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Diagnosis and classification of drug-induced autoimmunity (DIA)

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ABSTRACT

Since sulfadiazine associated lupus-like symptoms were first described in 1945, certain drugs have been reported to interfere with the immune system and induce a series of autoimmune diseases (named drug-induced autoimmunity, DIA), exemplified by systemic lupus erythematosus (SLE). Among the drugs, procainamide and hydralazine are considered to be associated with the highest risk for developing lupus, while quinidine has a moderate risk, and all other drugs have low or very low risk. More recently, drug-induced lupus has been associated with the use of newer biological modulators, such as tumor necrosis factor (TNF)-alpha inhibitors and cytokines. In addition to lupus, other major autoimmune diseases, including vasculitis and arthritis, have also been associated with drugs. Because resolution of symptoms generally occurs after cessation of the offending drugs, early diagnosis is crucial for treatment strategy and improvement of prognosis. Unfortunately, it is difficult to establish standardized criteria for DIA diagnosis. Diagnosis of DIA requires identification of a temporal relationship between drug administration and the onset of symptoms, but the relative risk with respect to dose and duration for each drug has rarely been determined. DIA is affected by multiple genetic and environmental factors, leading to difficulties in establishing a list of global clinical features that are characteristic of most or all DIA patients. Moreover, the distinction between authentic DIA and unmasking of a latent autoimmune disease also poses challenges. In this review, we summarize the highly variable clinical features and laboratory findings of DIA, with an emphasis on the diagnostic criteria.

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1. Introduction

Drug-induced autoimmunity (DIA) is an immune related drug reaction temporally related to continuous drug exposure which resolves after withdrawal of the offending drug. DIA is idiosyncratic, falling into the category of 'Type B' drug reactions. These are reactions that are unpredictable, and many factors (genetic susceptibility, the patient's overall health, any concurrent illness including that for which the drug is being used to treat, interaction with other drugs, foods, environmental factors) may contribute to their development. This is in contrast to 'Type A' reactions, which are primarily drug dependent and reproducible in the majority of patients, and generally include agents with known biochemical or biophysiological effects.

One of the most common autoimmune diseases is systemic lupus erythematosus (SLE), which occurs at a rate of between 15,000 and 30,000 cases per year. Approximately 10% of SLE cases can be related to drugs [1]. Drug-induced lupus (DIL) is the most

common form of an iatrogenic induced autoimmune disease. Drugs have also been implicated in other autoimmune diseases, including rheumatoid arthritis, polymyositis, dermatomyositis, myasthenia gravis, pemphigus, pemphigoid, membranous glomerulonephritis, autoimmune hepatitis, autoimmune thyroiditis, autoimmune hemolytic anemia, Sjogren's syndrome and scleroderma [2].

Restricted by the lack of an in-depth understanding of the mechanisms of DIA, our ability to treat DIL is somewhat limited. Early recognition of a role of drugs upon presentation is critical, because the early termination of inciting drugs substantially improves prognosis. The purpose of this review is to summarize the history, epidemiology, clinical features and laboratory abnormalities of drug-induced autoimmunity, and to discuss the diagnosis criteria of DIA.

2. History and epidemiology

SLE-like symptoms in sulfadiazine users were first described in 1945. Hydralazine was reported to induce a syndrome mimicking lupus in 1953, just two years after its introduction [3]. To date more than 100 drugs spanning over ten drug categories have been

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Table 1
Drugs associated with lupus.

