have large effects on waste clearance and immune complex deposition [70].

An abnormal subset of neutrophils has been identified in patients with SLE. The so-called low-density granulocytes are characterised by increased NETosis, a mechanism of cell death that occurs in response to various stimuli including contact with infectious agents and oxidative stress. It involves the extrusion of chromatin and other nuclear, cytoplasmic and granular material to the extracellular compartment. Neutrophil NETs contain inflammatory cytokines, antimicrobial peptides, enzymes and nucleosomes, which represent key autoantigens in SLE [71–74]. Furthermore, neutrophil NETs contribute to the expression of type I interferons by plasmacytoid dendritic cells (pDCs) through the activation of TLR9. In turn, type I interferons prime neutrophils for NETosis, which suggests a positive feedback loop that increases inflammation and tissue damage in SLE [15,75,76].

Moreover, **monocytes** from patients with SLE exhibit altered function. They express increased amounts of proinflammatory CC chemokine ligand 2 (CCL2), which is regulated by LPS or interferons [77]. Furthermore, monocytes from patients with SLE exhibit epigenetic patterns allowing for increased expression of tumour necrosis factor (TNF)-α [78], which may contribute to monocyte maturation and downstream pro-inflammatory cytokine and chemokine expression [4]. Indeed, infiltration of monocytes to the kidneys mirrors inflammation and tissue damage and even allows prognostic assessment [77,79,80]. Thus, monocytes and tissue macrophages may play a critical role in the development of tissue damage in SLE.

Dysregulated antigen presentation by **dendritic cells (DCs)** may contribute to the loss of self-tolerance of B and T cells in SLE. Various DC anomalies have been reported in patients with SLE, including a shift away from classical DC phenotypes toward increased numbers of plasmacytoid DCs (pDCs), the main cellular source of type I interferons [81]. Plasmacytoid DCs take up immune complexes through low-affinity FcγR2a receptors. Presentation to endosomal TLRs 7 and 9 induces interferon expression [82]. Therefore, this pathway may centrally contribute to the so-called type I interferon signature in ‘classical’ SLE and complement deficiencies [16]. Furthermore, conventional DCs in patients with SLE appear to promote autoreactivity rather than self-tolerance. In turn, activated T lymphocytes also promote type I interferon expression by pDCs [15,83,84].

Significant dysregulation of **T lymphocyte** function is a hallmark of SLE, and several of the aforementioned risk alleles influence T cell function (Table 2). T cells in patients with SLE are characterised by altered cytokine expression, reduced numbers of regulatory phenotypes, and increased numbers of effector T cells [2–6,85–88]. In T cells from patients with SLE, the ‘normal’ CD3ζ chain is replaced by the FcRγ chain. This results in interactions and activation of SYK tyrosine kinases instead of the physiological activation of ZAP-70, resulting in overactivated T cell receptor signalling pathways [2,89,90]. Regardless of their increased activation status, T cells from patients with SLE fail to express IL-2, which is caused by several molecular disturbances orchestrated by the transcription factor cAMP response element modulator (CREM)-α [2,86,87,91]. Reduced IL-2 expression may contribute to impaired activation-induced cell death, reduced cytotoxicity of $CD8^+$ T cells and increased numbers of effector T cells in SLE. Indeed, T cells from patients with SLE exhibit effector phenotypes in the $CD4^+$ and $CD3^+CD4^-CD8^-$ ‘double negative’ (DN) T cell compartment that are characterised by the increased expression of IL-17A [3,86,92–95]. The numbers of DN T cells are increased in the peripheral blood of juvenile and adult patients with SLE, and the cells infiltrate the kidneys where they produce pro-inflammatory IL-17A, a central contributor to tissue damage [3,92–94,96]. Regulatory T cell (T_{regs}) phenotypes are reduced, and their function is impaired in patients with SLE. Under physiological conditions, both B and T lymphocytes are subject to regulation by T_{regs}. Of note, T_{reg} differentiation is dependent on IL-2, which fails to be expressed in SLE. Treatment of patients with SLE and lupus-prone mice with recombinant IL-2 resulted in an increase in T_{regs} numbers, restored their function, and limited pro-inflammatory cytokine expression from effector DN T cells [97–99].

