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REVIEW

Drug-induced lupus erythematosus

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Abstract Drug-induced lupus erythematosus (DILE) is defined as a lupus-like syndrome temporally related to continuous drug exposure which resolves after discontinuation of the offending drug. There are currently no standard diagnostic criteria for DILE and the pathomechanisms are still unclear. Similarly to idiopathic lupus, DILE can be diveded into systemic (SLE), subacute cutaneous (SCLE) and chronic cutaneous lupus (CCLE). Systemic DILE is characterized by typical lupus-like symptoms including skin signs, usually mild systemic involvement and a typical laboratory profile with positive antinuclear and anti-histone antibodies, while anti-double strand (ds) DNA and anti-extractable nuclear antigens antibodies are rare. High risk drugs include hydralazine, procainamide and isoniazid. Drug-induced SCLE is very similar to idiopathic SCLE in terms of clinical and serologic characteristic, and it is more common than the systemic form of DILE. Drugs associated with SCLE include calcium channel blockers, angiotensin-converting enzyme inhibitors, interferons, thiazide diuretics and terbinafine. Drug-induced CCLE is very rarely reported in the literature and usually refers to fluorouracile agents or non steroidal anti-inflammatory drugs. Recently, cases of DILE have been reported with anti-TNFα agents. These cases present with disparate clinical features including arthritis/arthralgia, skin rash, serositis, cytopenia and variable laboratory abnormalities. DILE to anti-TNFα agents differs in several ways to classic DILE. The incidence of rashes is higher compared to classical systemic DILE. In most cases of classic DILE visceral involvement is rare, whereas several cases of anti-TNFα DILE with evidence of renal disease have been reported. Low serum complement levels as well as anti-extractable nuclear antigen antibodies and anti-dsDNA antibodies are rarely present in classic DILE, whereas they are reported in half the cases of anti-TNFα DILE; in contrast, anti-histone antibodies are described in classic DILE more often than in anti-TNFα DILE. Recognition of DILE in patients receiving anti-TNFα therapy can be difficult due to the symptoms of their underlying disease. A temporal association (months to years) of the offending drug with characteristic or suggestive symptoms, and resolution of symptoms on drug withdrawal is the best evidence for this diagnosis of DILE.

Keywords Drug-induced lupus erythematosus · Anti-TNFα-induced lupus · Antinuclear antibodies (ANA) · Anti-histone antibodies · Subacute cutaneous drug-induced lupus (SCLE) · Drug reactions

Introduction

A wide range of pharmacologic agents have the potential to induce toxicities, some of which mimic primary rheumatic or autoimmune syndromes [10, 33]. This review focuses on the characteristics of lupus erythematosus induced by commonly used drugs, including biologic agents.

Systemic lupus erythematosus (SLE) is an autoimmune connective-tissue disorder with a wide range of clinical features, significant morbidity and mortality, and an etiology that has not yet been fully described but believed to be multifactorial. The prevalence is about 15–40 per 100,000 persons and the incidence is between 2 and 8 per 100,000

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person-year. It is more common in women than in men (ratio of 9:1), and in those of African descent (prevalence of more than 200 per 100,000 persons), with a peak age of onset typically between 25 and 45 years [9, 11, 15, 26, 35, 40]. A review of 32 studies has summarised the incidence and prevalence of SLE in several countries and documented the increased disease burden, especially in non-white populations. Although there is wide variation in the prevalence of lupus worldwide, the highest prevalences were reported in Italy, Spain, Martinique, and UK Afro-Caribbean population [20].

Drug-induced lupus erythematosus (DILE) is a lupus-like syndrome temporally related to continuous drug exposure (from 1 month to as long as over a decade) which resolves after discontinuation of the drug. There are currently no standard diagnostic criteria for DILE, and in many cases patients with DILE do not satisfy the American College of Rheumatology criteria for SLE. The range of symptoms which are typically positive and could be employed as diagnostic criteria is confined to four (arthritis, serositis, anti-nuclear and antihistone antibodies); in addition the symptoms must have begun after initiation of the treatment with a drug and must resolve on discontinuation of that drug treatment [17, 39]. It has been estimated that up to 10% of SLE cases are drug induced and that 15,000–30,000 cases of DILE occur in the United States every year. DILE shows less predilection for females and African Americans, and generally affects older patients than idiopathic SLE. Similarly to idiopathic lupus, DILE can be diveded into SLE, subacute cutaneous (SCLE) and chronic cutaneous lupus (CCLE).

