Drug-induced autoimmunity

Fatma Dedeoglu

Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Fatma Dedeoglu, MD, Children's Hospital Boston, Harvard Medical School, 300 Longwood Avenue Fegan 6, Boston, MA 02115, USA
Tel: +1 617 355 6117; fax: +1 617 730 0249;
e-mail: fatma.dedeoglu@childrens.harvard.edu

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Purpose of review

This review aims to draw attention to the increased spectrum of the features of drug-induced autoimmunity (DIA), including both clinical and autoantibody profiles in addition to the potential chronicity of the syndrome.

Recent findings

In recent years, not only has the number of medications causing DIA increased but the spectrum of the features has broadened as well. With the use of newer medications, especially biologics, mostly directed towards immune system manipulation, the range of signs and symptoms of DIA as well as the patterns of autoantibody profiles have widened. Rashes and visceral involvement have started to be reported more often, especially with tumor necrosis factor antagonists. In addition, autoantibodies such as antidouble-stranded DNA, which are usually seen with idiopathic systemic lupus erythematosus, are appearing in place of the antihistone antibodies, typically found in drug-induced lupus. Finally, some medications have been implicated in causing the very same entity, which they may be used to treat. It is clear that progress in the field of pharmacogenetics and pharmacogenomics will help further our understanding of these and other adverse effects of medications.

Summary

Even though DIA has been known for many years, the underlying mechanisms remain unclear. However, with recently described new and unexpected features, novel hypotheses have been proposed, thus opening doors to further research in understanding these mechanisms.

Keywords

autoantibodies, drug metabolites, drug-induced lupus, drug-induced vasculitis, hypomethylation, tumor necrosis factor antagonists

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Introduction

Autoimmunity develops when there is a dysregulation of one or more components of the normal immune response. Despite many years of extensive research, in most cases the exact mechanism of this dysregulation has not been fully elucidated. The development of autoimmunity is multifactorial; genetic and epigenetic factors and environmental triggers appear to play a role in the initiation and sustenance of the process.

Drug-induced autoimmunity (DIA) is an autoimmune condition, in which the environmental trigger appears to be a medication. This association may allow some insight for investigators to better understand the pathways that lead to specific immune dysregulation and it has the potential of shedding light on autoimmunity in general.

There has been an increase in reports of DIA over the last decade [1••,2,3••,4•,5,6]. The number of medications implicated has increased exponentially, related perhaps to some of the newer medications developed over the last decade. Medications, such as biologics, are geared toward targeting specific immune mechanisms, and they may skew the immune response dramatically. More than 90 medications have been implicated in DIA to date.

Convincing evidence exists for DIA triggered by some drugs, including hydralazine, procainamide, isoniazid, methyldopa, quinidine, minocycline and chlorpromazine [7]. Interestingly, some drugs implicated in DIA have had unexpected effects, as in the case of tumor necrosis factor (TNF) inhibitors, which are effective in treating psoriasis in the majority of patients but have been found to cause or flare psoriasis in some individuals [8–11,12•]. Similarly, leflunomide has been reported in the successful treatment as well as the development of subacute cutaneous lupus erythematosus (SCLE) [13,14].

Following many observations in DIA, new hypotheses have been developed in the pathophysiology of autoimmunity, opening doors for further research, exemplifying bedside to bench, and back to bedside, research. In addition, development in other areas of medicine such

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as pharmacogenomics holds great promise in understanding the mechanisms of both immunologic and nonimmunologic drug sensitivity [15•,16,17].

Traditionally, DIA has been divided into separate entities such as drug-induced vasculitis, lupus, hepatitis, arthritis or pneumonitis. However, as we have found in minocycline-induced autoimmunity (MIA), an overlap is seen among these entities, suggesting that they represent a wide spectrum of a single process [18•].

General features

Autoimmune syndromes induced by drugs have been described for many years; drug-induced lupus (DIL) is a classic example. Ten percent of systemic lupus erythematosus (SLE) cases are estimated to be drug-induced, with 15 000–30 000 cases occurring in the United States [7]. Similarly, about 10% of cutaneous vasculitis is reported to be drug-induced, with purpuric and maculopapular rashes being the most common [19].

The first recognition of this entity goes back to the 1950s, in patients who were treated with sulphadiazine and hydralazine [4•]. About 7% of patients treated with hydralazine developed these features in the 1950s, and this remains true to date (5–8%).