Although SLE is a highly heterogeneous disease, most patients with SLE exhibit **B cell activation and high titres of autoantibodies** directed against nuclear antigens. Autoantibody production may be genetically predetermined and/or triggered by the overabundance of extracellular chromatin components (detailed above) [4,15,16,59,100]. Furthermore, B cell tolerance can also be breached by the exposure to cytokines (including the B cell promoting factors BAFF/BLyS) [101,102]. Indeed, studies in humans have demonstrated both acquired environmental and heritable genetic contributions to autoreactivity of B cells with gradually increasing autoreactive capacities of B cells in autoimmune/inflammatory disease [15,103–107]. Autoantibody production is a key event in SLE. It induces inflammatory responses through the formation of immune complexes, which activate complement, low-affinity Fc receptors, and a wide range of immune cells [2,15].

Complications of jSLE in light of ‘age-specific’ pathomechanisms

Inflammatory organ involvement and tissue damage is more common in jSLE compared to aSLE. Furthermore, organ complications frequently exist already at the time of diagnosis in patients with jSLE [7,9,10]. Given the aforementioned contribution of genetic factors to early disease presentation and their statistical association with more severe disease courses [59], it is tempting to hypothesise that genetic factors may contribute to specific organ manifestations and complications, potentially allowing for patient stratification. In this case, genomic associations may aid in assessing individual risk and offering targeted treatment options. Indeed, individual genetic variants have been associated with organ involvement and/or disease outcomes. SLE-associated variants in *TREX1* indicate increased risk for neurological manifestations [57], and certain Fcγ receptor variants are more common in patients with severe lupus nephritis (*FCGR3A*) [67]. Although we are only at the very beginning of understanding the exact contribution of genomic variants to disease expression, phenotypes and outcomes, available reports promise potential for patient stratification based on impaired molecular mechanisms allowing for individualised management [3].

Treatment options in jSLE

Treatment of jSLE is complex and less standardised compared to aSLE. Regardless of differences in the pathophysiology of eoSLE vs. jSLE vs. aSLE, classification criteria and commonly used treatment options are identical, and age-specific differences fail to be appreciated. Another layer of complexity is added in jSLE with the occurrence of potentially toxic events and treatment-related side effects alongside the ongoing physical, mental and psychosocial developmental processes of childhood. Patients with JSLE require higher doses of corticosteroids and immune suppressive drugs, which is likely due to alternative pathomechanisms and higher incidence of tissue and organ damage at diagnosis and during the disease course [3,7,9,10] than in aSLE.

To provide guidance and to optimise and harmonise diagnostic approaches and treatment of patients with jSLE, the SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) initiative has provided evidence-based consensus recommendations for jSLE, lupus nephritis and disease-associated anti-phospholipid syndrome [108–110].

Conventional immune modulation or suppression

Glucocorticoids are the backbone of jSLE treatment in the acute phase. Strong and rapid immunosuppressive effects through inhibition of prostaglandin and cytokine production, inhibition of cell proliferation and induction of apoptosis of B and T lymphocytes as well as macrophages are the main events. Multiple studies demonstrated improved survival with corticosteroid use. However, steroid use must be limited because of significant toxicity and side effects including but not limited to reduced bone density, metabolic syndromes, hypertension, dysphoria, glaucoma, cataract and increased risk for infection [111–116].

Unless contraindicated in individual patients, **anti-malarial medications** should be introduced in all patients with jSLE [108,110]. In jSLE, usually hydroxychloroquine and in some countries chloroquine are used. Our understanding of their mode of action is very limited. Both medications appear to affect phagocytosis and leukocyte migration and to reduce the activation of TLRs [117,118]. Antimalarial medications reduce the frequency of disease flares, delay the onset of further symptoms in early disease and prevent thromboembolic events [116,119,120]. During pregnancy (in all women with Ro/SSA or La/SSB antibodies, not only patients with SLE), hydroxychloroquine may reduce the risk of congenital hearth block associated with neonatal lupus syndrome [121]. Toxicity and side effect are usually limited. Retinal toxicity, although a big concern for most providers particularly in young patients, is a rare event [122].

