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Drug-induced lupus erythematosus: an update on drugs and mechanisms

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Abstract

Purpose of review—Rapid introduction of newly developed drugs in the absence of clear understanding of the pathophysiologic mechanisms behind drug-induced lupus erythematosus (DILE) can sometimes make DILE difficult to recognize in clinical practice. The purpose of this review is to summarize drugs most recently reported to be involved in DILE and discuss the current landscape of diverse mechanisms involved.

Recent findings—A large number of proton pump inhibitor (PPI)-induced subacute cutaneous lupus erythematosus cases have been reported, suggesting a shift over time in the spectrum of drugs implicated in DILE. Twenty-two articles comprising 29 DILE case reports published within the last 2 years are summarized in this review, including 12 (41.4%) systemic DILE. Antitumor necrosis factor (anti-TNF) drugs were the most frequently (41.7%) reported to introduce systemic DILE in these cases. Chemotherapeutic drugs were the most common drug class (54.5%) involved in subacute cutaneous lupus erythematosus, with an observed higher incidence in female patients. Enhanced neutrophil extracellular trap (NET) formation induced by procainamide and hydralazine could be a new mechanism contributing to the pathogenesis of DILE.

Summary—The list of drugs implicated in triggering DILE is expanding as new drugs with novel mechanisms of action are being developed. It is important to recognize culprit drugs that may induce lupus erythematosus, as discontinuation usually results in improvement of drug-induced manifestations. Characterizing the mechanisms involved might help better understand the cause of idiopathic autoimmunity.

Keywords

autoimmunity; drug-induced lupus erythematosus; drugs; mechanisms

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INTRODUCTION

Drug-induced lupus erythematosus (DILE) is a lupus-like autoimmune disorder, which usually occurs with chronic exposure to certain drugs (months to years) and resolves after cessation of the culprit medication. The recognition of DILE is usually attributed to Hoffman, who first reported lupus-like symptoms following sulfadiazine treatment in 1945 [1]. Later in 1985, hydrochlorothiazide was reported to induce subacute cutaneous lupus erythematosus (SCLE), which introduced the concept of drug-induced SCLE [2]. To date, over 100 drugs from more than 10 drug categories have been implicated in DILE [3,4], but only procainamide and hydralazine are regarded as two high-risk drugs with 20% [5] and 5–8% [6] risk of developing DILE, respectively. Fewer cases of DILE induced by these two drugs are being reported as their use in clinical practice declines, yet cases of DILE triggered by newer oncology drugs and biological modulators in patients with neoplastic and autoimmune diseases are expanding recently [7].

Similar to idiopathic lupus, DILE can be classified into three major forms: systemic DILE, drug-induced subacute cutaneous lupus erythematosus (DISCLE) and chronic cutaneous DILE. The latter two forms could also be defined as drug-induced cutaneous lupus erythematosus (DICLE). Systemic DILE is characterized by mild arthralgia, myalgia, serositis and constitutional symptoms [8]. DISCLE is the most common subtype with predominant skin involvement and is more frequently seen in older female patients [9]. Chronic cutaneous DILE is rare and often associated with fluorouracil compounds [10]. Discoid skin lesions are more distinctly found in chronic cutaneous DILE than the other two subtypes. Patients exposed to different drugs would develop different forms of DILE, whose clinical manifestations and serological characteristics can extremely vary.

Guidelines proposed by Borchers *et al.* in 2007 [11] and further advanced by Xiao and Chang [12], could aid to confirm a DILE diagnosis to some extent. Notably, diagnosis of DILE must be made after overall examination, medication and history review, and comprehensive evaluation of the disease during the time course following causative drug exposure and withdrawal.

Recognizing the offending drug linked to DILE is the first and utmost step in DILE management. However, DILE can be easily overlooked in clinical practice given the following factors: Delayed insidious association between drug exposure and symptom onset; Rapid introduction of new drugs developed with limitations in predicting their long-term effect during treatment; and Lack of understanding of the pathophysiologic mechanisms in DILE. This review will summarize the spectrum of drugs linked to DILE and shape a current landscape of diverse mechanisms behind DILE, with an emphasis on updating drugs and mechanisms reported within the last 2 years.

