Journal of Autoimmunity 48-49 (2014) 66–72

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Diagnosis and classification of drug-induced autoimmunity (DIA)

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ARTICLE INFO

Article history:
Received 7 October 2013
Accepted 13 November 2013

Keywords:
Drug induced lupus
Systemic lupus erythematosus
Anti-phospholipid syndrome
Procainamide
Anti-histone antibodies
Anti-nuclear antibodies

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.

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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http://dx.doi.org/10.1016/j.jaut.2014.01.005

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–Schonlein 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	Antiarrthymics	Acecainide	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]
		Metaprolol	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]
		Leuprolide acetate	GnRH analog	DIL, autoimmune thyroiditis	[98,99]
	Thyroid drugs	Methimazole	Thyroperoxidase inhibitor	DIL	[100]
		Methylthiouracil	Thyroperoxidase inhibitor	DIL	[101]
		Propylthiouracil	Thyroperoxidase inhibitor	DIL	[100]
		Thionamide drugs	Thyroperoxidase inhibitor	DIL	[100]
Neuropsychiatric drugs	Anticonvulsants	Carbamazepine	Blocker of voltage-gated sodium channel	DIL	[102]
		Diphenylhydantoin		DIL, linear IgA bullous disease	[103,104]

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