Drugs implicated in DILE

Usually, years of exposure to the offending drug are required for the development of DILE, which resolves within weeks of drug discontinuation. Instead exposure to low levels of certain drugs (antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsivant and estrogens) for relatively short periods may exacerbate underlying SLE, which remains or recurs after withdrawal of the implicated drug [39]. Over 80 drugs have been implicated in DILE, and the number is increasing constantly [17, 31, 39]. The evidence for a causal association is convincing for hydralazine, procainamide, isoniazid, methyldopa, quinidine, minocycline and chlorpromazine (Table 1). The highest risk drugs are procainamide and hydralazine, with approximately 20% incidence for procainamide and 5–8% for hydralazine (particularly for slow acetylator and HLA-DR4 positive subjects) during 1 year of therapy at currently used doses. The risk for developing lupus-like disease for the remainder of the drugs is much lower, considerably less than 1% of treated patients [31, 39]. Quinidine can be considered moderate risk. Quinidine-induced lupus seems to be associated with decreased levels of complement, which is unusual in classic DILE. Methyldopa, isoniazid, chlorpromazine and minocycline are relatively low risk drugs. Two large studies have confirmed the association between SLE and minocycline, a semisynthetic tetracycline frequently used in the treatment of acne vulgaris [25, 36]. Minocycline-induced DILE is relatively uncommon and is characterized by typical DILE features but also by unusual cutaneous features (Raynaud's, polyarteritis nodosa, erythema nodosum), hepatic manifestations and is rarely associated with positive anti-histone antibodies. A recent controlled large study has shown a strong relationship between duration of exposure to minocycline (>300 days) and total dose (>50,000 mg) and lupus erythematosus. It has been estimated that those who used this antibiotic had a more than threefold increased risk of developing lupus erythematosus, with a rate of 16.2 cases per 100,000 person-year of exposure to minocycline. It has also been shown that women are not much more likely to develop minocycline-DILE than men, that there is not statistical interaction between age and minocycline use, and that other tetracyclines do not carry any risk of inducing DILE [25]. The remaining drugs carry a very low risk based on the paucity of case reports in the literature. SLE associated with interferon-α therapy has also been reported [22]. These cases were distinct from lupus induced by other drugs with a high frequency of mucocutaneous and renal involvement, and anti-dsDNA antibodies developing in 50% of cases. Arthralgia was also common and often occurring as the first symptom. An increasing number of reports suggest that long-term exposure to statins may trigger lupus erythematosus in the form of SLE or SCLE [34]. However, as for minocycline, considering the large number of patients treated with these lipid-lowering agents, the risk seems to be very low. There is growing evidence that anti-TNFα therapy causes lupus. In a French national survey including almost all patients treated with anti-TNFα therapy, the incidence of DILE meeting ACR criteria for the diagnosis of SLE was 0.19 and 0.18% for patients exposed to infliximab and etanercept, respectively [24].

Mechanisms of DILE

The pathogenic mechanisms of DILE remain unclear, and available data strongly suggest that there is no single mechanism responsible for the induction of autoimmunity by all lupus-inducing drugs. Slow acetylator status, HLA-DR4, HLA-DR2, HLA-DR3 and complement factor C4 null allele are risk factors for DILE [17]. DILE is unlike typical drug hypersensitivity reactions for several reasons: there is no

Table 1 Drugs implicated in DILE (Adapted from ref 4and 33)

