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An update in drug-induced subacute cutaneous lupus erythematosus

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Abstract

Background: It has been over three decades since the first report of drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) was described. With an increasing variety of implicated drugs and the potential for publication bias, we must consider: 1) has there been a change in drugs most often reported in DI-SCLE over time, and, 2) if so, of which drugs should clinicians be most suspicious in the setting of possible DI-SCLE?

Objective: To determine which drug(s) present the highest risk for inducing DI-SCLE.

Methods: The PubMed database was queried for reports of DI-SCLE from August, 2009 until May, 2016. Cases reported in the English language were organized by drug class and compared with the results of our previous review.

Results: From 55 selected publications, 95 qualified reports of DI-SCLE were identified. With the exception of a population-based study from Sweden, all other reports of DI-SCLE appeared as case reports or small case series. Cases associated with proton pump inhibitors relative to all other medications were increased by 34.1%. Reports associated with antihypertensive and antifungal medications decreased by 28.9% and 22.4%, respectively during this timeframe. The majority of new reports were associated with drugs not previously described. Greater than 70% of reports since August, 2009 were from European countries.

Conclusions: The number of drugs associated with DI-SCLE is increasing. However, a form of publication bias has likely contributed to this shift in reporting. There is a need for additional large, population-based studies in this area.

Keywords: subacute cutaneous lupus erythematosus (SCLE), drug-induced, photosensitivity, proton pump inhibitors

Introduction

In 1985, Reed et al. [1] described five patients with the development of subacute cutaneous lupus erythematosus (SCLE) skin lesions that appeared to be associated with hydrochlorothiazide therapy. After a successful re-challenge with a thiazide diuretic in one these patients, the concept of drug-induced subacute cutaneous lupus erythematosus (DI-SCLE) was born. Subsequently, thiazides, calcium channel blockers and antifungals (especially terbinafine) were thought to be the most common triggers of DI-SCLE. Now, more than 40 drugs have been associated with the development of SCLE [2]. This number continues to rise with case reports of new culprit drugs published every year.

Now that the clinical concept of DI-SCLE is three decades old, how much do we really know about the drugs most likely to cause DI-SCLE? The increasing variety of reported triggering agents can in part be attributed to the development and availability of new medications. In addition, there may be some degree of case reporting bias at play here. Case reports are extremely useful as a flexible and rapid method to present new clinical and educational information. Although case reporting often draws value from presenting the atypical and rare, our attention might be distracted from the common diseases and problems [3].

In this regard, several questions have been raised in our minds as to the reason(s) why an increasing

array of drugs have been reported to be capable of triggering DI-SCLE. Has there has been a significant shift in drug classes that have been reported to be triggers of DI-SCLE? If so, have geographical variation in medical practice and/or advances pharmaceutical therapeutics contributed to this shift? We sought to better address these and related questions by performing a review of the new cases of DI-SCLE reported between August, 2009 and May, 2016.

Methods

Case definitions. The primary case definition for this study is that previously described of DI-SCLE and used in prior review of the literature [2] (i.e. the initial appearance of typical clinical, histopathological, immunopathological and laboratory manifestations of SCLE following the administration of one or more systemically administered drugs).

Case identification. The Medline database was queried via PubMed with the terms 'drug induced subacute cutaneous lupus erythematosus', 'induced subacute cutaneous lupus', and 'drug induced lupus' from August, 2009 to June, 2016. Case identification was based on prior methods [2], and non-English language publications were excluded from analysis. If a case had been accepted as having DI-SCLE by the medical journal's review process, it was deemed appropriate to include in our analysis. To better preserve consistency in case selection, those with limited clinical detail as part of a larger series were included only if biopsy findings were also supportive of SCLE diagnosis.

Study design. Qualifying publications were reviewed and information was collected from reports meeting the case definition for this study. Data including the investigator, journal, number of cases, patient's age, sex and gender, country of corresponding author, and implicated drug(s) were collected for each case and documented. If details of multiple DI-SCLE events were described affecting the same individual, each qualified episode was counted individually.

Data analysis. We analyzed the data based on the information available for each identified case in the literature. There were several authors who reported patients taking multiple drugs at DI-SCLE diagnosis. For statistical analysis, the causative agent was attributed to the drug the author(s) named as such. If the implicated drug could not be named, it was selected based on the presence of prior evidence in causing DI-SCLE. Implicated drugs were grouped according to drug class. Immunomodulating agents considered to be "biologic" were categorized separately from other "non-biologic" immunomodulators. Incidence was calculated for each drug class or category from the number of total cases identified for each time period.

Results

Review of the PubMed literature revealed 95 cases of DI-SCLE from August, 2009 to June, 2016. Of these, 81 (85%) involved patients who were female. The mean age was 59 years. In cases that reported ethnicity, 6 of 14 involved Caucasian patients. **Table 1** (See Supplement) presents all drugs identified to be associated with DI-SCLE to date. In addition to these listed, other drugs have been anecdotally implicated as potential triggers of DI-SCLE including spironolactone and glyburide [4]. Of the 95 newly identified cases, 55 (58%) described a novel drug association with DI-SCLE since our prior review.