DRUGS IMPLICATED IN DRUG-INDUCED LUPUS ERYTHEMATOSUS

Drugs associated with DILE have various chemical structures such as aromatic amines, hydrazine and sulfhydryl groups, indicating that no single unifying chemical configuration accounts for DILE [13]. Meanwhile, drugs that induce DILE possess distinguishable

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distribution patterns in different forms of DILE, most of which are well summarized in a wealth of literature [14-17].

In general, drugs involved in systemic DILE are identified in four categories, which are drugs definitely, probably, possibly and recently reported to induce DILE [15,16], or they can also be grouped into high, moderate, low or very low risk categories by the risk levels. The most common drugs causing systemic DILE are hydralazine (high risk), procainamide (high risk), isoniazid (moderate risk), minocycline (very low risk) and more recently reported tumour necrosis factor-α (TNF-α) inhibitors (very low risk) [4,11,18]. Drugs most likely to trigger SCLE include hydrochlorothiazide [2], calcium channel blockers and angiotensin-converting enzyme inhibitors [16]. Drugs such as proton-pump inhibitors (PPIs) [19,20■,21■], terbinafine [22-24], immunomodulators (leflunomide [25,26], TNF-α inhibitors [27]) and chemotherapeutic agents [28-30] can also induce SCLE. A population-based matched case–control study performed by Gronhagen *et al.* [31] confirmed association between certain suspected drugs and SCLE, with significantly increased odds ratio (OR) found for terbinafine (OR 52.9), TNF-α inhibitors (OR 8.0), antiepileptics (OR 3.4) and PPIs (OR 2.9). Chronic cutaneous DILE has usually been triggered by fluorouracil compounds or their modern derivatives such as capecitabine [32,33].

Systemic DILE induced by TNF-α inhibitors is well described in the literature and received widespread attention [17,34-37], while PPI-induced SCLE is worth more awareness in clinical practice, as PPI-associated SCLE cases have been increasingly reported in a large scale. PPIs, often prescribed to treat peptic ulcer and gastroesophageal reflux disease (GERD), reduce gastric acid secretion by inhibiting the K+/H+ ATPase pump in gastric parietal cells [38]. In a case–control study reported by Gronhagen *et al.* [31], 66 out of 234 SCLE cases from Sweden were found to be associated with PPIs. Four years later, in 2014, 24 patients with PPI-induced SCLE were identified in a retrospective medical chart review of 429 CLE patients from Denmark [39]. Most recently, a study by Michaelis *et al.* [20■] revealed that, from August 2009 to May 2016 (case–control study from Sweden by Gronhangen *et al.* [31] was excluded), cases associated with PPIs were increased by 34.1% compared with all other medications, whereas reports in antihypertensive and antifungal medications decreased by 28.9 and 22.4%, respectively [20■]. A recent retrospective chart review presenting 88 cases with DISCLE identified PPIs are one of the most common culprit drug classes involved [21■]. Future efforts to investigate the mechanisms behind PPI-associated SCLE, which are currently unclear, are warranted.

SYSTEMATIC REVIEW OF DRUG-INDUCED LUPUS ERYTHEMATOSUS REPORTED IN THE LAST 2 YEARS

To investigate if there has been a shift in drugs implicated in triggering DILE within the last 2 years, we conducted a literature review. We searched PubMed for clinical case reports of DILE published from 1 January 2016 to 10 May 2018. Searches were performed with the phrase ‘drug induced lupus’. Only case reports in English full text were included. Impact factors of publishing journals were ignored. Large case series of PPI-associated DISCLE in

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this timeframe [20■,21■] were discussed separately in this article, and thus were excluded in following literature analysis.

There were 29 cases of DILE reported in 22 articles (Table 1) [35■,40-42,43■-45■,46,47,48■,49-60], among which 12 (41.4%) cases were systemic DILE, 11 (37.9%) cases were DISCLE and six (20.7%) cases were DICLE without further differentiation into DISCLE or chronic cutaneous DILE. The 12 systemic DILE cases included nine female patients (75%) and three male patients (25%), with a mean age of 44 years (range 9–91). Anti-TNF-α drugs were the most frequently reported drugs to induce systemic DILE within the last 2 years (five cases; four were associated with infliximab and one with adalimumab). Of note, two systemic DILE cases respectively associated with infliximab and carbamazepine, occurred in paediatric population, which is less frequently seen in DILE, implying DILE should also be suspected in younger patients with long-term treatment of certain medications. All three cases of systemic DILE induced by hydralazine were with negative antinuclear antibody (ANA), as opposed to serologic findings of positive serum ANA in most hydralazine-induced lupus erythematosus patients, suggesting that diagnosis of hydralazine-induced lupus erythematosus shall not be ruled out if ANA was negative.