Category	Subcategory	Drug	Action	DIA effect	Reference
Allergy, immunology and rheumatology drugs	Antihistamines	Cimetidine	H2 receptor antagonist	Autoimmune hemolytic anemia	[19]
		Cinnarizine	H1 receptor antagonist	DIL	[20]
	Antiinflammatories	Benoxaprofen	NSAID	Vasculitis	[21]
		Ibuprofen	NSAID	Autoimmune hemolytic anemia	[22]
		Mesalazine	5-Aminosalicylic acid	DIL, idiosyncratic thrombocytopenia, autoimmune hepatitis	[23–25]
		Para-amino salicylic acid	4-Aminosalicylic acid	Autoimmune hemolytic anemia	[26]
		Sulindac	NSAID	Autoimmune hemolytic anemia	[27,28]
		Sulfasalazine	5-Aminosalicylic acid	DIL, vasculitis	[29,30]
		Tolmetin	NSAID	Autoimmune hemolytic anemia	[31]
	Biologicals	Adalimumab	TNF-inhibitor	DIL, vasculitis, antiphospholipid syndrome	[32–34]
		Etanercept	TNF-inhibitor	DIL, vasculitis, granulomatous lung disease, sarcoidosis, Henoch–Schönlein purpura	[35–39]
		Golimumab	TNF-inhibitor	SCLE	[10]
		Infliximab	TNF-inhibitor	DIL, vasculitis, interstitial lung disease, inflammatory myopathies	[32,34,40,41]
		Interferon alpha	Cytokine	Thyroid autoimmunity, DIL, vasculitis, autoimmune hepatitis	[42,43]
		Interferon beta	Cytokine	Thyroid autoimmunity, DIL, vasculitis	[44–46]
		Interleukin 2	T cell cytokine	Thyroid autoimmunity, chronic inflammatory arthritis	[47,48]
	Other	Gold salts	Metal-based drug	Immune complex-mediated glomerulonephritis, autoimmune thrombocytopenia	[49]
Anti-infectives	Antibiotics	Cefuroxime	Cephalosporin antibiotic	Pemphigus erythematosus, DIL	[50,51]
		Isoniazid	Tuberculostatics	DIL, autoimmune hemolytic anemia	[52–54]
		Minocycline	Tetracycline-derived antibiotics	DIL, autoimmune hepatitis, vasculitis	[11,55–57]
		Nalidixic acid	Quinolone antibiotics	DIL, autoimmune hemolytic anemia	[58,59]
		Nitrofurantoin	Furan derivative	Autoimmune hepatitis	[60]
		Penicillin	Beta-lactam antibiotic	Autoimmune hemolytic anemia	[61]
		Streptomycin	Aminoglycosides	DIL, autoimmune hemolytic anemia	[62,63]
		Sulfadimethoxine	Sulfonamide antibiotic	DIL	[64]
		Sulfamethoxypyridazine	Sulfonamide antibiotic	DIL	[64]
		Tetracycline	Polyketide antibiotic	DIL, vasculitis, autoimmune hemolytic anemia	[65–67]
	Antifungals	Griseofulvin	Mitosis inhibitor	DIL	[68]
	Antimalarials	Quinine	Alkaloid	DIL, vasculitis, immune thrombocytopenia	[69–71]
Cardiac	Antiarrhythmics	Acecinide	Class III antiarrhythmic agent	DIL	[72]
		Procainamide	Class I a antiarrhythmic agent	DIL	[73,74]
		Propafenone	Class I c antiarrhythmic agent	DIL	[75]
		Quinidine	Class I a antiarrhythmic agent	DIL	[76]
	Antihypertensives	Acebutolol	Beta-blocker	DIL	[77,78]
		Atenolol	Beta-blocker	DIL	[79]
		Captopril	Angiotensin converting enzyme	DIL, autoimmune thrombocytopenia	[80,81]
		Enalapril	Angiotensin converting enzyme	DIL, vasculitis	[82]
		Hydralazine	Diuretic	DIL, vasculitis	[5,83]
		Labetalol	Beta-blocker	DIL	[84]
		Metoprolol	Beta-blocker	DIL	[85]
		Oxprenolol	Beta-blocker	DIL	[86]
		Practolol	Beta-blocker	DIL	[87]
		Propranolol	Beta-blocker	DIL	[88]
		Spironolactone	Diuretic	DIL	[89]
		Timolol	Beta-blocker	DIL	[90]
	Other	Clonidine	Alpha-adrenergic	DIL	[91]
Endocrine drugs	Aromatase inhibitors	Aminoglutethimide	Anti-steroid drug	DIL, Sjogren's syndrome	[92,93]
	Chelating agents	1,2-Dimethyl-3-hydroxypyridin-4-one	Iron chelator	DIL	[94]
	Statins	Atorvastatin	HMG-CoA reductase inhibitors	DIL, dermatomyositis, polymyositis	[15]
		Fluvastatin	HMG-CoA reductase inhibitors	DIL, polymyositis, dermatomyositis	[15,95]
		Lovastatin	HMG-CoA reductase inhibitors	DIL, dermatomyositis,	[15]
		Pravastatin	HMG-CoA reductase inhibitors	DIL, dermatomyositis, polymyositis,	[15]
		Simvastatin	HMG-CoA reductase inhibitors	DIL, dermatomyositis, polymyositis, lichen planus pemphigoides	[15,96]
	Hormone replacement	Danazol	Modified progestogen	DIL	[97]
	Thyroid drugs	Leuprolide acetate	GnRH analog	DIL, autoimmune thyroiditis	[98,99]
		Methimazole	Thyropoxidase inhibitor	DIL	[100]
		Methylthiouracil	Thyropoxidase inhibitor	DIL	[101]
		Propylthiouracil	Thyropoxidase inhibitor	DIL	[100]
		Thionamide drugs	Thyropoxidase inhibitor	DIL	[100]
Neuropsychiatric drugs	Anticonvulsants	Carbamazepine	Blocker of voltage-gated sodium channel	DIL	[102]
		Diphenylhydantoin	Blocker of voltage-gated sodium channel	DIL, linear IgA bullous disease	[103,104]