There are no definite diagnostic criteria for DIA, but there is a general consensus in making this diagnosis. There should be a temporal relationship between the drug in question and the clinical findings: the condition should not be present in the patient prior to the use of the drug in question, and the condition should resolve or improve with the withdrawal of the offending agent [2,4•]. For further confirmation of DIA, reexposure to the drug should trigger similar symptoms; however, rechallenge is usually not reasonable because of the possibility of a more severe response with reexposure.

Although this approach seems straight forward, in clinical practice, diagnosing DIA often proves to be challenging, as patients may be on multiple medications, and if a detailed medication history is not obtained, the association between a particular medicine and the patient's symptoms cannot be made. This problem is well documented with minocycline, which has also been the author's experience. As its major indication is for acne, patients often do not consider it to be a medication, and they may fail to mention it when queried. Furthermore, some autoimmune processes may take a while to resolve, even after the triggering agent has been removed, making the association difficult. Another difficulty may be encountered if some features of DIA are shared with the underlying disease for which the offending drug is given, such as arthralgia/arthritis in rheumatoid arthritis (RA).

Except for a few drugs, such as hydralazine, there does not appear to be a correlation between the dosage of the drug and the development of autoimmunity. On the contrary, it seems that a cumulative dose must be reached before the development of DIA. Recently, a meta-analysis [20] of DIA in patients treated with tetracycline antibiotics for acne showed that exposure to more than 50 000 mg of minocycline conferred the highest risk. There was no association between development of autoimmunity and other type of tetracyclines [20]. Vaccines should also be included as potential agents in causing DIA; for example, vasculitis with influenza vaccination, arthritis and Sjogren's syndrome with hepatitis B vaccination and reactive arthritis with Bacillus Calmette–Guérin [3••].

Many of the DIA syndromes are mild and self-limiting, but severe and chronic courses have also been reported, especially in patients with prominent features of vasculitis. It is not clear whether chronic cases represent an actual idiopathic form, that is, unmasked by the suspected offending agent. Distinct from hypersensitivity reactions, DIA has more insidious onset with mild symptoms that gradually worsen over a long period of time. In addition, the duration of medication use is relatively long, up to several years in most cases.

The experience in our center with MIA revealed chronicity in substantial group of these patients [18•]. Many patients with DIA have common features, including arthralgia (90%), myalgia (50%) and constitutional symptoms (malaise, fever and anorexia). Serositis, hepatitis and lymphadenopathy may also be seen.

Similar to the idiopathic form of SLE, DIL can present with systemic features or primarily cutaneous forms such as SCLE and chronic cutaneous lupus erythematosus (CCLE) [21]. Typical idiopathic SLE skin findings, such as malar rash or discoid lesions, are less common in DIL; instead, purpura, photosensitivity and erythema nodosum are more often seen. Interestingly, in the vasculitis spectrum of DIA, skin and subcutaneous tissue involvement is quite common. In a recent study [22•], 71 published cases of drug-induced SCLE were described. Antihypertensives and antifungals were the most common drugs in SCLE, and anti-Ro antibodies were often detected with anti-La positivity in half of the cases, whereas antihistone antibodies were less common than is true of systemic DIL [22•]. The fact that different drugs are involved and autoantibody profiles are different suggests that different immune pathways are affected in systemic DIL versus cutaneous DIL. Major organ involvement, such as central nervous system or renal involvement, is uncommon in DIA but occurs more often in those with vasculitis. Allopurinol, diphenylhydantoin, thyroid medications (propylthiouracil and methimazole

being the most widely studied), NSAIDs, antibiotics (penicillins, sulfonamides and gentamicin), food additives, herbicides and insecticides are among the commonly seen triggers of cutaneous leukocytoclastic vasculitis [23,24].

Most patients have elevated inflammatory markers and positive autoantibodies including antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) and antihistone antibodies. ANA is generally required for the diagnosis of DIL, but in some cases with typical features of DIA, the ANA may remain negative [7]. Interestingly, in lupus and vasculitis-like presentations of DIA, ANA, ANCA and antihistone antibodies have been documented simultaneously, although with different frequencies. This further supports the possibility that these entities disparate manifestations along the same spectrum.

In general, it seems that particular drugs cause stereotypical presentation in different patients, but this is not always the case. The same drug can cause a vasculitic process in some patients, and a lupus-like process in others. Thus, propilthiouracil, the drug used in treatment of Graves disease may cause both [25] drug-induced vasculitis and DIL, and patients may fit into both categories.

