

DRUG-INDUCED AUTOIMMUNE DISORDERS

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Drug-induced autoimmune disorders have been recognized for over 50 years. In 1945, Hoffman⁶⁰ reported drug-induced lupus (DIL) in a 19-year-old man receiving sulfadiazine who developed fever, skin rash, myalgia, nephritis, and an elevated sedimentation rate. Since then, over 70 drugs have been reported to cause a lupus-like illness. Recognition of the development of drug-induced autoimmune disorders and the development of alternative drugs to replace common offenders, such as procainamide and hydralazine, have resulted in a reduction of the incidence of DIL. With increasing use of agents that target cytokine and other immunologic pathways, however, it is possible that we may see more drug-induced autoimmune disorders in the future. This article discusses the common nonhematologic, drug-induced autoimmune disorders, including DIL, and some of the newer descriptions of autoimmune disorders believed to be related to the use of some biological agents.

DRUG-INDUCED LUPUS

DIL is a syndrome that resembles mild systemic lupus erythematosus (SLE), which can complicate treatment with a number of unrelated drugs.⁹⁰ There are currently no established criteria for the diagnosis of DIL. The American College of Rheumatology classification requires 4 of 11 criteria to be present for the diagnosis of idiopathic SLE.¹¹⁷ Many patients with DIL do not fulfill these criteria because they may only present with one or two symptoms.³⁶ More important is the temporal association of the clinical manifestations to the drug initiation and the development of positive serologies. A remission or improvement of clinical symptoms with discontinuation of the drug is essential for the diagnosis. Drug

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rechallenge is rarely performed because of the risk of recurrence and the availability of alternative drugs.

More than 70 drugs are believed to induce a lupus-like syndrome (Table 1).^{13, 19, 22, 42, 46, 62, 91, 93} Some of these associations are very strong and have been validated by prospective trials.⁵⁶ Others are based on case reports without definite proof. DIL is characterized by the induction of autoimmunity manifested most notably by the development of antinuclear antibodies. Clinical manifestations are much less common and generally appear after several months of drug therapy, and usually disappear after discontinuation of the drug. This syndrome is different from immune complex (i.e., serum sickness) disease, which results from an antibody response to a drug with the formation of drug-antidrug immune complexes that deposit in tissues and mediate a local inflammatory response. Serum sickness generally occurs within a few weeks of the first exposure to the drug or after a few days in a patient previously sensitized to the drug. Exposure to other environmental agents may play a role in the development of DIL, as well as in idiopathic SLE.^{57, 58}

Historical Background

The first report of DIL was by Hoffman in 1945.⁶⁰ With the discovery of the lupus erythematosus (LE) cell by Hargraves in 1948,⁵⁵ clinicians had a tool to detect a marker of autoimmunity, which facilitated the diagnosis of both idiopathic SLE and DIL. With the subsequent development of very sensitive antinuclear antibody (ANA) assays, as well as many specific autoantibody tests, the development of autoantibodies in association with the use of many drugs can now be documented.

The first well-documented drug associated with DIL was the antihypertensive agent, hydralazine. Morrow⁸⁷ reported lupus-like symptoms in 14 of 253 patients treated with hydralazine for hypertension in 1953. This finding was verified by several other reports. With the development of newer hypertension

Table 1. MEDICATIONS IMPLICATED IN DIL

Antiarrhythmics	Antituberculosis Agents	Psychotropics
Procainamide*	Isoniazid*	Chlorpromazine
Quinidine*	Antihypertensives	Lithium carbonate
Antibacterial Agents	Acetololol	Phenelzine
Nitrofurantoin	Atenolol	Biological Agents
Sulfadiazine (or other sulfonamides)	Captopril	Interferon- α
Tetracycline	Hydralazine*	Interleukin-2
Minocycline	Labetalol	TNF- α antibodies
Anticonvulsants	Methyldopa*	Miscellaneous
Carbamazepine	Metoprolol	Levodopa
Ethosuximide	Pindolol	Oral contraceptives
Mephenytoin	Propranolol	Penicillamine*
Phenytoin*	NSAIDs	Sulfasalazine
Trimethadione	Benoxaprofen	Tolazamide
Sodium valproate	Diclofenac	
	Ibuprofen	
	Phenylbutazone	
	Sulindac	
	Tolmetin	