Table 1 (continued)

Category	Subcategory	Drug	Action	DIA effect	Reference
		Ethosuximide	Blocker of T-type Ca ²⁺ channel	DIL	[105]
		Phenytoin	Blocker of voltage-gated sodium channel	DIL, linear IgA bullous disease	[103,104]
		Primidone	Blocker of voltage-gated sodium channel	DIL	[106]
		Trimethadione	Channel blocker	DIL	[106]
		Nomifensine	Norepinephrine-dopamine reuptake inhibitor	DIL	[107]
		Phenelzine	Monoamine oxidase inhibitor (MAOI)	DIL	[108]
	Antimigraines	Methylsergide	5-HT _{2B} receptor antagonist	Localized systemic sclerosis	[109]
	Antiparkinsons	Levodopa	Precursor to catecholamines	Autoimmune hemolytic anemia, thrombocytopenia, DIL	[110–112]
	Antipsychotics	Chlorpromazine	Dopamine antagonist	DIL	[113]
		Chlorprothixene	Blocker of 5-HT ₂ , dopamine, mACh, alpha1-adrenergic receptors	DIL	[114]
		Levomeprazine	Blocker of Ach, alpha1, 5-HT _{2a} receptors	DIL	[115]
	Uncategorized	Perphenazine	Dopamine antagonist	DIL	[116]
		Metrizamide	Nonionic radiopaque contrast agent	DIL	[117]
		Minoxidil	Agonist of nitric oxide	DIL	[118]
		Oxyphenisatin	Laxative	Autoimmune hepatitis	[119]
		Psoralen	High UV absorbance, mutagen	DIL	[120]

associated with DIA (Table 1) [2], but only two drugs, procainamide and hydralazine, are considered high risk for developing DIL. According to investigations in past decades, the incidence of procainamide-induced lupus is estimated to be approximately 20% during the first year of therapy [4], and the incidence of hydralazine-induced lupus is approximately 5–8% [5]. Most other drugs are classified as either low risk or very low risk, except for the only one moderate risk drug, quinidine, with an incidence of less than 1% [6].

Since the development of more effective and safer drugs, the prescription of traditional high risk or moderate risk drugs, quinidine, hydralazine and procainamide, has dramatically decreased. However, the emerging biological modulators for treatment of neoplastic and autoimmune diseases, including tumor necrosis factor (TNF) inhibitors and cytokines, has led to the recognition that these newer drugs can also be associated with DIL. Biological modulators targeting TNF-alpha are FDA-approved drugs for a number of autoimmune diseases, such as Crohn's disease and rheumatoid arthritis. Five TNF-alpha inhibitors are currently available for general clinical use: etanercept, infliximab, adalimumab, certolizumab pegol and golimumab. Infliximab and etanercept were the earliest released TNF-alpha inhibitors, and both of these drugs have been associated with DIL. Although it does appear that the risk for generating autoantibodies is very high for infliximab and etanercept users, the actual rate of developing symptomatic DIL is only 0.5–1% [7,8]. To date, no certolizumab pegol-associated SLE case has been reported in the literature, and only a single case of golimumab-exacerbated subacute cutaneous lupus erythematosus (SCLE) has been described since its introduction in 2009 [9,10].