Cutaneous DIL, granulomatous rashes and vasculitis appear to be common with TNF inhibitors [26,27]. Other autoimmune conditions reported with TNF inhibitor use include multiple sclerosis-like demyelination and psoriasis, most commonly psoritic palmoplantaris pustulosis (PPPP) [3••,5,8,12•]. The offending drug should be discontinued if concerns are present for a demyelinating process. On the contrary, it can be continued in certain skin problems such as PPPP, which can be treated with topical agents. Interestingly, almost all clinically significant lupus-like symptoms seem to occur in patients who are ANA positive at baseline. A recent meta-analysis [6] reported 233 patients with TNF inhibitor-induced autoimmunity from 1990 to 2006: 113 with vasculitis, 92 with lupus, 24 with interstitial lung disease (ILD) and four with other autoimmune processes. It should be noted that about a quarter of vasculitis patients had extracutaneous involvement. In some patients, features were very similar to idiopathic SLE, raising the possibility of unmasking of an underlying case of lupus or an overlap connective tissue disease by the TNF inhibitor. Unlike other typical drug-induced entities, which are usually self-limited, ILD patients were shown to have a poor prognosis, with methotrexate possibly playing an adjuvant role [6]. The report from the British Society for Rheumatology Biologics Register, which prospectively collects data on all patients with RA receiving biologic therapy in the UK, showed a 6.5-fold higher mortality in patients with preexisting lung disease [6]. It was concluded that because of the shared features of the drug-induced phenomenon and the underlying diseases for which TNF inhibitors are used, it is important to document initial clinical presentation and to consider baseline immunologic screening prior to starting these agents.

In addition to lupus and vasculitis-like features, there are a few other specific autoimmune entities that appear to develop in relation to particular medications; associations have been found between sarcoidosis and interferon (IFN) therapy [3••], polymyositis or ankylosing spondylitis and interleukin (IL)-2 therapy, inflammatory myositis with anti-Jo-1 antibodies and statins therapy and DIL and Churg–Strauss syndrome (CSS) with leukotriene antagonists (LTAs). The association between LTAs and the development of CSS is controversial [28•,29,30]. As CSS is a very rare condition, studying the association has been challenging and reporting bias may be a confounding factor. In addition, the severity of asthma and use of other daily asthma medications may also have an association with the development of CSS independent of LTA use [29].

Does autoantibody positivity mean clinical autoimmunity?

Medications can induce different autoantibodies such as ANA or ANCA, but the presence of the autoantibodies alone without clinical features is not an indication to stop treatment in all patients. For example, almost 90% of patients treated with procainamide, one of the most common agents to cause DIL, develop a detectable ANA, but only 30% develop the features of DIL [1••]. This is the case for many medications; in clinical trials and registries of patients treated with anti-TNF agents, development of DIA remained low (generally $<1\%$), whereas autoantibodies develop in almost two-thirds of the patients [1••,3••,5,31,32]. Generally, the antibody titers fall over time when the drug is stopped, though it may take months for them to become undetectable. This is also the case in patients who develop DIA. Despite the self-limited, short duration of the symptoms, antibodies may remain positive for many months.

The ANA pattern in DIA is typically homogenous, representing the chromatin binding, targeting both DNA and the subnucleosomal complex (H2A–H2B) as well as certain high-mobility groups (HMGs) such as nucleosomal core proteins, HMG-14 and HMG-17 [4•]. Positive antihistone antibody is the hallmark of DIL, shown in more than 90% of the cases, but this is less common for some drugs such as minocycline [18•] and TNF inhibitors [5]. Unlike the ANA of idiopathic SLE, the ANA in DIL does not have complement-fixing properties [2,7]. Consequently, one distinction between idiopathic and drug-induced lupus is often the presence

of normal complement levels in the latter.The presence of antidouble stranded (ds) DNA antibodies has generally been a rare finding in DIA, although higher rates of anti-dsDNAs [usually immunoglobulin (Ig)M and sometimes IgA antibodies] are found in patients treated with TNF inhibitors [1••,3••,5]. In cutaneous forms of DIL, anti-Ro autoantibody positivity is common [12•,22•], and antiphospholipid antibodies are found in a subgroup of patients with both drug-induced vasculitis and DIL. The presence of these antibodies may be helpful in differentiating the idiopathic vasculitis from drug-induced vasculitis, as antiphospholipid antibodies are rare in the idiopathic form [4•]. Additionally, in drug-induced vasculitis, ANCA most commonly has a perinuclear staining pattern with MPO specificity. ANCAs to other proteins such as cathepsin G, HLE, elastase and lactoferrin have also been described. In contrast to idiopathic vasculitis, in drug-induced cases p-ANCA positivity may be directed to more than one antigen [4•].

