REVIEW ARTICLE

Drug-Induced Lupus Erythematosus
Incidence, Management and Prevention

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Abstract

The generation of autoantibodies and autoimmune diseases such as systemic lupus erythematosus has been associated with the use of certain drugs in humans. Early reports suggested that procainamide and hydralazine were associated with the highest risk of developing lupus, quinidine with a moderate risk and all other drugs were considered low or very low risk. More recently, drug-induced lupus has been associated with the use of the newer biological modulators such as tumour necrosis factor (TNF)-α inhibitors and interferons. The clinical features and laboratory findings of TNFα inhibitor-induced lupus are different from that of traditional drug-induced lupus or idiopathic lupus, and standardized criteria for the diagnosis of drug-induced lupus have not been established. The mechanism(s) responsible for the development of drug-induced lupus may vary depending on the drug or even on the patient. Besides lupus, other autoimmune diseases have been associated with drugs or toxins. Diagnosis of drug-induced lupus requires identification of a temporal relationship between drug administration and symptom

development, and in traditional drug-induced lupus there must be no pre-existing lupus. Resolution of symptoms generally occurs after cessation of the drug.

In this review, we will discuss those drugs that are more commonly associated with drug-induced lupus, with an emphasis on the new biologicals and the difficulty of making the diagnosis of drug-induced lupus against a backdrop of the autoimmune diseases that these drugs are used to treat. Stimulation of the immune system by these drugs to cause autoimmunity may in fact be associated with an increased effectiveness in treating the pathology for which they are prescribed, leading to the dilemma of deciding which is worse, the original disease or the adverse effect of the drug. Optimistically, one must hope that ongoing research in drug development and in pharmacogenetics will help to treat patients with the maximum effectiveness while minimizing side effects. Vigilance and early diagnosis are critical. The purpose of this review is to summarize the most recent developments in our understanding of the incidence, pathogenesis, diagnosis and treatment of drug-induced lupus.

Autoimmune disease affects up to 10% of the world's population. Target antigens have been identified in some but not all autoimmune diseases. In addition, the triggering event leading to the onset of an autoimmune disease is not always discernable. One of the most common autoimmune diseases is systemic lupus erythematosus (SLE), which has an incidence of between 15 000 and 30 000 cases per year. Approximately 10% of these cases can be related to drugs. 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 haemolytic anaemia, Sjogren's syndrome and scleroderma.[1,2] The number of drugs that have been implicated in causing autoimmune diseases now exceeds 100, from over ten different drug classes (table I).

Drug-induced autoimmunity is idiosyncratic, falling into the category of 'Type B' drug reactions. These are reactions that are unpredictable, and many factors may contribute to their development. This is in contrast to 'Type A' reactions, which are primarily drug dependent and, as a result, are predictable adverse effects of a drug that can be expected to occur in almost all patients exposed to the medication. An example of a Type A reaction is a sedative response to first-generation antihistamines. Type B reactions, on the other hand, may depend on 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 such as sunlight or even physical activity or inactivity. Allergic reactions to drugs, which may or may not be IgE-mediated, are a form of a Type B reaction. The distinction between Type A and Type B reactions is not always absolutely clear because even in type A reactions the expected adverse effect is not necessarily universal, and in type B reactions the frequency for adverse effects can be widely variable.

The purpose of this review is to summarize the history of drug-induced lupus, and to discuss recent cutting edge developments in our understanding of the pathophysiology, management and prevention of drug-induced lupus.

1. The History and Epidemiology of Drug-Induced Lupus

The role of the environment in inducing autoimmune diseases has been known for some time – particularly the interplay between genetic predisposition and autoimmunity – and there are a considerable number of agents that have been implicated. These have been recently reviewed.[2-10]

The earliest report of a case of drug-induced lupus involved the drug sulfadiazine. This was reported in 1945 but may actually have been a

Table I. Drugs associated with lupus (adapted from Chang and Gershwin[2])

Antiarrhythmics

Procainamide, quinidine, acecainide, amoproxan, disopyramide, propafenone

Antihypertensives

ACE inhibitors: captopril, enalapril

β-Blockers: acebutalol, atenolol, labetalol, metaprolol, oxprenolol, practolol, prindolol, propranolol, timolol eyedrops

Other: hydralazine, clonidine, guanoxan, methyldopa, prazosin, chlorthalidone, spironolactone

Antidepressants

Lithium carbonate, normifensine, phenelzine

Antipsychotics

Chlorpromazine, chlorprothixene, levomeprazine, perazine, perphenazine, reserpine, thioridazine

Antibacterials

Cefuroxime, isoniazid, minocycline, nalidixic acid, nitrofurantoin, penicillin, streptomycin, sulfadimethoxine, sulfamethoxypyridazine, tetracycline

Anti-inflammatories

Benoxaprofen, diclofenac, ibuprofen, mesalazine, para-amino salicylic acid, phenylbutazone, sulindac, sulfasalazine, tolmetin

Thyroid drugs

Methimazole, methylthiouracil, propylthiouracil, thionamide drugs

Xanthine oxidase inhibitors

Allopurinol

Hormonal drugs

Danazol, leuprolide acetate

Antimigraine drugs

Methylsergide

Anticonvulsants

Carbamazepine, dipheylhydantoin, ethosuximide, pheneturide (ethylphenacemide), mephenytoin, phenylethylacetylurea, phenytoin, primadone, trimethadione

Antifungals

Griseofulvin

Chelating agents

1,2-dimethyl-3-hydroxy-pyride-4-1

Antihistaminics

Cimetidine, cinnarizine, promethazine, pyrathiazine

Antiparasitics

Anthiomaline

Antiparkinson drugs

Levodopa

Aromatase inhibitors

Aminoglutethimide

HMG-CoA reductase inhibitors ('statins')

Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin

Other

Gold salts (antiarthritic), metrizamide (contrast media), minoxidil (vasodilator – treatment of baldness), oxyphenisatin (laxative), psoralen (furocoumarin), quinine (antimalarial), tolazamide (sulfonylurea), aminoglutethimide

Biological modulators

Tumor necrosis factor-α inhibitors: infliximab, etanercept, adulimumab, golimumab, certolizumab pegol

IFNs: IFNα, IFNβ

Interleukin-2

IFN = interferon.

hypersensitivity reaction.[11] The prototype drug for drug-induced lupus is procainamide,[12] which is a class Ia antiarrhythmic first introduced in 1951. Another drug that has been unequivocally linked to drug-induced lupus is hydralazine, which was first reported to cause drug-induced lupus in 1953, just 2 years after its introduction.[13] Minocycline, a tetracycline antibiotic, is considered a low-risk drug for drug-induced lupus but deserves special consideration because it has well documented and somewhat unique autoimmune adverse effects, including autoimmune hepatitis. Because of the low frequency at which most drugs cause drug-induced lupus, most are classified as either low risk or very low risk. Only two drugs have been classified as high risk, procainamide and hydralazine, and only one as moderate risk, quinidine (table I).