3. Clinical manifestation and laboratory abnormalities

There are many clinical features shared by idiopathic SLE and DIL, but there are also several key differences. For example, the male to female ratio in idiopathic SLE is 1:9, whereas only a slight predominance in females is observed in DIL. DIL tends to occur in older people, when compared to idiopathic SLE. The only exception to these characteristics is minocycline-induced lupus, which has a significantly higher incidence in women than men, and in younger

than older patients [11]. Like patients with SLE, those with DIL frequently exhibit arthralgias, myalgias, arthritis, fever and serositis, but this often present as a milder form than idiopathic SLE. Cutaneous manifestation, particularly the typically malar rash, photosensitivity and oral ulcers, are much less common in DIL than in idiopathic SLE. It is also noteworthy that the occurrence of serious major organ system involvement, such as renal or central nervous system, is rare in DIL.

DIL has an extremely variable presentation, depending on the inciting drug and on patient differences, which makes establishment of diagnostic criteria difficult. There are, however, multiple common symptoms that the clinician can look for. For instance, the typical symptoms of both procainamide- and hydralazine-induced lupus include arthralgias, myalgias, and constitutional symptoms such as fever, rash and pleuritis. However, pleuritis and pericarditis are more often reported in the procainamide group, whereas dermatological manifestations are more often seen in the hydralazine group. Hepatosplenomegaly occurs with similar frequency (15% in hydralazine-induced lupus and 25% in procainamide-induced lupus), and other symptoms such as glomerulonephritis, vasculitis and neuropsychiatric symptoms occur in less than 10% of patients for both drugs [5]. Quinidine-induced lupus is unique for its high incidence of cutaneous manifestations and neurological involvement (7/23 patients), the latter of which is otherwise rare in DIL [12]. Compared with traditional drug-induced lupus, TNF-alpha inhibitor-induced lupus has a higher incidence of rash, which presents in approximately 80% of cases [13,14].

As in idiopathic SLE, laboratory studies reveal that antinuclear antibodies (ANA) with homogeneous immune-staining present in a high percentage of DIL cases [6], although its absence does not rule out the possibility of DIA. Diffused, speckled, or nucleolar patterns of ANA have also been described, particularly in patients with quinidine-induced lupus [12]. In DIL, ANAs frequently target the histone–DNA macromolecular complex in the cell nucleus. Generally, anti-histone antibodies are present in >90% of overall DIL patients, although with certain drugs, this number may be much lower. For example, in minocycline, propylthiouracil, TNF-alpha inhibitor and statin-associated DIL, anti-histone antibodies were detected in only 32%, 42%, 57%, and <50% of cases respectively [11,14–16].

Importantly, a difference in the staining pattern of ANAs may be detected in patients with different drugs induced lupus. In a study by Burlingame et al. (1991), all patients with symptomatic procainamide-induced lupus and some of the patients with quinidine-induced lupus had IgG antibodies specifically targeting the (H2A–H2B)–DNA complex, which is rare in hydralazine-induced lupus. Interestingly, ANAs developed by patients taking procainamide but without lupus-like symptoms are almost IgM and did not show any particular pattern [17]. In hydralazine-induced lupus, IgM antibodies displayed more reactivity with DNA-free histones than with the corresponding histone–DNA complexes and almost no binding to H1-stripped chromatin [17]. In general, anti-dsDNA antibodies, one of the markers of idiopathic SLE, are rarely seen in traditional DIL (<1%). However, nearly all cases of TNF inhibitor-induced lupus in patients with rheumatic arthritis or Crohn's disease are positive for anti-dsDNA antibodies [14].