	High risk	Moderate risk	Low risk	Very low risk
Antiarrhythmics	Procainamide (15–20%)	Quinidine (<1%)		Disopyramide, Propafenone
Antihypertensives	Hydralazine (5–8%)		Methyldopa, Captopril, Acebutol	Clonidine, Enalapril, Labetalol, Minoxidil, Pindolol, Prazosin
Antipsychotics			Chlorpromazine	Chlorprothixene, Lithium carbonate, Phenelzine
Antibiotics			Isoniazid, Minocycline	Nitrofurantoin
Anticonvulsants			Carbamazepine	Ethosuximide, Phenytoin, Primidone, Trimethadione
Antithyroidals			Propylthiouracil	
Anti-inflammatories			D-Penicillamine, Sulfasalazine	Phenylbutazone
Diuretics				Chlorthalidone, Hydrochlorothiazide
Anticholesterolemics				Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin
Biologicals				Etanercept, Infliximab, Adalimumab, IFN-α, IL-2

evidence of drug-specific T cells or antibodies, and the target autoantigens are not directly affected by the inducing drug; months or years of exposure are required before DILE occurs with the development of DILE depending on the cumulative drug dose; and finally, the recurrence of symptoms after rechallenge generally takes 1–2 days, indicating the absence of immune sensitization to the drugs [23, 39].

Several studies showed that the lupus-inducing drugs are readly oxidized to reactive citotoxic species by activated leucocytes. Formation of reactive metabolites with similar characteristics may explain why chemically and pharmacologically diverse drugs can induce a similar clinical condition and they are strong candidates for triggering autoimmunity. There are many hypothesis as to what these metabolites bind to and what happens next [32, 39]: Haptens or altered self antigens: this concept is based on the presumed capacity of reactive metabolites to form stable complexes with self-macromolecules or to directly stimulate lymphocytes. Autoantibodies might develop if an immune response to the drug in the form of a hapten or to a self-antigen altered by the drug induces antibodies that cross-react with or cause spreading of the immune response to native self-macromolecules. Although there are data suggesting that drugs or their reactive metabolites induce specific T cell responses, apparently to altered self proteins, there is no convincing evidence that this results in autoimmunity. Citotoxicity and apoptosis*:* reactive metabolites exhibit considerable citotoxicity so they could directly cause cell death. However, it cannot by itself explain the autoimmune features of DILE. There are indications that the citotoxicity of reactive metabolites involves apoptosis rather than necrosis and apoptotic cell bodies contain high concentrations of autoantigens (abnormal macromolecular forms or unusual peptides) that may induce immune responses [40]. Distruption of central immune tolerance: murine models have shown that intra-thymic injections of these reactive metabolites interfered with the establishment of tolerance to endogenous self-antigens that are normally presented by the MHC on thymic epithelial cells during the positive selection of thymocytes. This resulted in the export of autoreactive T cells to the periphery where they provided T-helper cell function to B cells with potential to produce autoantibodies. Altered T cell function due to hypomethylation: methylation of DNA is an important mechanism for regulating gene expression. Drugs as procainamide or hydralazine are inhibitor of DNA methyltransferase. Hypomethylation of T cell DNA alters T cell gene expression profiles and T cell function, e.g. is associated with increased expression of lymphocyte functional antigen-1, an adhesion molecule that helps stabilize the interaction between T cells and antigen presenting cells (APC). Longer contact between the T cell receptor on T cells and mayor histocompatibility complex (MHC) molecules on APC may promote T cell activation upon contact with low affinity self-antigens.

The mechanisms by which anti-TNFα therapy induces lupus remain unclear but are likely to differ from classic DILE. One hypothesis could be the ability of the therapeutic anti-TNFα antibodies to bind to cell surface TNFα and to induce apoptotic cell death. This would then result in the release of antinucleosomal autoantigens and the induction of anti-dsDNA antibodies [7]. Another hypothesis is that the suppression of the T-helper type 1 response by TNF blockers could favour a T-helper type 2 response leading to

SLE [5]. A final hypothesis is the role of bacterial infections which are increased with TNF blockers and are also powerful stimulants leading to polyclonal B-lymphocyte activation and autoantibody production [6].

Clinical signs and symptoms of DILE

Although DILE and idiopathic SLE cannot be solely differentiated on the basis of the signs and symptoms, the usual clinical picture is somewhat different and the clinical abnormalities in DILE are usually milder than those seen in idiopathic SLE.