The history of drug-induced lupus can be divided into two distinct periods, the dividing line being the introduction of biological modulators to treat neoplastic and autoimmune diseases. Infliximab, the first tumour necrosis factor (TNF)-α inhibitor to be released, was first approved in the US for the treatment of Crohn's disease in 1998. The risk classification system applied to traditional drug-induced lupus has not yet been extended to include the newer biological modulators. This is primarily due to difficulty in establishing criteria for the diagnosis of drug-induced lupus in patients placed on these drugs whom, in all likelihood, may have pre-existing, or be predisposed to, lupus or autoimmunity (overlap syndrome). However, it does appear that the risk for developing autoantibodies is very high for this class of drugs and, because of the nature of their potential mechanisms of action, autoimmune diseases may also occur with a higher frequency than originally thought, though the percentage of patients with autoantibodies who go on to develop autoimmune disease is still small.

2. Drug-Induced Subacute Cutaneous Lupus Erythematosus and Chronic Cutaneous Lupus Erythematosus

Besides SLE, drugs have also been reported to induce a clinical syndrome consistent with sub-acute cutaneous lupus erythematosus (SCLE). As of 2008, there were at least 71 reports in the literature. The drugs most commonly associated with this condition include antihypertensives (calcium channel antagonists, thiazide diuretics, ACE inhibitors), but it has also been reported to occur with interferons (IFNs), terbinafine and other drugs (table II). Recently, the platelet aggregation inhibitor ticlopidine has been associated with both drug-induced lupus[14] and drug-induced SCLE.[15]

Drug-induced SCLE primarily occurs in older patients (mean age 59 years) and onset of the disease can occur weeks to years after starting the drug. After termination of the drug, it can take up to 2–3 months for resolution to occur.[16] The most common dermatological manifestations are photodistributed erythema and scaly annular plaques. The serological profile for SCLE includes positivity to antinuclear antibody (ANA), Ro/SSA

Table II. Drugs associated with subacute cutaneous lupus erythematosus (SCLE) and chronic cutaneous lupus erythematosus (CCLE)

SCLE
Antihypertensives
calcium channel antagonists: diltiazem, verapamil, nifedipine
ACE inhibitors: cilazapril
thiazide diuretics: hydrochlorthiazide
β-blockers: acebutolol
HMG-CoA reductase inhibitors ('statins')
Interferon-α and -β
Antifungals
terbinafine, griseofulvin
Antiplatelets
ticlopidine
NSAIDs
piroxicam, naproxen
Antidepressants
bupropion
Others
lansoprazole, tamoxifen, leflunomide, docetaxel
Biologicals
efalizumab, etanercept, infliximab, interferon-β
CCLE
Fluorouracil drugs
NSAIDs

and La/SSB. Antihistone antibodies may be present, but anti-DNA and anti-ribonucleoprotein (RNP) are rarely seen. Serologic resolution lags behind clinical improvement in most cases of SCLE.[17,18] Chronic cutaneous lupus erythematosus has also been rarely reported in conjunction with fluorouracil agents or NSAIDs.[19]

3. Clinical Presentation and Laboratory Abnormalities

3.1 Traditional Drug-Induced Lupus

3.1.1 High-Risk Drugs

Procainamide is one of the two drugs considered high risk for causing lupus, with reported incidence estimates of approximately 20% during the first year of therapy.[20] Procainamide acts by prolonging cardiac action potential and by slowing conduction, and is therefore effective in treating both ventricular and supraventricular arrhythmias; however, in 1962 an association between procainamide and symptoms and signs of lupus was reported.[21] A study of 52 patients with no previous history of connective tissue disease revealed the appearance of ANAs in 43 patients, and also antihistone antibodies in 34 patients.[22]

Hydralazine is the other drug classified as high risk for causing lupus. Hydralazine was first introduced in 1951. Two years later the first case of hydralazine-induced lupus was reported.[23] Of the 50% of patients receiving hydralazine who develop positive ANAs, approximately one-tenth present with symptoms of lupus. Overall, the incidence of hydralazine-induced lupus is approximately 5–8%. A review of the literature revealed a mean age of 49 years, and a female predominance of approximately 60%. Antihistone antibodies were almost always present.[24] The main features of procainamide-induced lupus include arthralgias, arthritis and myalgias, which are present in 80–85% of patients. Constitutional symptoms follow next in frequency, with fever, weight loss and fatigue occurring in 40–45% of patients. The typical symptoms of hydralazine-induced lupus include arthralgias, myalgias, constitutional symptoms such as fever and rash, pleuritis and leukopenia. Rarely, glomerulonephritis and vasculitis can occur. Hydralazine was

first reported to be associated with a vasculitis in 1980.[25] A recent review of the literature revealed 18 papers describing 66 cases of hydralazine-induced vasculitis.[26] Pleuritis and pericarditis are more common in the procainamide group and dermatological manifestations are more common in the hydralazine group. Hepatosplenomegaly can occur with similar frequency (15% in hydralazine-induced lupus and 25% in procainamide-induced lupus), and other symptoms such as glomerulonephritis and neuropsychiatric symptoms occur in less than 10% of patients for both drugs.[26]

The most common autoantibody detected in procainamide-induced lupus patients was against a component of the nucleosome consisting of an H2A-H2B dimer.[27,28] In the case of symptomatic procainamide-induced lupus, antibodies are of the IgG class and are directed specifically against this highly antigenic entity. Antihistone antibodies are also detectable in patients who are asymptomatic after treatment with a variety of drugs, but these are typically IgM and not specific for any particular component of the histone complex.