The presence of perinuclear antineutrophil cytoplasmic antibody (p-ANCA) is not a common finding in DIL, but it has been reported in 50% of propylthiouracil-induced cases and in 67–100% of patients with lupus linked to minocycline, with myeloperoxidase (MPO) as the auto-antigen. Other autoantibodies in DIL include rheumatoid factor (in 20–50% of DIL patients), anticardiolipin (in 5–20% of procainamide- and hydralazine-induced cases and 26–33% of minocycline-induced cases), and anti-Smith antibodies (in 7/17 or 41% of patients with minocycline-induced lupus) [18].

In addition to autoantibodies, other laboratory markers include elevated erythrocyte sedimentation rate (ESR), increased C-reactive protein (CRP), anemia, leukopenia, thrombocytopenia and hypocomplementaemia. Minocycline-induced autoimmunity involves an unusually high frequency of hepatic injury, indicated by elevated liver enzymes and histologic features resembling autoimmune hepatitis [11]. TNF-alpha inhibitor-induced lupus has a higher frequency of hypocomplementaemia, leukopenia and thrombocytopenia than traditional DIL [14]. A comparison of features of specific agents associated DIL is summarized in Table 2 [2].

4. Diagnostic criteria

Due to the highly variability in presentation caused by various drugs, it is difficult to establish standard criteria for the diagnosis of drug-induced autoimmunity. In 2007, Borchers et al. [18] first proposed a set of criteria for the diagnosis of drug-induced lupus, which include 1) sufficient and continuous exposure to the drug, 2) at least one characteristic of SLE, 3) no previous evidence of SLE or autoimmune disease, and 4) resolution of the disease within weeks or months of discontinuation of the drug. The criteria may help with the diagnosis of most drug induced lupus, and items 1), 3) and 4) can be applied to the diagnosis of other drug-induced

autoimmune diseases. However, these criteria are fraught with significant limitations.

With regard to the first criterion, even though DIA usually occurs at higher doses and also positively correlates with the cumulative dose of drugs, the identification of a threshold dose for developing DIA is difficult due to confounding factors such as genetic susceptibility and the overall health status of patients. The issue surrounding criterion 2) as mentioned above is that there are often very few distinguishing clinical and laboratory features between DIL and idiopathic SLE. Hence the strict application of standard criteria for idiopathic SLE or other autoimmune disease would dampen the efficiency for diagnosing DIA. It is quite possible that patients with DIL may only present with a few laboratory characteristics of classic SLE (or other autoimmune diseases), including the presence of auto-antibodies, but remain asymptomatic. Regarding the third criterion, TNF-alpha inhibitors or other biological modulators are frequently used for autoimmune diseases, leading to an inherent difficulty in distinguishing true DIA from exacerbation of pre-existing autoimmunity, or unmasking of a second autoimmune disease. For 4), after the termination of the suspicious agents, the clinical symptoms may disappear after a short period of time, but the autoantibodies may last for an extended period of time, which can further confound the diagnosis.

Given these facts, the diagnosis of drug-induced autoimmunity should be carefully established by the following steps (as illustrated in Fig. 1): 1) determining whether the clinical symptoms and laboratory findings are consistent with SLE or other autoimmune diseases. To this end, a detailed history must be taken to identify parameters that may help to establish the diagnosis and exclude other possibilities. Important questions in the history include patient's previous and family history of autoimmune diseases, clinical symptoms, including any constitutional, cutaneous, musculoskeletal, hematological, cardiovascular, neurological, renal and gastroenterological symptoms, and necessary laboratory tests. 2) Determining whether the disease is drug-related. In this respect, the temporal relationship between drug administration and symptom onset must be identified. The dosage and duration of drug use should be investigated carefully. In addition, a consideration of previous data regarding which drugs are known to be associated with DIL is important. 3) Discontinuing the suspicious agents and observing if the symptoms resolve. 4) Once the drug is reintroduced and the symptoms recur, the probability of DIA may be increased. However, even if the symptoms do not recur, DIA is not excluded.

5. Conclusions

The difficulty in diagnosing DIA is rooted in the lack of understanding of the pathophysiologic mechanisms of DIA, especially since each drug that has historically been associated with DIA

Table 2
A comparison of features of specific agents associated with drug-induced lupus.