*Drugs with the best evidence of association.

agents, clinicians are finding less hydralazine-related DIL. Anticonvulsants were reported to be associated with DIL in children in 1962.¹² In 1962, Ladd⁷² described a patient taking procainamide who developed a lupus-like syndrome with pleurisy and musculoskeletal symptoms. Although the use of procainamide has diminished, it remains one of the most common causes of DIL.⁷⁴ Isoniazid was reported to induce DIL in 1966,⁷⁴ and remains an important cause of DIL with the continued battle against tuberculosis. Although many drug classes have been associated with the development of DIL (Table 1), only procainamide and hydralazine have been examined in prospective and retrospective studies.^{22, 56} The majority of information about the clinical features of DIL and the mechanisms of DIL comes from work with procainamide and hydralazine.

Epidemiology and Demographics

The incidence of DIL is very difficult to determine because of the changing pattern of drug use and the emergence of new drugs and biological agents that may induce DIL.⁶⁴ It has been estimated that approximately 300,000 people in the United States have lupus and that 5% to 10% may have DIL. It is possible that the true incidence of DIL is much higher because of the mild nature of many of the presentations and lack of recognition by the practitioner.

The epidemiology of DIL differs from idiopathic SLE in many ways (Table 2). The age of patients developing DIL is greater than those with SLE. This is in part because of the fact that the population exposed to the drugs that cause DIL is typically older, with diseases such as hypertension and cardiac arrhythmia. Children receiving anticonvulsants, however, can develop a DIL syndrome, suggesting that age alone is not the primary risk factor for the development of DIL. The female to male ratio of 9:1 seen in idiopathic SLE is much lower in DIL. It is uncommon for blacks to develop DIL in contrast to the increased black to white population ratio observed in idiopathic SLE. The epidemiology of DIL may change depending on the use of newer agents and the target population being treated.¹¹⁹

Table 2. CLINICAL FEATURES ASSOCIATED WITH DIL

Clinical Feature	Idiopathic SLE	DIL
	Ratio	
Female:Male	9:1	1-1.6:1
Black:white	2.7:1	0.3:1
Age at onset	15-40	Older
	Percent (%)	Percent (%)
Fever	84	14-50
Arthralgia/arthritis	95	75-95
Rash	50-70	5-34
Pleuritis	16-20	14-52
Pericarditis	20-30	2-18
Neurologic involvement	25-70	0-2
Renal involvement	34-50	0-13
Raynaud's phenomenon	18-45	0-5

Clinical Features

Because there is no consensus on the diagnostic criteria for DIL, the diagnosis is made based on the appearance of clinical and laboratory features known to be associated with DIL in the patient taking a drug that has been associated with the induction of DIL. The diagnosis should be suspected when a patient develops at least one clinical feature of lupus and a positive ANA after an appropriate duration of drug treatment. Generally, the symptoms improve after discontinuation of the drug, but may take more than a year for both the symptoms and serologic changes to resolve. If the patient's symptoms and serologic abnormalities do not resolve after a prolonged period of observation, the diagnosis of idiopathic SLE must be considered.

The symptoms of DIL usually appear several months after the initiation of the offending drug. The onset of symptoms may be fairly abrupt with the development of musculoskeletal symptoms or serositis. Patients with DIL can present with many of the same symptoms as those with idiopathic SLE, but usually have milder symptoms and rarely develop life-threatening organ involvement (Table 3). Constitutional symptoms, such as fever, malaise, and weight loss, are common. Pulmonary manifestations include pleurisy, pleural effusions, and pulmonary infiltrates.^{27, 68} Pericarditis and pericardial effusions are fairly common^{20, 51, 115} and can rarely result in cardiac tamponade.^{6, 9, 28, 37, 49, 54, 85} Pericardial involvement appears to be found more often in patients taking procainamide.⁴¹ These patients often already have cardiac disease and their management can be very challenging, especially if procainamide has been useful in management of their rhythm disturbance.