3.1.2 Moderate-Risk Drugs

Quinidine is a type Ia antiarrhythmic used in the treatment of atrial and ventricular arrhythmias. It has been generally categorized as a moderate-risk drug for drug-induced lupus, but a review of the literature reveals only case reports of quinidine associated drug-induced lupus.[29] A total of only 16 cases were reported up to 1985. Over the next 2 decades the use of quinidine has steadily decreased, in part because of the large number of adverse effects of the drug, including arrhythmias (ventricular fibrillation), gastrointestinal symptoms (diarrhoea, anorexia, nausea and vomiting), tinnitus, visual blurring, confusion, a lymphoma-like syndrome and blood dyscrasias such as coagulopathies but also because of the subsequent development of safer drugs. Clinical features of quinidine-induced lupus include polyarthritis and, to a lesser extent, pleuritis, peripheral abnormalities and the clotting abnormalities mentioned previously. Laboratory findings of quinidine-induced lupus have included polyarthritis, an elevated erythrocyte sedimenta-

tion rate (ESR), positive ANA and positive anti-histone antibodies (including histone H1 and the H2A.H2B and H3.H4 complexes) in some patients. In general, quinidine-associated drug-induced lupus resolved after discontinuation of the drug.

Because there are only case reports, there are no exact figures on incidence or risk but given the fact that quinidine was widely used in the mid-20th century, the classification of quinidine as a moderate-risk drug for drug-induced lupus may be inaccurate, and perhaps the risk is not as great as previously believed. It is interesting to note that two factors may contribute to the decrease in incidence of quinidine-induced and also procainamide-induced lupus, the first being the reduction in use of the drugs and the second being that, even when these drugs are used nowadays, the doses may not be pushed as high as before because of the availability of other alternatives.

3.1.3 Low-Risk Drugs

Minocycline is an antibacterial of the tetracycline class. Besides its antimicrobial function, it is used in the treatment of inflammatory acne vulgaris and has also been used in the treatment of rheumatoid arthritis. Adverse effects of minocycline include gastrointestinal and hypersensitivity symptoms, as well as a serum sickness disease and autoimmune hepatitis.[30] The first reports of minocycline-induced lupus appeared in 1992.[31] Minocycline-induced lupus appears to affect a younger group of patients. Typical symptoms include polyarthralgias, arthritis and other constitutional symptoms, including fever, weight loss and malaise. Dermatological manifestations such as rash, livedo reticularis, subcutaneous nodules, alopecia and oral ulcers are present in approximately 25% of cases. The median duration of therapy in minocycline-induced lupus was 19 months. Positive laboratory tests included elevated ESR, increased C-reactive protein (CRP), ANA positivity, antineutrophil cytoplasmic antibody (ANCA), anti-double-stranded DNA (anti-dsDNA) antibodies, anticardiolipin antibodies and antibodies to histone proteins,[32] although this was only present in 37% of the patients who were tested. Autoimmune hepatitis appeared to

be a relatively frequent problem related to minocycline. Patients generally improved within 1 month of discontinuation of minocycline, except in the case of autoimmune hepatitis. The incidence of minocycline-induced lupus was calculated to be 14.2 cases per 100 000 prescriptions, with a significantly higher incidence for women than for men (32.7 vs 2.3 cases per 100 000 prescriptions). The single-use risk ratio for developing minocycline-induced lupus ranged from 8.5 to 16 depending on the length of treatment with minocycline, compared with non-users.[32]

Minocycline-induced autoimmunity has also been described in children. Twenty-seven children with minocycline-induced autoimmunity were followed at a single paediatric rheumatology service.[33] The most common symptoms were constitutional patients (in all 27 children), polyarthralgias (22 patients) and arthritis (17 patients). Most of the patients had resolution of symptoms after cessation of minocycline, but seven developed a chronic course. Serological abnormalities found in minocycline-induced lupus include ANAs, anti-dsDNA antibodies, pANCA and anticardiolipin IgG antibodies. In a series of 23 patients with minocycline-induced lupus, elevated liver enzymes were detected in 8 patients, and hypergammaglobulinaemia in 12 of 19 patients. Interestingly, antihistone antibodies were negative in nine of nine of the patients in whom this test was performed.[34] The role of genetic susceptibility was illustrated in 13 patients with minocycline-induced lupus. All patients were either HLA-DR4 or HLA-DR2 positive, and all had an *HLA-DQB1* allele encoding for tyrosine at position 30 of the first domain.[35] However, it should be emphasized that although minocycline-induced lupus is less common than other drugs, the total number of patients is actually higher because of the frequency in which minocycline is used to treat acne. We encourage discussion between physicians and patients so that they are aware of the risks and alternatives, particularly since minocycline-induced lupus and minocycline-induced autoimmunity can be very severe.

Penicillamine is used in the treatment of autoimmune diseases, such as rheumatoid arthritis and scleroderma. It is also used as a chelating agent in

Wilson's disease and cystinuria. Of 120 patients with Wilson's disease treated with penicillamine, 8 developed serological changes consistent with lupus, while 6 developed an immune complex nephritis.[36] Otherwise, only case reports of penicillamine-induced lupus have been reported. Penicillamine causes a lupus-like syndrome in mice, and this serves as an animal model for some types of drug-induced lupus. There have been case reports of sulfasalazine-induced lupus in patients with Crohn's disease.[37] The autoantibody profile was primarily IgG against the H2A-H2B-DNA complex. In another study, 4 of 41 rheumatoid arthritis patients receiving sulfasalazine developed positive ANA and/or rashes.[38]

There are several case reports of HMG-CoA reductase inhibitor ('statin')-induced autoimmunity. A total of 28 cases had been reported up to 2005. SLE occurred in ten cases, while SCLE occurred in three cases. Dermatomyositis and polymyositis developed in 14 cases, and lichen planus pemphigoides developed in one case. While most patients recovered after discontinuation of the drug, it is of interest to note that two patients died.[39]

Antithyroid drugs have been associated with drug-induced autoimmunity. Of 16 patients who developed positive ANCA after receiving propylthiouracil or methimazole, 10 developed skin lesions and 1 developed pulmonary and renal involvement. There was a higher frequency of myeloperoxidase-specific-ANCA, ANA, antihistone antibody, anticardiolipin antibody, cryoglobulins and low C4 in the thyroid drug-induced disease group than in a control group with idiopathic systemic vasculitis.[40]

Chlorpromazine was first reported to be associated with drug-induced lupus in 1959.[41] Only case reports have been published, illustrating the rarity of this condition. Anticardiolipin and antiphospholipid antibodies have been detected.[42,43] Aromatase inhibitors, used in the treatment of cancer, have been associated with a number of autoimmune diseases, in particular Sjogren's syndrome.[44] In approximately half of these patients, an elevated ANA was detected. The relationship between estrogen depletion and the development of sicca syndrome was reported in 2007.[44] Interestingly, ciclosporin, an immunosuppressive agent, has been linked to drug-induced lupus, and ciclosporin-induced autoimmunity in rodents is an experimental model for scleroderma in humans.[45] A comparison of the features of traditional drug-induced lupus for the most common drugs is shown in table III.