In 11 cases of DISCLE, there were 10 female patients and one male patient, with an average age of nearly 47.6 years (range 14–69, two patients without accurate age record). The highest drug class associated with DISCLE was chemotherapeutics, with six cases reported being induced by mitotane, gemcitabine, capecitabine, annastrozole, hydroxyurea and palbociclib. Mitotane, the antifibrotic drug prifenidone, and antiretroviral HIV therapy were newly identified as triggers of DISCLE, never described in previous DISCLE cases.

IgG treatment-induced cutaneous lupus erythematosus was reported in case series with DICLE in three female patients and three male patients (average age of 55 years, range 42–67).

MECHANISMS INVOLVED IN DRUG-INDUCED LUPUS ERYTHEMATOSUS

Despite that a variety of drugs within different classes and with different mechanisms of action have been associated with DILE, most studies exploring pathogenic mechanisms in DILE have been primarily focused on procainamide and hydralazine. Several mechanisms have been proposed, including genetic predisposition, drug biotransformation and epigenetic dysregulation in different immune cells. Mechanisms underlying the pathogenesis of DILE are summarized in Fig. 1.

Genetic predisposition

It is widely accepted that genetic susceptibility plays a role in development of DILE. Drugs such as procainamide, hydralazine and isoniazid contain a structure of aromatic amines or hydrazines, and are predominantly metabolized by acetylation utilizing N-acetyltransferase enzymes [13]. The majority of patients with procainamide or hydralazine-induced lupus erythematosus are found to be slow acetylators, who are more prone for autoantibodies accumulation after exposure to procainamide or hydralazine compared with fast acetylators

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[61-63]. Interestingly, the risk of developing DILE is about the same in patients with the same serum concentration of procainamide, regardless of the acetylator phenotype [64]. Unlike the findings in procainamide and hydralazine, isoniazid-implicated DILE seems to be less related to acetylator phenotype though isoniazid is also metabolized by acetylation [65,66]. In addition, associations between DILE occurrence and certain human leukocyte antigen (HLA), like HLA-DR2, HLA-DR3, class III C4A and C4B null complement alleles, have been suggested by some studies, but these findings were not always consistent [67-69]. The complement system might also play a role in the pathogenic mechanisms of DILE. Sim *et al.* [70,71] reported that hydralazine, penicillamine, isoniazid and metabolic products of procainamide could be potent inhibitors of the covalent binding reaction of complement component C4, which might inhibit the activation of complement component C3 in the classical complement pathway, hindering the clearance of immune complexes.

Drug biotransformation

Procainamide is oxidized by activated neutrophils resulting in the production of a toxic metabolite called procainamide hydroxylamine (PAHA). PAHA, together with myeloperoxidase (MPO) and reactive oxygen species released during oxidative metabolism of procainamide, contribute to the cytotoxicity [72-74]. In addition, autoantibodies against myeloperoxidase were found in the serum of DILE patients, which indirectly supported a role of myeloperoxidase-mediated metabolism in the development of DILE [75]. Other drugs, including hydralazine, quinidine, phenytoin, sulfone, penicillamine, chlorpromazine and isoniazid, undergo the biotransformation similar to procainamide, which generates reactive metabolites triggering DILE. On the contrary, drugs in small molecules can bind to proteins, a process called haptenization, then stimulate immune responses [14].