Cutaneous features of lupus, such as malar rash, discoid lupus, or other nonspecific macular or maculopapular rashes, have been reported in DIL, but are much less common than in SLE. Three cases of acute neutrophilic dermatosis (i.e., Sweet's syndrome) have been reported in patients with presumed DIL.^{92, 101, 102} Resolution of Sweet's syndrome occurred in all three patients with discontinuation of the drug. Rarely, patients with DIL develop cutaneous vasculitis.^{15, 40, 67, 79} Raynaud's phenomena is much less common in patients with DIL than in patients with idiopathic SLE.

Fortunately, very few patients develop serious neurologic or renal disease. Mild renal involvement with hematuria or proteinuria without diminished renal function that reverses after discontinuation of the drug is fairly common.¹⁰³ Renal involvement may be more common with hydralazine^{16, 66, 80, 113} than with other drugs; however, there have been reports of procainamide^{125, 135} and penicillamine³⁸ causing renal involvement. Patients rarely have gone on to develop

Table 3. LABORATORY FEATURES ASSOCIATED WITH DIL

Feature	Idiopathic SLE (%)	DIL (%)
ANA	> 95	100
Anemia	57	0-46
Leukopenia	43	2-33
Complement	Decreased	Usually normal
False positive VDRL	10-20	5-41
Antihistone antibodies	Up to 60	70-95
Anti-Smith antibody	25	< 5
Anti-dsDNA antibodies	50	< 5

significant renal impairment, but renal failure can occur.¹⁰⁹ The findings on renal biopsy are indistinguishable from those of idiopathic SLE.

Laboratory Features

The laboratory features of DIL are similar to idiopathic SLE, but usually reflect a milder disease (Table 3).^{17, 65} Tests reflecting systemic inflammation, such as the erythrocyte sedimentation rate, are often elevated. It is not unusual for patients to develop a mild, normochromic, normocytic anemia. Clinically significant thrombocytopenia and leukopenia are rare. A positive Coombs' test is not uncommon in DIL, but clinically significant hemolytic anemia is unusual. False positive VDRL and the presence of lupus anticoagulants, as well as anti-phospholipid antibodies, have been reported in patients with DIL.^{48, 59, 124} The incidence of thrombosis appears to be low, although there have been reports of recurrent thrombosis.^{6, 75, 76, 88} Inhibition of complement components have been reported in DIL.^{107, 108} Synovial fluid analysis in patients with DIL resembles the finding in patients with idiopathic SLE.¹²¹

By definition, all patients with DIL will have a positive ANA. It is very unusual to develop antibodies against double-stranded DNA or anti-Smith antibodies. These antibodies are very specific for idiopathic SLE and may correlate with the development of significant renal disease. Antihistone antibodies are found in more than 90% of patients with DIL; however, they are also found in as many as 60% of patients with idiopathic SLE.^{44, 47, 50} Therefore, antihistone antibodies are not diagnostic for DIL.

Many patients taking a drug known to induce DIL develop a positive ANA if tested.^{56, 86} Only a small percentage of those patients develop the clinical features of DIL.¹²⁶ The percentage of patients who develop a positive ANA, as well the percentage who further develop DIL, is well described for several drugs (Table 4). Given the high percentage of patients that develop a positive ANA, it is probably not necessary to order an ANA test for patients taking these drugs unless they develop lupus-like symptoms.