Finally, other toxins or environmental exposures have been associated with lupus, and the mechanism of action for these cases may be completely different.[46,47] Vaccine-induced autoimmunity has been reported during the recent swine flu epidemic, and heavy metals such as mercury[48] have been reported to cause lupus. Particulate matter, ozone and other airborne pollutants have been associated with autoimmune diseases, as have components of cleaning products, household goods, cosmetology agents or dental prostheses such as vinyl chloride, organic solvents, anilides and acrylamine.[49] Food components such as iodine and L-tryptophan have been associated with autoimmunity, although a cause-effect relationship has proven difficult to establish.

3.2 Biological Modulators and Drug-Induced Lupus

3.2.1 Tumor Necrosis Factor Inhibitors

The most widely used class of biological modulators targets TNFα. These drugs are FDA-approved in the US for a number of autoimmune diseases, including Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis and ulcerative colitis.

There are five TNFα inhibitors now available for general clinical use; these are etanercept, infliximab. adulimumab, certolizumab pegol and golimumab. The latter two are recently introduced; therefore, there are minimal data on adverse effects of autoantibodies and autoimmune disease. Etanercept is a fusion protein consisting of the p75 fragment of the TNFα receptor and the Fc portion of human IgG1. The others are antibodies to TNFα. Infliximab was the earliest TNFα inhibitor to be released, therefore, there is a greater wealth of data regarding drug-induced lupus for this drug.

The production of autoantibodies in patients treated with TNF inhibitors was initially reported

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

Characteristic	Procainamide	Hydralazine	Quinidine	Minocycline	TNF inhibitors
Risk category	High	High	Moderate	Low	ND
Year of first report	1962	1953	1988	1992	1993
Incidence (risk ratios)	20%	5–8%	Case reports only	>60 cases	~0.2%
Mean age (y)	ND	49	Case reports only	21 (median age)	Unknown
Major clinical features	Polyarthritis, polyarthralgias, constitutional symptoms, pleuritis, pericarditis	Rash, fever, myalgias, pleuritis, polyarthritis, polyarthralgias, glomerulonephritis	Cutaneous and neurological manifestations	Arthritis, arthralgias, fever, malaise, myalgias, hepatitis	Skin manifestations, glomerulonephritis
Distinguishing laboratory features	Anaemia	Anaemia, leukopenia	Thrombocytopenia, hypocomplementaemia	Elevated liver enzymes	Thrombocytopenia
Autoantibodies	Anti-H2A-H2B-DNA, antihistone, anticardiolipin antibody	ANA, anti-dsDNA, ANCA, anti-H1 histone antibody	Anti-H2A-H2B-DNA	ANA, pANCA, anti-dsDNA	Anti-dsDNA, antinucleosome, anticardiolipin, ANA
Possible mechanism(s) of action	Inhibition of central tolerance Apoptosis DNA hypomethylation	DNA hypomethylation Macrophage activation	Apoptosis	Antigen modification Haptenization	Cytokine shift Apoptosis Bacterial infection

ANA = antinuclear antibody; **ANCA** = antineutrophil cytoplasmic antibody; **Anti-dsDNA** = anti-double-stranded DNA; **ND** = no data; **pANCA** = protoplasmic-staining ANCA; **TNF** = tumour necrosis factor.

during the early clinical trials for infliximab in the treatment of rheumatoid arthritis.[50-52] The ANA positivity rate in these patients increased from 22% to 53%, but only one patient actually developed clinical lupus.[53,54] Anti-dsDNA antibodies are commonly seen.[55] A literature review undertaken in 2007 revealed 233 cases of autoimmune disease following anti-TNF therapy, including 92 with lupus, 113 with vasculitis and 24 with interstitial lung disease.[56] A prospective study of 125 consecutive patients with Crohn's disease treated with infliximab was conducted in 2003. None had positive ANA titres prior to therapy. At 24 months, 56.8% of patients had a positive ANA. Of those who were subtyped, 32.6% had anti-dsDNA, 39.5% had anti-single-strand DNA and 20.9% had antihistone antibodies. Only two developed drug-induced lupus, and one developed autoimmune haemolytic anaemia.[57] A 2008 literature review reported on 56 cases of TNFα inhibitor-induced lupus: 53 from the literature and 3 of their own. In all, 36 satisfied criteria for SLE and, of these, 21 were attributable to infliximab, 10 to etanercept and 2 to adulimumab. The major

differences that they noted between TNFα inhibitor-induced lupus and traditional drug-induced lupus included a higher incidence of rash and anti-DNS antibodies, increases in the frequency of hypocomplementaemia, leukopenia and thrombocytopenia, and a lower incidence of antihistone antibodies. The frequency of other characteristics such as fevers, arthralgias, arthritis and nephritis were not significantly different.[58]

