Evolving and expanding scope of lupus-inducing drugs

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Drug-induced lupus (DIL) is a side effect of long-term treatment with various medications, an idiosyncratic adverse drug reaction (ADR) that has been documented for some seven decades. While symptoms can be severe, DIL, unlike systemic lupus erythematosus (SLE), is fully reversible simply by discontinuation of the inducing medication, although full recovery can take several months. However, as with SLE, diagnosis of DIL is often missed or delayed in part because onset of symptoms can be gradual and variable and because the temporal link to the implicated drug is often not apparent. DIL typically develops after many months or years of largely symptom-free continuous drug use. While bonafide SLE or other idiopathic autoimmune disease would naturally be included in the differential diagnosis of someone who develops lupus-like symptoms, awareness that symptoms could be iatrogenic due to chronic medication can be the most important factor in making a correct and prompt diagnosis. Failure to do this often results in prolonged and worsening symptoms and unnecessary or ineffective anti-inflammatory/immunosuppressive treatment.

The literature is replete with well-documented case reports of DIL due to some 70 different drugs as well as numerous reviews on this subject that list reported lupus-inducing drugs and their relative risk of causing this adverse side effect. However, because many drugs have a low or very low risk of causing lupus-like symptoms, it can be challenging to recognise DIL as the underlying cause of symptom development. In addition, increased use of new medications and/or the absence of publications of full case reports raise the possibility that other drugs exist with a DIL propensity. Gratefully, with the creation of Vigibase by the WHO in 1967,¹ a mechanism for reporting potential lupus-inducing drugs has been facilitated without the formality of fully documented case reports. This Individual

Case Safety Reports (ICSR) database now contains >16 million reports of suspected ADRs, usually contributed by hospitals, healthcare professionals or pharmaceutical companies from over 130 countries. Using the standard term 'SLE' for the symptom category in the ICSR in Vigibase, data on medications for which there is no or little awareness of their possible lupus-inducing propensity continues to be collected.

Arnaud *et al*², have now extracted from Vigibase 8163 ICSRs in the category of new-onset SLE in association with 118 medications along with the statistical estimate of the degree of each drug's association with lupus-like symptoms. A sort of relative risk, the 'Information Component (IC)' was created, which is a measure of the disproportionate prevalence of new-onset SLE-like symptoms during treatment with a particular drug. The IC is normalised to reports of SLE-like symptoms from all drugs included in Vigibase (the 'Nexpected' value) to neutralise pervasive false reports of lupus-like symptoms due to incorrect assessment of symptoms. To provide a conservative, 95% credibility interval for the IC, IC₀₂₅ values were used, which are the lower end (the 25th–75th percentile IQR) around the median report prevalence. In this way, any positive IC₀₂₅ value, that is, >0, is a statistically significant measure of disproportionate cases of SLE-like symptoms for any drug included in Vigibase. However, a relatively high IC₀₂₅ for a particular drug does not necessarily translate to a high propensity for causing lupus-like symptoms but may in part be a reflection of high drug usage and awareness or insight of report contributors to detect new-onset SLE. On the other hand, a low IC₀₂₅ value does not necessarily mean that the drug is unlikely to cause DIL but may be a reflection of its tendency to be associated with other adverse side effects as well.

The findings in this report are validated in part by the successful mining from Vigibase of drugs that were previously described in the literature as having lupus-inducing propensity based on MEDLARS Online search of publications (Medline) using the Mesh terms 'Lupus Erythematosus, Systemic/chemically

induced'. Further, drugs known from the literature to have a particular high risk for DIL (procainamide and hydralazine) also had high IC₀₂₅ values (7.48 and 6.63, respectively). Additional validation is the observation of a median delay between initiation of therapy and appearance of symptoms of 172 days and up to 2 years, consistent with published case reports and systematic studies on the relatively long lag time during continuous drug exposure for this type of ADR to develop. However, a curious finding in the present report was that for almost all of the drugs, there was a greater number of women with suspected DIL, with an overall average female/male ratio of 4.3. While it has been previously reported that a disproportionate percentage of women treated with procainamide³ and hydralazine⁴ develop DIL, it is possible that the female skewing in the current findings reflects in part the female preponderance of drug prescriptions. This is likely true for the drug categories of genitourinary systems, sex hormones, systemic hormonal preparations and immunomodulating agents and may underlie the reported high prevalence in women of drug-induced subcutaneous lupus erythematosus^{5, 6} and DIL associated with antitumour necrosis alpha (TNF α) agents.⁵ In the case of procainamide, in which the Vigibase reported only 38% females with DIL, this apparent exception presumably reflects the predominant use of this drug in men with heart arrhythmia. Overall, however, the findings of a strong skewing towards women with DIL mirrors the well-described female association with the majority of idiopathic autoimmune diseases as well.⁷ It has been suggested that, during onset of autoimmune diseases such as SLE, the female sex hormone estradiol E2 promotes nascent Th2 cell-driven autoreactive B cell survival through oestrogen receptor (ER)- β ⁸ and activates type 1 interferon-inducible genes in plasmacytoid dendritic cells through ER- α ,⁹ thereby enhancing incipient autoimmunity. A similar phenomenon may underlie DIL. However, the immunomodulating effects of estrogens, progesterone and androgens depend on many factors, which confound a universal mechanistic explanation for sexual dimorphism in systemic autoimmune diseases such as SLE and DIL.¹⁰