Epigenetic dysregulation in adaptive immune cells and other mechanisms of autoreactivity

Biotransformed culprit drugs or their metabolites have been reported to alter epigenetic properties of immune cells then ultimately lead to DILE. In early epigenetic mechanism studies of DILE, several mechanisms involving T cells or B cells were put forward. Hydralazine and procainamide were shown to inhibit T cell DNA methylation [76]. More specifically, procainamide acts as a competitive DNA methyltransferase inhibitor, while hydralazine prevents induction of DNA methyltransferase by inhibiting ERK signalling pathway [77,78]. DNA hypomethylation in T cells results in increased lymphocyte function associated antigen 1 (LFA-1) expression, which consequently induces autoreactivity. Adoptive transfer of these autoreactive T cells into mice caused a lupus-like disease [79,80].

Other studies suggest that PAHA, a procainamide metabolite, interferes with T cell central tolerance, resulting in the production of autoreactive T cells possibly triggering autoimmunity [81,82]. Similarly, hydralazine is able to subvert B cell tolerance and contributes to the generation of pathogenic autoreactivity by disrupting receptor editing via inhibition of the ERK signalling pathway [83]. Quinidine and procainamide at therapeutic range concentrations were reported to inhibit uptake of apoptotic thymocytes by macrophages, which could render these accumulated cells a source for uncontrolled uptake of self-antigens in certain settings [84].

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Sontheimer *et al.* [85] discussed an evidence likely pertaining to the pathogenesis of DISCLE, pointing out that drugs involved in DISCLE are capable of causing photosensitivity further amplifying cutaneous immune responses that give rise to an increase in local type I interferon production and downstream molecules such as chemokine (C-X-C motif) ligand 9 (CXCL9).

Role of NETosis and the innate immune system

More recently, a role for NETosis, a unique mechanism of neutrophil cell death, has been described in DILE. Neutrophil extracellular traps (NETs) are weblike structure containing nuclear DNA and cytosolic proteins secreted by activated neutrophils after specific stimuli [86]. Autoantigen-rich nuclear material and granular proteins can be externalized during NETosis, which subsequently induces autoimmunity [87]. In 2018, Irizarry-Caro *et al.* [88■■] described that procainamide and hydralazine, known to induce lupus erythematosus, promote NET formation via triggering neutrophil muscarinic receptors and increasing intracellular calcium flux *in vitro*, respectively, demonstrating the contribution of innate immune responses in the development of DILE. Interestingly, it was also pointed out in the same article that minocycline and clozapine, another two drugs less commonly associated with DILE, do not induce NETosis. Additional future experiments both *in vitro* and *in vivo* are suggested to confirm and characterize this mechanism of drug-induced NETosis in DILE [89■].

CONCLUSION

This article summarizes the current knowledge in DILE, with an emphasis on recent developments in the field. We performed a systematic review for new cases of DILE reported over the last 2 years to highlight the observed shift in DILE-implicated drugs over time, though publication bias is an obvious limitation. This analysis highlighted drugs recently described to trigger DILE and rare cases of DILE in paediatric patients. DILE associated with PPIs and anti-TNF therapies might be more commonly encountered in current rheumatology practices than less used drugs such as procainamide and hydralazine. We expect a plethora of DILE reports in the future with the increasing use and expanding targets of immunotherapy in cancer patients, including check-point inhibitors.

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KEY POINTS

- New DILE cases published within the last 2-year period in PubMed database are summarized in this review.
- DISCLE associated with PPI and chemotherapeutic drugs deserves more attention owing to increasing numbers of case reports.
- Enhanced NET formation could be a new mechanism contributing to the pathogenesis of DILE.