The alkylating agent **cyclophosphamide (CPM)** has strong anti-proliferative and cytotoxic effects on immune cells. It is used for severe jSLE manifestations, particularly CNS disease and proliferative lupus nephritis. Particularly in childhood, intravenous pulse therapy is preferred because of likely reduced side effects compared to oral treatment schemes [123,124]. Severe side effects and toxicity may limit the use of CPM and include opportunistic infections, secondary malignancies, renal and bladder toxicity, ovarian failure and azoospermia [116,125–127].

Mycophenolate mofetil (MMF) inhibits DNA synthesis, resulting in reduced proliferation of B and T lymphocytes. Because of its lower side-effect profile compared to CMP, MMF is used for induction and maintenance treatment in jSLE, particularly with renal involvement [128–132]. Indeed, MMF may even be superior to CMP induction therapy in African Americans and Hispanics with SLE [133]. MMF displays relatively limited side effects (gastrointestinal complaints, sometimes leukopenia and/or infections); therefore, MMF is commonly used in the treatment of jSLE and may even replace CPM in lupus nephritis induction treatment [110].

Azathioprine (AZA) is a pro-drug that on activation becomes 6-mercaptopurine, a purine analogue. This inhibits DNA synthesis and lymphocyte proliferation [134]. For induction treatment, AZA is inferior to CMP and MMF, but it can be useful as maintenance treatment in lupus nephritis [129,135,136]. AZA is metabolised by the enzyme thiopurin methyltransferase (TPMT) whose activity is subject to inter-individual variability secondary to polymorphisms in the *TMPT* gene. Although toxicity and side effects (particularly myelosuppression, hepatotoxicity, infections and pancreatitis) are generally more common in AZA compared to MMF, an individual's risk can be assessed by screening for *TPMT* polymorphisms of the TPMT enzyme activity before treatment initiation [116,134].

The folic acid analogue **methotrexate (MTX)** inhibits purine synthesis and adenosine deaminase activity. It has anti-proliferative effects on lymphocytes and modulates pro-inflammatory cytokine expression. Effects of MTX in jSLE are usually modest, and its use is limited to arthritis, skin inflammation and sometimes diseases associated with the CNS. Treatment-associated side effects include nausea, hepatotoxicity, pulmonary damage and rarely myelosuppression [137–139].

Available target-directed approaches

The presence of autoantibodies, altered clearance of immune complexes and the fact that B and T cells interact and co-stimulate one another have resulted in the introduction of B cell-directed treatment strategies in SLE. **Rituximab (RTX)**, a chimeric antibody directed against CD20, depletes circulating B cells but does not affect plasma cells [116,140,141]. While approved for the treatment of other autoimmune/inflammatory conditions, approval for SLE treatment is lacking, in part because of difficulties arising from the design of the initial study and subsequent failure for it to reach its primary end points [142,143]. However, in a number of post hoc analyses and large case collection

studies, including the paediatric age group, RTX has been demonstrated to have steroid-sparing effects, to reduce the number of flares and to be effective in otherwise treatment-resistant cases of lupus nephritis [116,143–147]. Although usually quite well-tolerated, adverse events and toxicity can occur. Allergic reactions, infections and transitory and persistent hypo- or agammaglobulinaemia have been reported [148–150].

Activation and function of B lymphocytes can be targeted by inhibition of the cytokine B lymphocyte stimulator (BLyS) or B cell activating factor (BAFF) with **belimumab**, a humanised monoclonal antibody against BLyS/BAFF. Recently, regardless of relatively mild effects in most patients, belimumab was approved for the use in aSLE excluding patients with CNS involvement or active lupus nephritis. Treatment with belimumab results in a reduction of autoantibody titres and partial B cell depletion. Thus, it may be hypothesised that belimumab may be a promising option in patients who received RTX to sustain anti-B cell effects. Clinical experience suggests that belimumab may be particularly effective in patients with high titres of autoantibodies and fatigue [102,151–154].