Mechanisms of drug-induced autoimmunity

Similar to other forms of autoimmunity, the development of autoimmunity in DIA is multifactorial. Many mechanisms have been implicated, which are summarized below.

Associations with certain human leukocyte antigen (HLA) haplotypes have been shown, including HLA-DR2, HLA-DR4 and HLA-DR3, in addition to the slow acetylator status and C4 null allele [2,7,33]. Hydralazine and procainamide alter the structure of the nucleosome. This is hypothesized to increase the immunogenicity of the nucleosome, triggering the production of autoantibodies. Quinidine and procainamide inhibit the uptake of apoptotic cells by macrophages, which may increase autoantibody production by making cellular antigens more readily available. Alternatively, inhibition of apoptotic pathways by drugs such as minocycline is also considered of DIA. The process could be mediated via inhibition of cytochrome *c* release or caspase-1 and 3, leading to decreased opsonization and phagocytosis of cell debris. In turn, this could allow nuclear debris to be available for immune recognition, thereby potentiating the development of autoantibodies [7,33,34].

Direct cytotoxicity of the drug metabolites is also implicated in DIA. This may explain how drugs from different classes trigger similar conditions. Autoantibodies may develop to haptenized drugs or to self-antigens altered by the drug (neoantigens), leading to the development of autoimmunity. Drugs may break self-tolerance either centrally in the thymus or peripherally [7,33,35]. There is a possible role of DNA hypomethylation; DNA methylation is an epigenetic process that can affect the expression of a gene without changing the DNA sequence. Inhibition of DNA methylation alters gene expression and cellular function. Both procainamide and hydralazine are known to cause T-cell DNA hypomethylation, in turn increasing expression of some key elements of the immune response such as lymphocyte function-associated antigen 1, perforin, CD40 ligand (CD40L) and various cytokines such as IL-4 and IFNγ. In recent years, details of this effect have been clarified for hydralazine, which causes decreased extracellular signal-regulated kinase pathway signaling, and for procainamide, which inhibits DNA methyltransferase [36,37•].

An additional mechanism of DIL proposed for TNF inhibitors involves shifting of the T-helper profile. SLE is considered to have a T helper cell (Th)2-type cytokine profile with significant B-cell activation. TNF inhibitors, by blocking the Th1 cytokine TNFα, may shift the immune system to a Th2 profile with the production of autoantibodies and the development of lupus-like features. Alternatively, it is hypothesized that by blocking TNF, there is an increase in infectious load, causing immunostimulation and polyclonal B-cell activation. Yet another possibility is increased apoptosis due to binding of TNF inhibitors to target cells. This in turn may lead to increased release of nuclear antigens, triggering autoantibody production by exposure of previously hidden antigens. It is known that TNFα levels are low during exacerbations of SLE [3••]. As etanercept does not bind cells, this theory cannot explain the development of autoimmunity with etanercept, the incidence of which is very similar to infliximab (0.18 versus 0.19%), although autoantibody production is reported to be higher with infliximab compared with etanercept [7,10]. It is also possible that by downregulating C-reactive protein, TNF inhibitors indirectly decrease the clearance of apoptotic cells [3••]. The decreased expression of CD44 by TNF inhibitors may also play a role as CD44 aids in apoptotic cell clearance [38]. The new antibody to the IL-6 receptor, tocilizumab, lowers CRP even more rapidly than TNF inhibitors. Thus, one test of this hypothesis will be whether the incidence of autoantibodies and DIL are similarly elevated in patients treated with tocilizumab.

Conclusion

Since the initial description of DIA, more than a half a century ago, significant progress has been made in understanding the underlying mechanisms of this entity. Although DIA is generally considered to be a benign condition, it must be emphasized that, as we have also found at our institution in patients with MIA, DIA may be chronic, with long-term morbidity. As new classes of medications for the treatment of many disorders are

developed, we expect that the number of agents causing the DIA will increase, especially in the era of targeted immune modulation. DIA and the unexpected effects of these newer medications continue to be described, demonstrating our present limited understanding of the immune system, and our inability to predict the consequences of manipulating its complex homeostatic mechanisms. Undoubtedly, understanding the mechanisms of DIA will aid in furthering our understanding of the normal functioning immune system, as well as the pathogenesis of autoimmune conditions in general.

References and recommended reading

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