Systemic DILE is rare and it is characterized by typical general lupus-like symptoms. Arthralgia is considered very characteristic, present in 90% of the patients, and is often the only clinical symptom. Myalgia is also typical and present in about 50%. Other signs include fever, pleurisy and pericarditis. Central nervous system and renal involvement is usually absent. Skin changes are generally less frequent and milder in DILE compared to SLE, with photosensitivity, purpura and erythema nodosum more frequent in DILE, and malar rash, alopecia, discoid lesions and oral ulcers rather rare. Laboratory findings may include mild cytopenia, an elevated erythrocyte sedimentation rate and the presence of antinuclear antibodies (ANA) with a homogenous pattern as the autoantibodies target predominantly nuclear histone proteins. Anti-histone antibodies are positive in up to 95% of DILE and their titre, together with ANA, gradually declines with the resolution of DILE. However, anti-histone antibodies are not pathognomonic of DILE as they are found in SLE and other rheumatic diseases such as scleroderma, rheumatoid arthritis and undifferentiated connective tissue disease. In contrast to idiopathic SLE, anti-double strand DNA (dsDNA) antibodies and anti-extractable nuclear antigens (ENA) are rare in DILE and ANA are not complement-fixing. Drug-induced SCLE is very similar to idiopathic SCLE in terms of both clinical and serologic characteristics, and is more common than the systemic form [38]. Many cases of idiopathic SCLE may be drug-induced. It presents with the typical photosensitive symmetric, nonscarring annular polycyclic or papulosquamous lesions, usually on sun-exposed areas. The immunological profile include the frequent presence of anti-Ro/SSA and/or anti-La/SSB, together with ANA and anti-histone antibodies. Drugs associated with SCLE include many commonly used drugs, particularly cardiovascular drugs such as angiotensin-converting enzyme inhibitors, calcium channel blockers, thiazide diuretics (Table 2). Part of the drugs associated to SCLE are photosensitizing agents, but no studies have addressed whether photo-patch testing with the culprit drug in these patients is of diagnostic value, and whether it results in an eczematous or lichenoid type reaction. Drug-induced CCLE is very rare and usually refers to fluorouracile agents or NSAIDs.

Table 2 Drugs associated with subacute cutaneous DILE

Thiazidic diuretics	Hydrochlorothiazide
Calcium channel blockers	Diltiazem, Verapamil, Nifedipine
ACE inhibitors	Cilazapril
Beta blockers	Acebutolol
Ticlopidine	
Statins	
Biologics	Efalizumab, Etanercept, Infliximab
Tamoxifen	
Antifungals	Terbinafine, Griseofulvin
NSAIDs	Piroxicam, Naproxene
Antidepressant	Bupropion
Proton pump inhibitors	Lansoprazole
Interferon beta	
Leflunomide	
Docexatel	

DILE due to anti-TNFα agents

TNFα-targeted therapies are increasingly used for a rapidly expanding number of rheumatic and autoimmune diseases as rheumatoid arthritis, psoriatic arthritis, spondyloarthropathies and inflammatory bowel disease [4, 14], and they have been involved in the induction of rare cases of lupus-like syndromes. Given the high number of patients exposed to these drugs, the occurrence of anti-TNFα DILE is relatively rare. Most of the case reports of DILE secondary to anti-TNFα therapy occurred in patients receiving etanercept or infliximab [29, 34]. The only few cases associated with adalimubab [1, 29] may simply reflect fewer years of patient exposure compared to infliximab or etanercept.

The most typical features of these patients were, as in classic DILE, general symptoms, musculo-skeletal manifestations, lupus-like cutaneous features and positive autoantibodies. However, DILE secondary to anti-TNFα agents differed in several ways to classic DILE in clinical signs and symptoms (Table 3). The incidence of skin changes is higher whereas myalgia is rarer, and the incidence of fever is similar. Cutaneous involvement includes malar rash, photosensitivity, SCLE and CCLE lesions. Clinically, SCLE and CCLE skin lesions were more frequently observed in patients who received etanercept (44 vs. 12%), whereas serositis was more frequently observed in those treated with infliximab (24 vs. 3%) [16]. In most cases of classic DILE visceral involvement is rare; in contrast, renal disease has been observed in several cases of anti-TNFα