Table 4. PERCENTAGE OF PATIENTS WHO DEVELOP SEROLOGIC OR CLINICAL EVIDENCE OF DIL

Drugs	Positive ANA	DIL (%)
Procainamide	> 90*	30
Hydralazine	50*	10*
Chlorpromazine	50‡	< 5
Isoniazid	25	< 1
Methyldopa	15	< 1
Penicillamine	67	2

*After 1 year of treatment

†200 mg/d

‡> 400 mg/d

Selected Drugs Implicated in Drug-Induced Lupus

Hydralazine

Approximately 50% of patients on hydralazine for a prolonged period of time develop a positive ANA. Approximately 10% develop DIL. The typical clinical features are arthritis, skin rash, and serositis. Renal involvement is more common with hydralazine than with other drugs, but is fairly rare and generally mild.^{16, 66, 80, 113}

Procainamide

Approximately 30% of patients on procainamide for more than a year develop features of DIL. Over 90% of patients on procainamide develop a positive ANA. Patients who develop DIL while taking procainamide may have a higher likelihood of developing pericarditis or pleuritis.

Chlorpromazine

Between 16% and 52% of patients who receive chlorpromazine develop a positive ANA, but less than 1% develop the clinical syndrome of DIL.²⁶ The most common clinical features are joint symptoms, skin rashes, and fever. Patients taking chlorpromazine may also develop anticardiolipin antibodies, but rarely develop a thrombotic event.²⁵

Isoniazid

The long-term use of isoniazid has been associated with the development of a positive ANA in approximately 25% of patients.^{24, 99} Development of clinical features of DIL is rare and occurs in less than 1% of patients receiving isoniazid. The clinical features associated with isoniazid include joint involvement, fever, and serositis. With the ongoing battle against tuberculosis, physicians will continue to see patients who develop isoniazid-induced lupus syndromes.

Anticonvulsants

The most common anticonvulsants associated with the development of autoimmune syndromes include diphenylhydantoin, carbamazepine, ethosuximide, and sodium valproate.^{5, 40, 110, 116} The development of significant clinical features of lupus is relatively rare.¹⁴ Some reports have stated that anticonvulsant-related lupus resembles idiopathic lupus, with a high incidence of anti-DNA antibodies and central nervous system involvement. It can be difficult to determine whether the seizure event represents a manifestation of idiopathic SLE or the anticonvulsant used to treat a seizure disorder has induced a secondary lupus-like disorder with positive serologies.

Quinidine

Since 1970, there have been several reports of quinidine-induced lupus.^{7, 11, 33, 39, 69, 82, 114} Generally, the patients reported are older patients who are being treated for cardiac disease. The typical clinical features are arthritis, fever, skin rash, and serositis. Renal¹³⁰ and peripheral nerve⁷³ involvement are rare but have been reported. In addition to positive ANAs, hypocomplementemia and the

lupus anticoagulant have been reported. Interestingly, there have been a few reports of patients with a history of procainamide-induced lupus who later developed a lupus-like syndrome when treated with quinidine.⁷³

D-Penicillamine

In addition to an association with the development of a lupus-like syndrome,^{30, 31, 38, 43} D-penicillamine has been associated with the development of myasthenia gravis,²¹ autoimmune thyroiditis, Sjögren's syndrome, pemphigus, Goodpasture's syndrome,¹¹² polymyositis, dermatomyositis,¹²⁷ and scleroderma. The percentage of patients with rheumatoid arthritis who develop a positive ANA after 1 year of D-penicillamine therapy has been reported as high as 67%.²³ Clinical features include arthritis, serositis, rash, and various cytopenias. With the risk of development of autoimmune syndromes and the side effects of proteinuria, rash, and oral ulceration, the use of D-penicillamine for the treatment of rheumatoid arthritis has dramatically decreased.

Sulfasalazine

Since the original report by Alarcon-Segovia in 1969,³ there have been many reports of sulfasalazine-induced lupus in patients with inflammatory bowel disease and inflammatory arthritis.^{29, 32, 35, 105, 120, 122} Joint involvement, serositis, and skin rash are the main clinical features. There has been one possible case of central nervous system involvement reported.⁸⁴ In addition to a positive ANA, many of these patients develop antibodies to dsDNA and hypocomplementemia. Like most drug-induced lupus profiles, antihistone antibodies have been reported.¹⁸ The use of sulfasalazine as a single agent or in combination with other antirheumatic drugs for the treatment of rheumatoid arthritis is probably increasing in the United States, and there may be more patients who develop autoimmune side effects associated with sulfasalazine.