All of the TNFα inhibitors can lead to autoantibody production or clinical drug-induced lupus; however, there are some differences amongst the different drugs. In a French study of 22 patients with drug-induced lupus secondary to TNFα inhibitors, the incidence of TNFα inhibitor-induced lupus was found to be 0.19% for infliximab and 0.18% for etanercept.[59] Of the 22 patients in the French study, 12 had full-blown lupus, as defined by the presence of at least 4 of the 11 American College of Rheumatology (ACR) criteria used in the diagnosis of SLE (figure 1). Similarly, a prospective study over 2 years demonstrated ANAs developing in 62% and 41% of patients treated with infliximab for spondyloarthropathy and

rheumatoid arthritis, respectively, whereas in the etanercept group only 15% and 10% in the corresponding groups developed ANAs. Seventy-one percent of the spondyloarthropathy and 49% of the rheumatoid arthritis patients treated with infliximab developed anti-dsDNA antibodies, compared with 0% in the etanercept group. These antibodies were predominantly IgM and IgA, with an absence of IgG antibodies. Another study demonstrated the development of IgG and IgM antibodies to dsDNA in 64% and 81% of rheumatoid patients receiving infliximab, respectively. The number of patients with positive ANA also increased from 24% pretreatment with infliximab to 77% after 30 weeks of treatment. Anti-cardiolipin antibodies have also been detected in patients on anti-TNFα agents.[60,61] In another study, IgM anti-dsDNA autoantibodies were only seen in the infliximab group.[62]

In yet another study, 53 patients with rheumatoid arthritis were treated with infliximab and 6 other patients were treated with etanercept for comparison. For patients receiving infliximab, IgG and IgM autoantibodies to anti-dsDNA increased significantly to 66% and 85%, respectively.[63] Antinucleosome antibodies and ANA also increased, but rheumatoid factor (RF) and anticardiolipin antibodies did not. None of the etanercept group patients developed autoantibodies to dsDNA and only one patient in the infliximab group developed autoimmunity. The difference in autoantibody profiles seen between the infliximab and etanercept treatment groups suggests that the production of autoantibodies is not a class effect.

As in the case of traditional drug-induced lupus, the presence of autoantibodies does not necessarily lead to clinical lupus. Symptoms of lupus in anti-TNFα patients include polyarthritis, discoid or malar rashes, photosensitivity, pericarditis, pleuritis or pericardial effusions. Leukocytoclastic vasculitis or glomerulonephritis can occur with both infliximab and etanercept, but rarely.[64-66] In a study of 16 patients with new-onset SLE developing after treatment with etanercept, both discoid lupus and subacute cutaneous lupus were observed. The development of symptoms can occur within weeks to months of starting therapy and usually resolve within 1–4 months of discontinuing therapy. The differences between drug-induced lupus, TNFα inhibitor-induced lupus and idiopathic lupus are shown in table IV.

3.2.2 Cytokines

IFNα therapies are indicated for the treatment of various cancers. In a sample of 135 patients being treated for malignant midgut carcinoid tumours with IFNα or IFNα-2b, 18 developed autoimmune thyroid disease after 9 months of therapy, 4 developed pernicious anaemia, 2 vasculitis and 1 SLE.[68] None of these patients had any pre-existing autoimmune disease. It is interesting to note that while type 1 IFNs can be promoters of T helper-1 cell (T_h1)-mediated inflammation, they can also act as inhibitors of T_h1 and T_h17-mediated inflammation, suggesting that the effects of IFN either as a treatment for autoimmunity or as a culprit in the development of drug-induced autoimmunity are probably dependent on many other factors.

Of particular interest is the use of IFN in the treatment of cancer. In a cohort of 200 patients who were part of a larger study on the treatment of stage IIA, IIB and III melanoma with IFNα-2b, it was noted that the appearance of autoantibodies actually correlated with an improved relapse-free survival rate and overall survival. The autoantibodies detected included antithyroid antibodies and the clinical manifestations of autoimmunity included vitiligo, thyrotoxicosis, autoimmune thrombocytopenic purpura with antiplatelet antibodies, arthralgias, myalgias and

Malar rash
Discoid rash
Photosensitivity
Oral ulcers
Arthritis[1]
Serositis[1]
Renal disorder
Neurological disorder
Haematological disorder[1]
Immunological disorder[1]
Antinuclear antibodies[1]

Fig. 1. American College of Rheumatology criteria for idiopathic systemic lupus erythematosus and its utility in diagnosing drug-induced lupus. **1** Features commonly seen in drug-induced lupus.

Table IV. Differences between traditional and biological-induced drug-induced lupus (DIL)[a]

Feature	Idiopathic lupus	Traditional DIL	Infliximab-induced lupus	Etanercept-induced lupus
Clinical features				
Mean age (y)	15–50	Varies	Unknown	Unknown
Sex distribution (F : M)	9 : 1	Depends on drug	Unknown	Unknown
Fever/fatigue/weight loss (%)	>80	40–45	50	50
Arthralgias/arthritis/myalgias (%)	87	80–85	51	51
Nephritis (%)	34–42	5–10	9	9
Rash (%)	71	5–25	72	72
Pericarditis (%)	15–20	5–15	Unknown	Unknown
Hepatosplenomegaly (%)	5–10	15–20	Unknown	Unknown
Vasculitis (%)	41	No data	Unknown	Case reports of leukocytoclastic vasculitis
Neuropsychiatric (%)	21–32	<5	Unknown	Unknown
Laboratory findings (%)				
Antinuclear antibodies	>95	>99	40.7–61.8[62]	10[62]
Anti-dsDNA antibodies	28–67	<5	49.2–70.6[62]	10[62]
Antihistone antibodies	54/70	<96	20.9%[57]	Unknown
Anti-ssDNA antibodies	Common	Unknown	39.5[57]	Unknown
Anti-(H2A-H2B-DNA) antibodies	70	43–96	57	57
Antineutrophil cytoplasmic antibody	16	Depends on drug	Exact figures unknown	Exact figures unknown
Anticardiolipin antibodies	35	5–20	Baseline 14 increasing to 29[b]	Baseline 18 increasing to 27
Rheumatoid factor	25–30	20–30	Exact figures unknown	Exact figures unknown
Hypocomplementaemia	64	<5	59	59
Anaemia	>50	20–35	Exact figures unknown	Exact figures unknown
Leukopenia	48	5–25	50	50
Thrombocytopenia	30–50	<5	27	27
Elevated CRP	Unknown	Unknown	Exact figures unknown	Exact figures unknown
Elevated ESR	>50	60–80	Exact figures unknown	Exact figures unknown
Elevated gammaglobulins	32	10–50	Exact figures unknown	Exact figures unknown

a   The frequency of symptoms and serological findings vary among studies. These are typical numbers found in a review of multiple studies.[20,26,58,67] The frequency of autoantibodies also appears to depend on the disease state being treated in the case of TNFα-induced lupus.

b   This indicates an increase from baseline as many patients treated with TNFα inhibitors have pre-existing autoantibodies.