Drug	Year of first report	Mean age	Major clinical features	Distinguishing laboratory features	Autoantibodies	Risk category
Hydralazine	1953	49	Rash, fever, myalgias, pleuritis, polyarthritis	Anemia, leukopenia	ANA, anti-dsDNA, ANCA, anti-H1-histone	High
Procainamide	1962	ND	Polyarthritis, polyarthralgias	Anemia	Anti-H2A–H2B–DNA, antihistone, anti-cardiolipin antibody	High
Quinidine	1988	Case reports	Cutaneous, neurological	Thrombocytopenia, hypocomplementemia	Anti-H2A–H2B–DNA	Mod
Minocycline	1992	21 (median)	Arthritis, arthralgias, fever	Elevated liver enzymes	ANA, pANCA, anti-dsDNA	Low
TNF-inhibitors	1993	ND	Skin manifestations	Thrombocytopenia	ANA, anti-dsDNA, anti-nucleosome, anti-cardiolipin	Unknown

ANA = anti-nuclear antibody, ANCA = anti-neutrophil cytoplasmic antibody, anti-dsDNA = anti-double-stranded DNA, Mod = moderate, ND = no data, pANCA = protoplasmic staining ANCA, TNF = tumor necrosis factor.

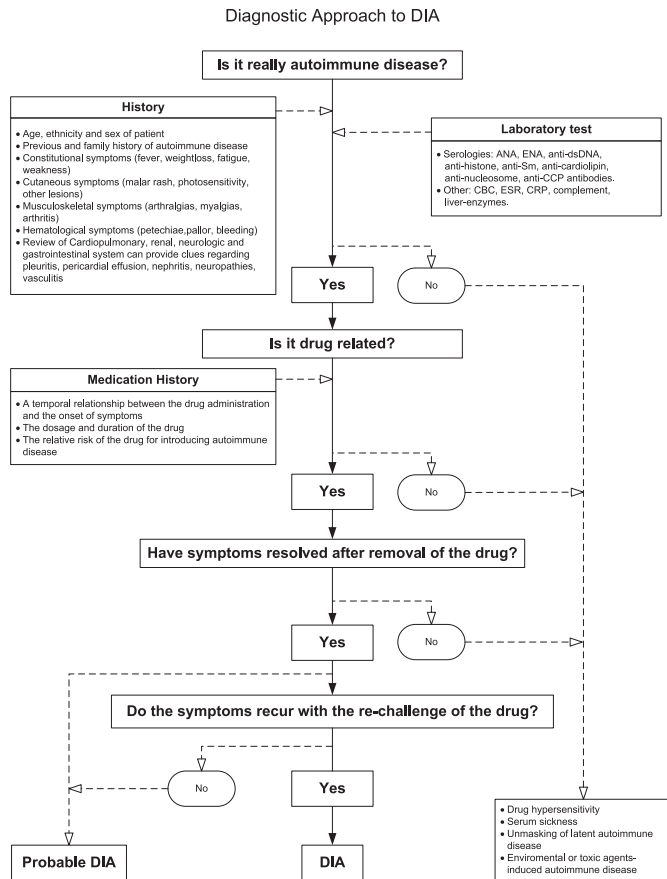


Fig. 1. Diagnostic approach to DIA.

possesses both common, and yet drug-specific clinical and laboratory presentations. The production of auto-antibodies resulting from a loss of tolerance to self-antigens has been widely reported. However, it is noteworthy that the generation of auto-antibodies is not sufficient to cause clinical disease. In fact, removal of the offending drug will frequently reverse the clinical course of DIA, but auto-antibodies can persist for a long time afterwards. Further research is needed to clarify the molecular and cellular mechanisms for the pathogenesis of DIA diseases. As we learn more about these drugs, and their interaction with host factors, we may become more capable of developing efficient biomarkers for diagnosis, as well as predicting drug response in individual patients [121–123]. The advent of computer simulations of genetic or transcriptional signatures, as well as proteomics and genomics will further advance our understanding of the disease.

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