Pathogenesis

Genetically determined acetylator phenotype of patients receiving hydralazine and procainamide is an important factor in the development of DIL.^{61, 78} Slow acetylators are homozygous for a recessive allele that controls hepatic acetyltransferase, whereas fast acetylators are either heterozygous or homozygous for the dominant allele. Hepatic acetyltransferase is critical for the metabolism of procainamide, hydralazine, and isoniazid. The distribution in the population of slow and fast acetylators is approximately equal in whites and blacks. The majority of patients who develop DIL are slow acetylators.⁵⁶ When compared with fast acetylators, patients who are slow acetylators develop positive ANAs and symptoms of DIL after a shorter duration of therapy and at a lower cumulative dose of the drug.¹²⁸ When the concentrations of procainamide are kept at the same level in both groups, the incidence of DIL is the same, suggesting that it is the parent drug rather than a metabolite that is responsible for inducing the autoimmune response. The evidence regarding acetylator status and the development of DIL with isoniazid is less conclusive.^{4, 45}

Although the mechanism by which procainamide and hydralazine or other drugs induce the formation of ANAs and the development of DIL is unknown, there has been considerable work in this field.¹³¹⁻¹³⁴ It is hoped that with increased understanding of the mechanisms of DIL insight may be gained into the

pathogenesis of idiopathic SLE. Procainamide is known to induce changes in immunoregulation.² Depending on the dose, procainamide either enhances or inhibits the mitogenic response of peripheral lymphocytes.² The production of immunoglobulin has been shown to be increased in patients treated with procainamide.^{70, 129}

An alternative mechanism for some drugs that induce DIL is suggested by work showing their ability to invoke changes in T-cell DNA methylation.^{94, 95} Methylation of DNA is crucial in the regulation of gene expression and cellular differentiation. Methylation of regulatory DNA sequences is generally associated with gene suppression, whereas hypomethylation of these regulatory sequences is associated with gene expression. Procainamide and hydralazine inhibit DNA methylation and induce autoreactivity, presumably because of an alteration in the expression of certain genes involved in T-cell activation.³⁴ Inhibition of DNA methylation has been associated with the overexpression of lymphocyte function-associated antigen 1 (LFA-1).¹³² Autoreactivity correlates with an increase in LFA-1 expression, and overexpression of LFA-1 by transfection causes a similar autoreactivity in vitro and autoimmune disease in vivo. T-cell methylation is also impaired in patients with idiopathic SLE,⁹⁶ raising the possibility that T-cell hypomethylation may play a role in the pathogenesis of idiopathic SLE as well.

Management of the Symptoms of DIL

Most symptoms of DIL are self-limited once the offending drug has been discontinued. Symptomatic management of musculoskeletal complaints can often be accomplished with aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). If NSAIDs are contraindicated, low doses of prednisone (e.g., 5 to 10 mg per day) may be used. If patients develop symptomatic serositis, moderate doses of prednisone (e.g., 20 to 60 mg per day) may be necessary. In the rare patient who develops significant renal disease with progressive renal function deterioration, treatment should be similar to idiopathic SLE with high doses of prednisone and immunosuppressives.

With the advent of many therapeutic substitutes, it is rarely necessary to consider rechallenging with the offending drug. *N*-acetylprocainamide, the pharmacologically active metabolite of procainamide, has been used safely in patients with drug-induced DIL from the parent compound.¹¹¹ In patients with hydralazine-induced DIL, cardalazine has been used safely.⁸⁹ Cardalazine is a vasodilator that is structurally similar to hydralazine, but the hydrazine group is masked by an ethoxycarbonyl group.