Table 3 Characteristics of idiopathic, classical DILE and anti-TNFα DILE

Characteristics	Idiopathic SLE	Classic DILE	Anti-TNFα DILE
Age of onset	Child-bearing age	Older	Older
Female : male	9:1	1:1	5:1
Clinical course	Chronic, relapsing	Remits with drug cessatation	Remits with drug cessation
Symptom severity	Mild to severe	Generally mild	Generally mild
Fever	80%	40%	50%
Myalgia	80%	44–57%	29%
Arthalgia/arthritis	80%	18–63%	31–51%
Serositis	20–40%	5–50%	3–24%
Mayor organ involvement (renal and neurologic)	Common	Rare	Rare; 7% nephropathy
Cutaneous involvement	54–70% (Malar, discoid rash, oral ulcers, photosensitivity)	<5–25% (Photosensitivity, purpura)	67% (Rash)
ANA	>99%	>99%	>99%
ENA	Up to 30%	<5%	Up to 10%
Anti-histone Ab	Up to 50%	Up to 95%	Up to 57%
Anti-dsDNA Ab	50%–70%	<5%	70%–90%
Hypocomplementemia	51%	<1%	59%

DILE [2, 16, 41]. Laboratory abnormalities in anti-TNFα DILE differ markedly from classic DILE. Anti-dsDNA antibodies, predominantly IgM or IgM/IgA isotypes, occur more frequently in anti-TNFα DILE than in classic DILE and anti-histone antibodies are more common in classic DILE than in anti-TNFα DILE. Low serum complement levels and ENA are rarely associated with classic DILE, whereas they are reported in half the cases of anti-TNFα DILE. As in classic DILE, ANA's titre is frequently high.

In contrast to the rarity of anti-TNFα DILE reported so far, induction of ANA and/or anti-DNA antibodies in patients treated with anti-TNFα therapy is very common and well established [3, 8, 12, 13, 18, 19, 21, 27, 28, 30, 37]. In most series 20–30% of patients develop low-medium ANA titre or show a two- to four-fold increase in the ANA titre compared to baseline. Moreover, 4–60% of patients develop anti-dsDNA antibodies. It also appears that ANA are more frequently observed in patients treated with infliximab compared to those receiving etanercept [8, 27]. Adalimumab administration is also associated with the development of ANA and anti-dsDNA antibodies [18]. Finally, use of anti-TNFα agents is associated with the emergence of other autoantibodies such as anti-cardiolipin antibodies. Recognition of DILE in patients receiving anti-TNFα therapy can be difficult due to the symptoms of their underlying disease and due to the wide range of clinical manifestation. A temporal association of the offending drug with characteristic or suggestive symptoms, and resolution of symptoms on withdrawal of the drug is the best evidence for this diagnosis.

Management of DILE

It is important a careful clinical and immunologic evaluation upon starting lupus-inducing drugs, and not overlook pre-existing features suggestive of an underlying autoimmune disease. There is general agreement that laboratory abnormalities are not pathognomonic so that discontinuation of the drug treatment is indicated only when symptoms develop in a patient who is taking a drug that is known to induce a lupus-like syndrome. The symptoms abate usually over a period of weeks; however the recovery can be relatively slow and may require a year. Also ANA and anti-histone titres gradually decline with the resolution of DILE. Rechallenge results in a recurrence and it is to be avoided. The symptoms can be controlled by administering NSAIDs while corticosteroids and other immunosuppressant agents should be reserved for patients with organ damage.

Conclusions

DILE is a reversible lupus-like condition due to exposure to an increasing number of drugs. Its symptoms are generally mild to moderate with resolution of both clinical and serological features over time following drug cessation. The possibility of DILE should always be considered because of the reversibility of the lesions and thus the importance of early diagnosis. Although DILE is relatively uncommon, it may represent an interesting opportunity to understand the

pathophysiology lupus erythematosus and other autoimmune disorders.

Conflict of interest statement The authors have no potential conflict of interest.

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