Anti-dsDNA = anti-double-stranded DNA; **Anti-ssDNA** = anti-single-stranded DNA; **CRP** = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **F** = female; **M** = male; **TNFα** = tumour necrosis factor-α.

signs and symptoms of rheumatoid arthritis, including elevated ANA and rheumatoid factor.[69]

Interleukin (IL)-2 is associated with autoimmune thyroiditis, with an incidence of approximately 15%.[70] Other autoimmune phenomena reported have included fibromyalgia, anti-insulin antibodies and vasculitis. In 1992, three patients receiving IL-2 for the treatment of metastatic cancer were reported to develop chronic inflammatory arthritis.[71]

4. Diagnosis

Unlike idiopathic SLE, there are no universal or standard criteria for the diagnosis of drug-induced lupus. Standard ACR criteria for diagnosing lupus are not always satisfied in the diagnosis of drug-induced lupus because of the variability in presentation depending on the inciting drug. Therefore, the first hurdle that must be overcome in diagnosing drug-induced lupus is to

answer the question as to whether or not the symptoms or signs are even consistent with lupus. As mentioned earlier, other autoimmune diseases have been associated with exposure to drugs, and there may be significant overlap in symptoms. Moreover, the illness may be a hypersensitivity reaction, rather than autoimmune disease. A careful history must be taken to identify parameters that help establish the diagnosis of lupus and to exclude other possibilities. Important questions in the history that need to be answered are shown in figure 2.

The differential diagnosis of drug-induced lupus includes drug hypersensitivity, serum sickness, exacerbation of pre-existing lupus or unmasking of lupus by the drug, eosinophilia-myalgia syndrome, drug-induced haemolytic anaemia, toxic oil syndrome and lupus caused by other environmental agents or heavy metals (figure 3).

Assuming the diagnosis of lupus is made, how can one be certain the drug is the culprit? A knowledge of which drugs have been linked to lupus and their risk for causing lupus is obviously important. However, although there are many case studies on numerous drugs and their association with drug-induced lupus, a cause and effect relationship cannot always be unequivocally established. Identifying a temporal relationship between drug administration and the onset of symptoms is critically important and can be

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Exacerbation of pre-existing lupus
Unmasking of idiopathic SLE
Autoimmune haemolytic anaemia
Drug hypersensitivity
Eosinophilia-myalgia syndrome
Serum sickness
Toxic oil syndrome
Other non-drug causes of environmentally-induced lupus

Fig. 3. Differential diagnosis of drug-induced lupus. **SLE** = systemic lupus erythematosus.

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helpful, but the duration of treatment and the dosage taken prior to development of symptoms can be highly variable. In general, a distinguishing factor between autoimmune adverse drug reactions and hypersensitivity reactions is that drug-induced autoimmunity usually occurs at a higher dose and also positively correlates with a cumulative dose. The presence of other exposures or illnesses, including toxins, foods or other medications, can further confound the diagnosis. Since these are Type B adverse drug reactions, host and genetic susceptibilities can also play a role.

Because of the absence of any standard criteria for the diagnosis of drug-induced lupus, in 2007 Borchers et al.[1] proposed a set of criteria for the diagnosis of drug-induced lupus, which include sufficient and continuous exposure to the drug, at least one characteristic of SLE, no previous evidence of SLE or autoimmune disease, and resolution of the disease within weeks or months of discontinuation of the drug. These criteria may help with the diagnosis of traditional drug-induced lupus.

On the other hand, the diagnosis of drug-induced lupus in the case of TNFα inhibitors or other biological modulators presents a special challenge in that many of these patients already have autoimmune diseases. As we mentioned earlier, one of the criteria for diagnosis of drug-induced lupus for traditional drugs is that there must be no pre-existing lupus. In the case of biological modulators, this criterion may not be met since this is the very disease these drugs are used to treat. Therefore, it is difficult to make a distinction between a true drug-induced lupus or an exacerbation of previous existing lupus, or an unmasking of a second autoimmune disease. A

Age, ethnicity and sex of patient
History of other autoimmune disease
Temporal relationship between commencement of drug use and onset of symptoms
Has drug been stopped? If so, have symptoms resolved?
Previous history of any drug reactions
Family history of autoimmune disease
Exposure to other environmental agents
Constitutional symptoms (fever, weight loss, fatigue, weakness)
Dermatological symptoms (malar rash, photosensitivity, other rashes, mucous membrane involvement)
Musculoskeletal system (arthralgias, arthritis, weakness)
Respiratory symptoms (chest pain, shortness of breath, wheezing)
Gastrointestinal symptoms (abdominal pain, nausea or vomiting, abdominal masses)
Haematological symptoms (petechiae, pallor, bleeding)
Review of system can provide clues regarding nephritis, vasculitis, neuropsychiatric symptoms

Fig. 2. History-taking in patients with drug-induced lupus.

useful observation that can help in the diagnosis of drug-induced lupus is that, upon removal of the drug, the disease almost always resolves and in most cases fairly rapidly, although exceptions can occur. Common symptoms that are present in both idiopathic and drug-induced lupus include myalgias, arthralgias, fever, serositis and skin rash, but these may present in a milder form than with lupus. The occurrence of serious major organ system involvement, such as renal or CNS, tends to be a rare event. In addition, there is a female predominance, as in idiopathic SLE, but the patient population tends to be of a more advanced age. Exceptions to the general patterns are frequent and presentation varies depending on the inciting agent.

5. Pathophysiology

The generation of an autoimmune response in drug-induced lupus may be under the control of a number of mechanisms.[20,72,73] These were reviewed in-depth in a recent article.[2] Because most drugs are small molecules, their immunogenicity is weak. However, small molecules can bind to a macromolecule such as a protein or glycoprotein and be rendered immunogenic, a process known as haptenization. The small molecular determinant remains the target epitope. With the recent development of biological modulators as drugs, these molecules are generally large enough themselves to be immunogenic, and the observation of TNFα inhibitor-induced autoimmunity has confirmed some of the expectations associated with the use of biologicals.