BIOLOGICAL AGENTS AND LUPUS SYNDROMES

With increasing use of biological agents for the treatment of malignancies, infectious diseases, and rheumatic diseases, there have been many reports of the development of lupus-like syndromes in patients receiving these agents. An understanding of the pathogenesis of these side effects may result in increased understanding of the pathogenesis of idiopathic SLE.

Interferon

Interferon- α (IFN- α) is of increasing clinical importance because of its use in the treatment of a variety of hematologic malignancies and viral hepatitis. Common, reversible and dose-dependent side effects attributed to its immunomodulatory effects include transient fever, chills, weight loss, and myalgia. Less commonly, patients develop significant clinical features of autoimmune disease.¹⁰ In one study of 135 patients receiving leukocyte IFN- α or interferon alfa-2b for malignant carcinoid tumors, 25 (19%) were found to have autoimmune disorders.⁹⁷ Four patients developed pernicious anemia. Eighteen developed thyroid disease, five of whom had autoimmune thyroiditis. Nineteen patients developed positive ANAs after treatment with interferon. One patient developed a lupus-like syndrome with arthritis, myalgias, positive ANA, and anti-dsDNA antibodies. With discontinuation of the IFN- α , the symptoms subsided. During a short course of reinstitution of the IFN- α treatment because of suspected tumor progression, the patient again developed the symptoms of arthralgias and myalgias. These symptoms disappeared with the subsequent discontinuation of the IFN- α . A patient receiving interferon alfa-2b for chronic myelogenous leukemia developed arthralgias, fever, rash, positive ANA, dsDNA antibodies, lymphopenia, hypocomplementemia, and mild proteinuria.⁸³ Because of the severity of the patient's illness, the interferon alfa-2b was discontinued and he was given prednisone. With discontinuation of the interferon alfa-2b, his leukemia relapsed. Treatment with IFN- α in patients with other malignancies has been reported to induce a lupus-like syndrome.^{98, 100, 118, 123} The presence of elevated IFN- α has been associated with various idiopathic autoimmune conditions.⁶³ Elevated levels of endogenous acid-labile IFN- α have been reported in clinically active rheumatoid arthritis, scleroderma, Sjögren's syndrome, and idiopathic SLE.¹⁰⁴ In patients with lupus, IFN- α levels correlate with clinical disease activity and serologic markers of disease activity, such as elevated anti-DNA titers and reduced levels of serum complement.

IFN- γ has been implicated in the induction of an exacerbation of SLE in a woman who had what was originally believed to be rheumatoid arthritis.⁵³ She had requested a trial of IFN- γ as a treatment for her inflammatory arthritis. Administration of IFN- γ has been found to exacerbate SLE.⁷⁷ It is known that animal models of SLE that use the NZB mouse have shown acceleration of disease exacerbation and increased mortality with the addition of exogenous interferon.¹ This case report and the *in vitro* work suggest that the use of IFN- γ is contradicted in patients with SLE.

Interleukin-2 (IL-2), a lymphokine released by helper T lymphocytes, has been associated with increased disease activity of rheumatoid arthritis and SLE.⁷¹ Exogenous administration has been reported to be associated with a number of autoimmune side effects, including autoimmune thyroid disease, pemphigus, vitiligo, vasculitis, and the development of anti-insulin antibodies.⁵² Although there have not been reports of patients developing DIL, the spectrum of clinical features and serologic features overlaps with lupus. Three patients undergoing treatment with IL-2 for malignancy developed inflammatory arthritis associated with positive rheumatoid factor and a positive ANA, and met the clinical criteria for the diagnosis of rheumatoid arthritis.⁸¹

SUMMARY

There have been many drugs and biological agents associated with the development of autoimmune side effects and lupus-like syndromes. Because of

therapeutic alternatives and the risk of these and other side effects, many of these drugs are rarely used. The development of new pharmacologic and biological agents certainly will result in additional descriptions of the development of autoimmune side effects, such as DIL. Further study of the mechanism of the development of DIL may result in an improved understanding of the pathophysiology of idiopathic SLE and the potential improvement of treatment for patients with SLE.

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