The current analysis shows that the TNF α -blocking biologics, particularly infliximab, adalimumab and etanercept have replaced the cardiovascular (CV) drugs procainamide, hydralazine

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and quinidine as the most commonly reported agents associated with DIL. This fact is presumably due to the decreased prescription and dosage of these CV agents largely because of their known lupus-inducing propensity and the now frequent use of macromolecular biologics in the treatment of rheumatic diseases. However, the mechanism whereby immunomodulating antirheumatic agents could cause DIL is different from that of the CV agents in that the TNF α -blockers have an intrinsic capacity to alter cytokine regulatory pathways towards SLE in mouse models.^{11 12} In addition, in contrast to CV disease, patients being treated with TNF α -blockers already have a pre-existing autoimmune disease and, therefore, are at risk for spontaneously evolving into another one such as SLE.

It is difficult to distinguish DIL from SLE merely on the basis of symptoms presentation, and even laboratory abnormalities show considerable overlap. The definitive feature of DIL is that symptoms and eventually signs resolve after stopping treatment, preferably without anti-inflammatory medications. VigiBase does not ask for this information. Therefore, some of the reports of DIL may be false because of coincident idiopathic SLE or other autoimmune or non-autoimmune diseases. Presumed examples of such false reports include those associated with the intravenous perfusion of inorganic salts or other natural solutes after a median of 120 days. Other inappropriate entries are the hundreds of reports of 'SLE' associated with at least four types of vaccines that appeared 1 day to almost 2 years after vaccination. Even without these obvious examples of misinformation, the accuracy of lupus-like disease being related to drugs reported in VigiBase is open to question, especially considering the difficulty of diagnosing SLE even by rheumatologists. On the other hand, because symptoms of DIL can often be protean or of a limited or mild nature such as only myalgia or arthralgia, SLE is likely to be an excessively rigid diagnostic consideration, resulting in failure to recognise DIL especially by non-healthcare individuals, which represented 46% of the reporters of clinical data in the current study.

Sustained blood levels of bonafide lupus-inducing drugs must generally be maintained for many months to years for development of lupus-like disease, consistent with many of the reports in VigiBase. With procainamide, the typical patient develops symptoms after 10

months treatment, and approximately one-fourth of patients do not develop symptoms until more than 2 years and some as long as 6 years of continuous drug exposure.^{13 14} Nevertheless, most procainamide-treated patients, especially slow drug acetylators, develop antide-natured DNA and antinuclear antibody during the first year of treatment¹⁵ but generally do not progress to symptomatic disease unless they develop immunoglobulin G anti-(H2A-H2B) antibodies.³ Interestingly, autoantibodies such as anti-Ro, anti-La and antiphospholipid also commonly appear several years before symptoms and diagnosis of SLE, at which time new specificities are detectable, particularly anti-double-stranded DNA, anti-Sm and antinuclear ribonucleoprotein antibodies.¹⁶ While there is little evidence that continuous exposure to environmental factors underlies SLE development, the apparent similarities between DIL and SLE in kinetics of serological changes prior to symptomatic disease likely reflects the inherent vulnerability of the immune system to undergo prototypic dysregulation, ultimately manifesting as lupus-like disease.

An ever-expanding range of treatment categories, chemical structures and pharmacological actions are included in this new list of possible lupus-inducing drugs. It remains puzzling as to what the common denominator is that links drugs with capacity to cause DIL. DIL is an idiosyncratic ADR unrelated to any known property of the inducing agent, with the possible exception of the cytokine-modulating biologics. However, in vivo metabolism of dissimilar drugs to products with a common, reactive property may explain how compounds with widely different pharmacological and chemical structures could induce similar adverse reactions. In addition to intrinsic, genetically determined differences in people for capacity to metabolise drugs, the composition and changes in the gut microbiota may contribute to variability in propensity for reactive drug metabolite generation.¹⁷ Ultimately, the requirement for a coincidence and/or sequence of events within an immune compartment is likely to underlie immune (self)-tolerance breakdown and development of autoimmunity and autoimmune disease.

A total of 42 drugs were identified by Arnaud *et al*² that have not previously been known to cause DIL. While these findings will need better documentation than just positive IC₀₂₅ values, they should help to sensitise the medical community

to increased vigilance of previously unreported DIL and motivate the publication of novel, convincing case reports. The WHO International Drug Monitoring Programme, the many contributors to individual case safety reports in VigiBase and especially the authors deserve our thanks and appreciation for their work, resulting in a valuable resource that offers promise to minimise the suffering of patients due to this ADR.

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