The mechanism by which drug-induced lupus occurs may vary depending on the inciting drug, environmental exposures and influences, or on host characteristics themselves. As an example of a host-dependent factor, some individuals are slow acetylators, which may retard clearance of highly reactive intermediate species that can stimulate loss of central tolerance or production of autoantibodies. In some cases, multiple mechanisms may be occurring simultaneously. As will be discussed below, a single agent may act via several mechanistic pathways to produce autoimmune disease. The ability to act through multiple path-

ways may explain why procainamide-induced lupus is one of the few drugs classified as high risk.

The principal mechanism of action of procainamide-induced lupus appears to be through the formation of highly reactive intermediates, including procainamide hydroxylamine. This and other metabolites can act on the lymphoid tissue to disrupt normal development of central T-cell tolerance[74,75] by interfering with positive selection of thymocytes.[76] It has been demonstrated that intrathymic administration of procainamide hydroxylamine, a highly reactive metabolite of procainamide, can lead to production of anti-(H2A-H2B)-DNA antibodies in mice.[75]

Alternatively, both quinidine and procainamide have been shown to inhibit macrophage uptake of apoptotic and necrotic cells in mice. It is proposed that altered handling of necrotic or apoptotic cells leads to the accumulation of nucleosomes in the peripheral blood. Nucleosomes can be targets of anti-DNA antibodies and have also been shown to induce an immunoproliferative response. Normally, apoptotic signalling pathways lead to the regulated and controlled removal of such nuclear excess. Any interference with these clearance mechanisms may lead to an inability to distinguish between self and non-self in the development of tolerance, thereby causing the production of autoantibodies to highly preferred molecules in the histone complex.[77] A defect in apoptosis may also play a role in drug-induced lupus associated with chlorpromazine,[78] statins, quinidine[77] and TNFα inhibitors.

The DNA hypomethylation observed in CD4+ cells of patients with idiopathic or drug-induced lupus erythematosus has been suggested as a mechanism for the development of autoimmunity.[79] In mammals, DNA methylation occurs on cytosine residues within polycytosine guanine (CpG) motifs. Methylation of the fifth carbon of the pyrimadine ring leads to the production of 5-methylcytosine. Most of the CpG motifs in humans are methylated and methylation generally correlates with genetic inactivity. Hypomethylation, on the other hand, can lead to activation of genes and downstream consequences of that can be production of autoantibodies. While

this is an extremely simplified view of one potential mechanism for developing autoimmunity, *in vitro* studies have demonstrated that hydralazine inhibits ERK pathway signalling, leading to decreased expression of DNA methyltransferase I and 3a expression and enzyme activity.[80] In a murine model of drug-induced lupus, Deng et al.[80] were able to induce anti-dsDNA antibodies in female inbred AKR mice by injection of hydralazine. Inhibition of ERK pathway signalling via impairment of protein kinase Cγ[81] leads to DNA hypomethylation, lymphocyte function-associated antigen-1 over-expression,[82,83] increased T-cell autoreactivity and then a lupus-like disease.[80,84] DNA hypomethylation may also occur with procainamide-induced lupus as well. Over-expression of CD70 and resultant overstimulation of IgG synthesis by both lupus T cells and hypomethylated T cells suggests that DNA hypomethylation may also be a mechanism for idiopathic SLE.[85,86]

These and many other mechanisms of action exist in the cases of drug-induced lupus caused by other low-risk drugs. Apoptosis has been proposed as a mechanism for the development of drug-induced autoimmunity.[87-89] It has been shown that both natural and synthetic statins can be cytotoxic to T and B cells by virtue of their proapoptotic properties.[88] This leads to an increase in the presence of nuclear antigens, inducing the production of antibodies. IFNγ production by lymph node cells in mice has been shown to be reduced by statins.[90] Moreover, statins such as atorvastatin have been demonstrated to induce signal transducer and activator of transcription factor 6 (STAT6) activity, leading to increased production of T_h2 cytokines IL-4, IL-5, IL-10 and transforming growth factor-β. This was accompanied by an inhibition in STAT4 activity and production of T_h1 cytokines IL-2 and IFNγ.[91] Thus, statins have been shown to favour a T_h2 shift in the T_h cell paradigm, leading to production of autoantibodies (similar to the cytokine shift described for TNFα inhibitors). However, statins have also been found to inhibit autoimmunity, possibly by their action on lipid rafts and the disruption of signalling pathways. Of course, whether autoimmune disease is stimulated or inhibited as a result of this disruption depends on whether a negative or positive signalling process is affected and for which cytokine or signalling pathway, suggesting that multiple end results may exist for each drug-host relationship.

The mechanism of penicillamine-induced lupus in Brown Norway rats involves the activation of macrophages as a result of the interaction between penicillamine and the aldehyde group on the cell membrane of macrophages. This has been used as a model for drug-induced lupus whereby the amine group on the drug acts in the same manner as the amine group on the cell membrane of T cells in inducing activation of the macrophages. In some patients, activation of macrophages can lead to autoimmunity. Evidence for activation of macrophages includes an increase in production of TNFα, IL-6 and IL-23, and the presence of a positive feedback loop between natural killer (NK) cells and macrophages was supported by the observation that IL-15 and IL-1β transcription was upregulated.[92] Macrophage activation may also be one mechanism that can contribute to lupus-inducing effects of hydralazine and isoniazid, as these drugs also possess the ability to bind to aldehyde groups on macrophages and, in fact, can be shown to activate macrophages *in vitro*.

The complexity of the mechanisms governing drug-induced lupus is further illustrated by the paradoxical effect of the immunosuppressive agent ciclosporin on the generation of autoimmunity. One would expect an inhibitory effect on autoimmunity but instead ciclosporin has been found to produce autoimmunity. Ciclosporin interferes with signal transduction upon T-cell receptor cross-linking and thus can inhibit T-cell activation, maturation and selection in the thymus. It has been proposed that ciclosporin interferes with negative selection in the thymocytes and thereby allows for the generation of autoreactive T cells. Subsequently, an inability to re-establish autoregulation of these T cells in the periphery (i.e. interference with peripheral tolerance) leads to the development of autoimmunity.[93]

The mechanism of action of TNFα inhibitor-induced lupus is unknown.[67] The cytokine shift

hypothesis has been employed to explain that inhibition of TNFα activity, as in the case of pharmacological manipulation through TNFα inhibitors, suppresses T_h1 cytokine production and shifts the immune response to a T_h2 paradigm. The cytokine profile leads to activation of signalling pathways that ultimately favour the production of autoantibodies and the development of lupus-like syndromes. It has also been proposed that interference with the normal programmed cell death, as in the case for procainamide, also occurs with the use of TNFα inhibitors. TNFα is a mediator of apoptosis and provides a means to terminate T-cell driven responses. Inhibition of TNFα activity can disrupt normal apoptosis and lead to autoantibody production against nuclear antigens.