Future direction in the treatment of jSLE

Individualised and target-directed treatment is a central goal in modern medicine. Currently, several biologic treatment options are already available for the use in the paediatric age group. However, none of them have been sufficiently tested or approved in aSLE or jSLE. Blockade of **IL-6 signalling** with tocilizumab showed significant improvement in a small series of patients with SLE [155,156]. **Inhibition of TNF-α** is a well-established concept in paediatric rheumatology, and patients with jSLE and arthritis in particular may benefit from TNF inhibition. However, development of dsDNA antibodies and drug-induced lupus are known side effects of at least some TNF inhibitors [157–159], leading to caution in the use of TNF inhibitors in SLE. Interleukin-17 plays a central role in the development of tissue inflammation and organ damage through the chemo-attraction of additional immune cells. Effector T cells are the main source of IL-17, and IL-23 plays a role in their priming. Thus, **blockade of IL-17 or IL-23** may be beneficial in SLE. However, although IL-17- and IL-23-directed treatments have been approved for the treatment of arthritis and/or psoriasis, they have not been tested in SLE yet [3,160,161].

As mentioned above, altered expression and activation of protein kinases (CaMK4, SYK, etc.) and transcription factors (CREMα, Stat family transcription factors) promise potential as therapeutic targets in SLE. Indeed, inhibitors of **Janus kinases (JAK), Stat phosphorylation and SYK kinases** are already available and are awaiting further pre-clinical and/or clinical testing [162–164]. In some rare monogenic forms of SLE or ‘SLE-like’ disease, small case series and/or individual case reports already indicate beneficial effects of JAK inhibition [165–167].

Finally, **tissue protection** is a significant concern in inflammatory disease. While established in other inflammatory conditions (e.g. myocardial remodelling after infarctions) [168], this concept has not been appreciated in systemic autoimmune/inflammatory disorders to the same extent. However, more recently, kidney protection through ACE inhibitor treatment [169,170] and the use of antioxidants (e.g. acetylcysteine) have been discussed [171,172]. Further studies targeting tissue factors that may contribute to organ damage are urgently needed to allow sufficient and individualised prevention of irreversible damage and organ failure.

Concluding remarks

Juvenile-onset SLE is characterised by severe presentations and aggressive clinical courses with high disease activity resulting in tissue damage. In analogy to other inflammatory conditions, jSLE can (although yet incompletely) be stratified along the ‘inflammatory spectrum’ from autoinflammation to autoimmunity with monogenic autoinflammatory disorders at one end and ‘classical’ disease courses at the other end (Fig. 2). Although affecting a small subset of patients, the identification of rare monogenic forms (e.g. complement deficiencies) has improved our understanding of the more common forms of SLE. In most instances, monogenic disease manifests early in life and is characterised by an almost equal gender distribution, while adolescent patients with jSLE will most likely develop ‘classical’ multi-factorial disease. The identification of risk alleles and their increased abundance in patients with jSLE promise potential for future patient stratification and the introduction of individualised, target-directed treatment options. To achieve this, international collaborations are required to promote meaningful research in a rare but debilitating disease.

Practice Points

- In SLE, age frequently inversely correlates with disease severity, with patients with jSLE more commonly developing complications compared to those with aSLE
- Patients with early-onset SLE frequently exhibit monogenic disease and do not have detectable autoantibodies
- Patients with jSLE require higher doses of corticosteroids and immune suppressants than those with aSLE
- Harmonisation of jSLE treatment is required, and the SHARE initiative has recently developed helpful international consensus recommendations

Research priorities

- Further evaluation of genetic and environmental contributors to jSLE to allow for preventative measures and/or early interventions that may delay or even prevent disease onset
- Patient stratification based on molecular mechanisms is required for biomarker identification and evaluation, individualised risk assessment, outcome prediction and the introduction of target-directed individualised treatment
- Therapeutic targeting of molecular pathways involved in jSLE will improve patient outcomes and reduce treatment-associated side effects
- Documentation of responses to available treatment options in registries, as well as randomised controlled clinical trials, is required to assess and improve treatment in jSLE.

Conflicts of interest

No personal conflict of interest.

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