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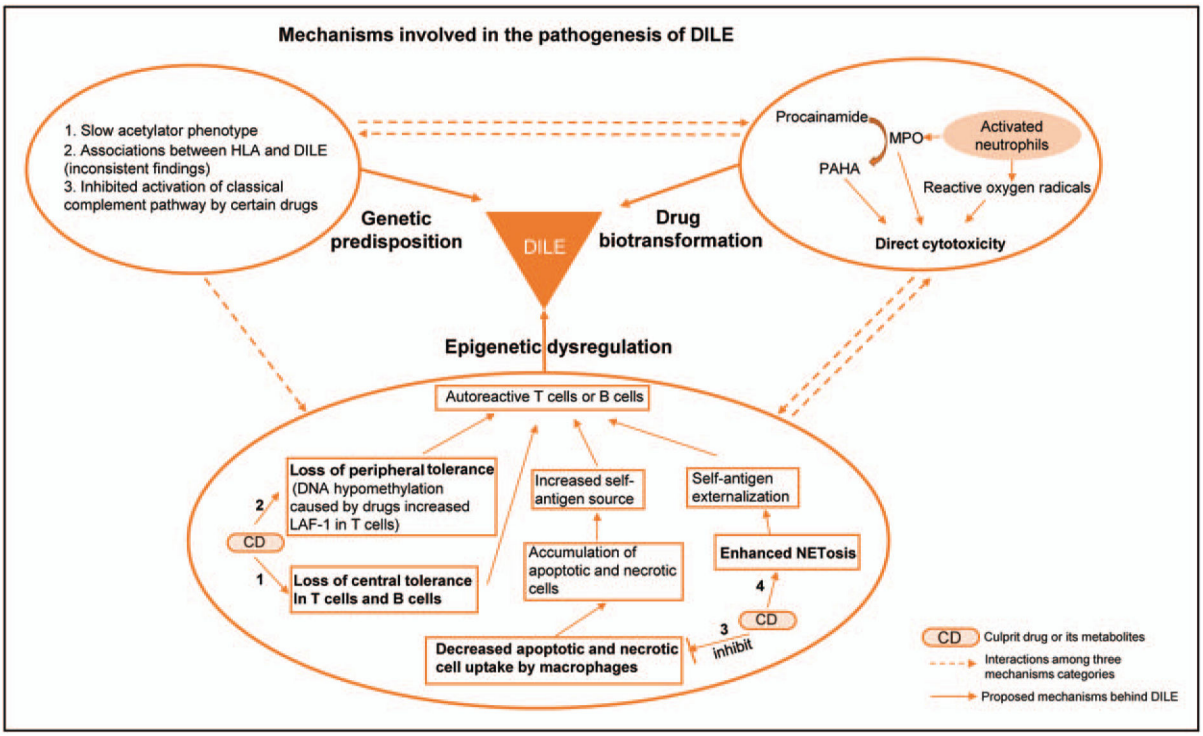

FIGURE 1.

Mechanisms involved in the pathogenesis of drug-induced lupus erythematosus. Genetic predisposition, drug biotransformation and epigenetic dysregulation are three important components of current proposed pathogenic mechanisms of DILE. Instead of working independently, these factors are likely to interact with each other to cause DILE. Genetic predisposition: Studies revealing genetic predisposition could be summarized in three main aspects, listed in the left upper circle. Biotransformation: Procainamide undergoes neutrophil-mediated oxidative metabolism to produce procainamide hydroxylamine (PAHA). PAHA, myeloperoxidase (MPO), and reactive oxygen species contribute to direct cytotoxicity. Epigenetic dysregulation: Drugs and some drug metabolites exert epigenetic dysregulation on T cells and B cells (1,2), macrophages (3) and neutrophils (4), which eventually leads to autoreactive T cell and B cell generation, triggering DILE.

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Table 1.

Summary of 29 case reports of DILE reported in the literature published on PubMed (January 2016–May 2018)