Infections are a known side effect of TNFα-inhibitor therapy. Whether bacterial DNA, with its immunostimulatory CpG motifs, can trigger autoantibody production was studied in eight patients treated with etanercept in 2002.[94] Anti-cardiolipin antibodies and anti-dsDNA antibodies were measured during and after treatment of a documented bacterial infection (bronchitis or urinary tract infection). While there appeared to be a connection between active infection and the presence of autoantibodies, the numbers are too small to make any valid conclusions. Furthermore, larger prospective studies would need to be conducted to determine if autoantibody production in some cases of TNFα-inhibitor treatment is an epiphenomenon of infection associated with the treatment.

In summary, because of the complexity and redundancy of the immune system, with its intricate pathways and interactions among multiple cells, signalling pathways and mediators, the mechanism of drug-induced lupus is clearly different for each known drug association. Ultimately, the final common denominator is a loss of tolerance to self. The defect may occur in loss of central tolerance during lymphocyte differentiation, loss of peripheral tolerance after cells have left the thymus or bone marrow, and/or may involve the production of cross-reactive antibodies upon exposure to an extraneous antigen with common epitopes to self-antigens. It is gen-erally believed that the loss of tolerance is a T-cell driven event, but there may be involvement of other cell types such as macrophages or NK cells, or humoral factors including various cytokines and chemokines, that can also play a role in development of autoimmunity. Finally, recent evidence linking TNFα inhibitor-induced auto-immunity to defects in normal apoptosis as a mechanism for developing autoimmunity has been particular enlightening.

6. Prevention and Treatment

Treatment of drug-induced lupus begins by establishing the correct diagnosis and by determining if there is a cause and effect relationship between the drug and disease. Assuming that the diagnosis has been established, the offending drug must be discontinued. Following that, corticosteroids are the primary pharmacological agent used to treat the condition. Patients should be warned of the potential adverse effects of long-term corticosteroids. Otherwise, management is supportive and symptoms usually resolve before the disappearance of autoantibodies. With some drugs, more serious disease can occur, such as autoimmune hepatitis in minocycline-induced lupus, and in some cases of statin-induced lupus death has occurred.[39] Unfortunately, it is difficult to predict those who may develop drug-induced lupus and there are no data showing any benefit of serological profile evaluation of patients prior to treatment with these agents. It is critical to emphasize the importance of early diagnosis so that patients are not inappropriately managed with corticosteroids and/or immunosuppressive drugs in an otherwise reversible condition.

Current research on the use of micro RNAs to affect post-transcriptional regulation of gene expression is a promising treatment avenue in autoimmune diseases. These agents act on the 3′-untranslated region of messenger RNA of target genes that stimulate the development of auto-antibodies. Thus, there may be potential benefits to this future therapy in the treatment of both idiopathic and drug-induced lupus. However, as the lessons of TNFα inhibitors have taught us,

when it comes to biological modulator therapy, unexpected and sometimes paradoxical results can occur.

7. Discussion

Drug-induced lupus is a well-described phenomenon. Historically, the class of drugs most frequently associated with drug-induced lupus has been cardiovascular drugs, particularly antiarrhythmics, although more and more drugs are being associated each year, and the list of drugs spans numerous drug classes. Drugs have also been associated with a variety of autoimmune diseases and not just lupus. Early use of relatively high doses of the antiarrhythmics procainamide and quinidine was associated with a higher frequency of drug-induced lupus, although the actual risk may need to be reassessed in an objective matter. This may all be moot, as the use of these drugs, particularly quinidine, has been drastically reduced as a result of the development of safer and more effective drugs. The same can perhaps be said for hydralazine, although hydralazine may be undergoing a resurgence because of the introduction of a combination product containing hydralazine and isosorbide dinitrate for use in congestive heart failure.

Perhaps a more relevant drug class to be concerned about are the biological modulators, particularly TNFα inhibitors. Obviously, one would expect more and more biological modulators to be introduced in the near future. The ability of TNFα inhibitors to produce autoantibodies has been shown to be significant, although most of these patients do not go on to develop TNFα inhibitor-induced lupus. It must be noted that, because these drugs are used to treat autoimmune disease, the method used to establish the diagnosis of drug-induced lupus is potentially thwart with inconsistencies and care must be taken when comparing studies on the incidence of drug-induced lupus attributable to TNFα inhibitors. Nevertheless, it is important to realize that drug-induced lupus is generally a rare phenomenon, while at the same time maintaining a vigilant mindset when using these drugs. Fortunately, once the diagnosis is established, recovery is usually quick following discontinuation of the inciting drug.

The fact that a drug used in the treatment of autoimmune diseases can lead to the exacerbation of existing disease or the development of a new autoimmune disease further expands the mystery of our immune system. In a way, this is not unexpected. After all, the immune system is endowed with an extensive redundancy in mechanistic pathways, where a single agent can have a number of independent functions and several agents or signalling molecules can lead to a common endpoint. Manipulation of the immune system with any of the agents to target one pathway invariably leads to changes in another. The ability to predict adverse effects based on pharmacogenetics is entirely relevant in the case of drug-induced lupus, and the day may come when we are able to delineate therapy based on minimizing adverse effects on a patient-by-patient basis. Identification of susceptible individuals to drug-induced lupus may be facilitated in the future by the use of biomarkers. Antineutrophil cytoplasmic antibodies have already been found to be present in higher frequency in patients with drug-induced lupus than with idiopathic lupus, and in combination with antihistone antibodies and/or β-2-glycoprotein 1 can provide an antibody profile for the diagnosis of drug-induced lupus.[95] Susceptible genes for the development of drug-induced lupus probably exist, and can serve as biomarkers to identify those that are at risk.

Acknowledgements

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