# Case	Sex/age (years)	Drug (doses)	Drug categories	DILE forms	Latency	Autoantibodies	Outcome symptom after drug removal	Ref.
1	M/39	Clozapine (25 mg/day)	Antipsychotics	Systemic DILE	8 days	ANA+	Remission	[40]
2	M/91	Minocycline (200 mg/day)	Antibiotics	Systemic DILE	2 years	ANA+, dsDNA+	Improvement	[41]
3	F/62	Trimethoprim/sulfamethoxazole	Antibiotics	Systemic DILE	1 week	ANA+, histone+, dsDNA−, SSA−, SSB−	Remission	[42]
4	M/21	Hydralazine (50mg TID)	Antihypersentsitives	Systemic DILE	2 months	histone+, ANA−	Remission	[43■]
5	F/36	Hydralazine (50mg TID)	Antihypersentsitives	Systemic DILE	18 months	histone+, dsDNA−, ANA−, SSA−, SSB−,	Improvement	[44■]
6	F/35	Hydralazine (10 mg, q8h)	Antihypersentsitives	Systemic DILE	4 weeks	histone+, ANA−, dsDNA−	Improvement	[45■]
7	F/14	Infliximab	Immunomodulators: TNF-α inhibitors	Systemic DILE	7 months	ANA+, dsDNA+	Remission	[35■]
8	F/64	Infliximab	Immunomodulators: TNF-α inhibitors	Systemic DILE	11 months	histone+, dsDNA−ANA+,	Remission	[35■]
9	F/67	Infliximab	Immunomodulators: TNF-α inhibitors	Systemic DILE	3 months	ANA+, antidsDNA	Remission	[35■]
10	F/48	Infliximab	Immunomodulators: TNF-α inhibitors	Systemic DILE	3 years	ANA+, dsDNA+	Remission	[46]
11	F/42	Adalimumab	Immunomodulators: TNF-α inhibitors	Systemic DILE	2 years	ANA+	Improvement	[47]
12	F/9	Carbamazepine (200 mg/day)	Anticonvulsives	Systemic DILE	3 years	ANA+, histone+	Remission	[48■]
13	F/ in 60s	Mitotane (300 mg, TID)	Chemotherapeutics	DISCLE	1 month	ANA−, SSA−, SSB−	Remission	[49]
14	M/42	Interferon alpha-2a	Immunomodulators	DISCLE	< 24 weeks	ANA−, histone−, ds-DNA−,	n.d	[50]
15	F/63	Gemcitabine	Chemotherapeutics	DISCLE	2 weeks	SSA−, SSB−, histone−	Remission	[51]
16	F/50	Leflunomide (20 mg/day)	Immunomodulators	DISCLE	3 years	ANA+, histone ++, SSA+, SSB−, dsDNA−	Improvement	[52]
17	F/67	Capecitabine	Chemotherapeutics	DISCLE	6 weeks	ANA+, SSA+	Improvement	[53]
18	F/54	Pirfenidone	Novel Antifibrosis drug	DISCLE	8 weeks	dsDNA+, ANA histone−, SSA−, SSB−	Improvement	[54]
19	F/ 69	Anastrozole	Chemotherapeutics	DISCLE	16 months	SSA+, ANA−, SSB−	Improvement	[55]
20	F/ 14	Hydroxyurea (1500 mg/day)	Chemotherapeutics	DISCLE	5 years	ANA+, histone+, SSA−, SSB−	Improvement	[56]
21	F/ 50s	Palbociclib	Chemotherapeutics agents	DISCLE	2 months	ANA+, dsDNA−, SSA−, SSB−	Remission	[57]

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# Case	Sex/age (years)	Drug (doses)	Drug categories	DILE forms	Latency	Autoantibodies	Outcome symptom after drug removal	Ref.
22	F/ 35	Emtricitabine, rilpivirine, tenofovir disoproxil fumarate (combination)	Antiretroviral Therapy	DISCLE	3 years	ANA+, dsDNA+, histone+	Remission	[58]
23	F/ 34	Terbinafine (topical cream)	Antifungal drugs	DISCLE	A number of years	ANA+, SSA+	Remission	[59]
24	F/62	IVIg (1.3 g/kg/month)	Immunomodulators	DICLE	6 weeks	n.d	Improvement	[60]
25	F/45	IVIg (1.2 g/kg/month)	Immunomodulators	DICLE	6 months	n.d	Improvement	[60]
26	M/42	IVIg (1.3 g/kg/month)	Immunomodulators	DICLE	2 weeks	SSA+	Improvement	[60]
27	F/67	IVIg (1 g/kg/month)	Immunomodulators	DICLE	<3 weeks	ENA+	Improvement	[60]
28	M/54	SCIg (1.8 g/kg/month)	Immunomodulators	DICLE	22 months	ANA+, ENA−	Remission	[60]
29	M/60	IVIg (0.8 g/kg/month)	Immunomodulators	DICLE	6 months	ENA+	Improvement	[60]

ANA, antinuclear antibodies; dsDNA, antidouble-stranded DNA; ENA, extractable nuclear antigen antibodies; histone, antihistone antibodies; IVIg, intravenous immunoglobulin; n.d, not determined; SCIg, subcutaneous immunoglobulin; SSA, anti-Ro/SSA; SSB, anti-La/SSB.

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