Figure 1 shows the relative change in reports by drug class from August, 2009 to present. The greatest shift in drug class reporting was seen with proton pump inhibitor medications, increasing by 34.1%. Also with notable increases were chemotherapeutic (12.6%) and biologic (11.7%) classes. Reports of non-biologic immunomodulators including leflunomide, interferon α and β, hydroxychloroquine, and imiquimod were only slightly increased in comparison (1.6%). The greatest decrease in reports occurred in antihypertensive (-28.9%) and antifungal (-22.4) classes.

Figure 2 illustrates the number of newly identified reports by continent. The majority of cases were reported from European countries (74%), followed by North American (18%), and Asian (5%). European countries also provided the majority of cases identifying novel drug associations.

Discussion

Analysis of the data reveals some trends in the reported frequency of drug classes over time, which raises several questions regarding what might be contributing to shifts in number of cases for a drug

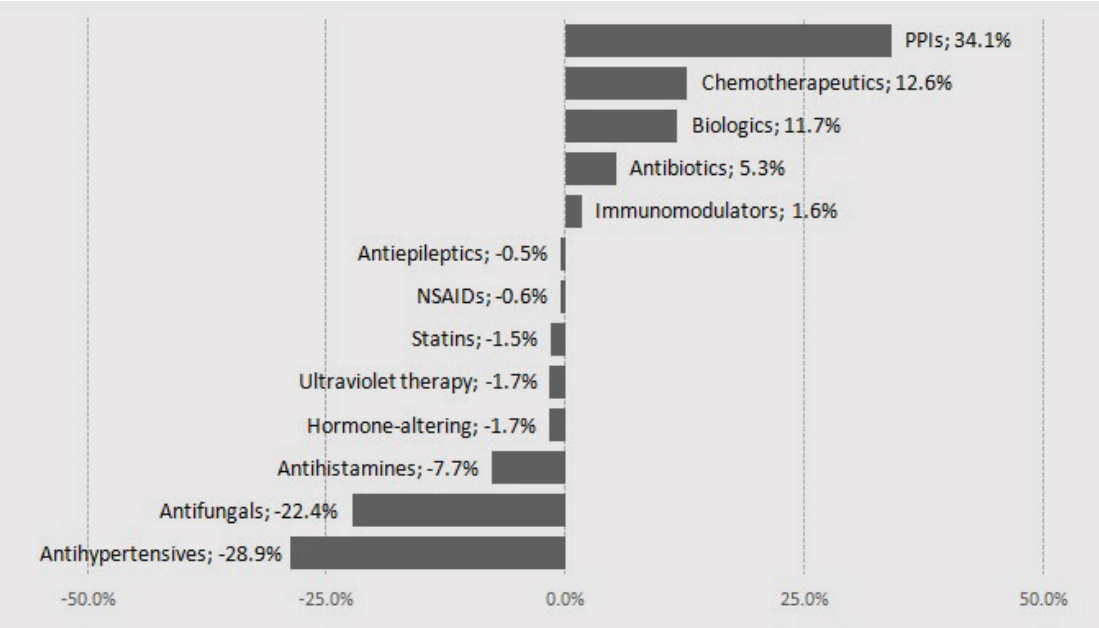

Figure 1. *Change in incidence of DI-SCLE reports by drug category since August 2009*

over time.

1 What role does bias have in the present analysis of the literature?
2 Could other factors have contributed to shifts in drug class reports over time?
3 Why might differences exist in the number of DI-SCLE reports geographically?
4 Which drugs should clinicians consider most imputable to DI-SCLE?

What role does bias have in the present analysis of the literature?

Some of the observed shift in DI-SCLE reports is certainly related to the presence of a form of publication bias. The major merits of case reporting include the detection of novelties, pharmacovigilance, and generating hypotheses [3]. Major limitations include the presence of publication bias and possible distraction of the reader when focusing on the unusual [3]. We observed the majority of recently published reports described drugs not previously associated with SCLE, supporting the hypothesis that a form of publication bias might exist for selection of rare or novel drug associations in the literature.

The conventional definition of publication bias is the type of bias that determines what type of academic research is selected for publication. For example, journal editors are more likely to select for publication studies having valid rather than flawed methodologies and positive results rather than negative results relating to a hypothesis. Likewise, journal editors are more likely to accept for publication a case report of a new drug trigger of SCLE compared to a report presenting additional cases of a previously-reported drug trigger of SCLE. Thus, it might not be surprising that a clinical observer would more likely choose to write-up and submit for publication a case report for a new drug class as a triggering agent for SCLE compared to a drug class that has been reported in the past.

The conventional use of the term "bias" in academic research is applied to original reports presenting new, hypothesis-driven data rather than observational case reports and reviews of published case reports. More hypothesis-driven, population-based, controlled epidemiologic studies of the DI-SCLE phenomenon such as that reported by Gronhagen et al. [5] are needed for further clarification relating to this important clinical question.

Could other factors have contributed to shifts in drug class reports over time?

Drug availability and/or popularity among a population may also have a role in changing the incidence of DI-SCLE for a drug class. Hydrochlorothiazide was associated with 11% of the total reported cases at the time of our last review, and in 1985 was the first drug associated with DI-SCLE [1]. Historically, hydrochlorothiazide has been a very popular drug in the United States, driven primarily by its familiarity from use in the country's first controlled trial for nonmalignant hypertension. Popularity has declined over time as newer medications have been introduced with evidence for better outcomes [6]. Two of the largest increases in reports have occurred in proton pump inhibitor and

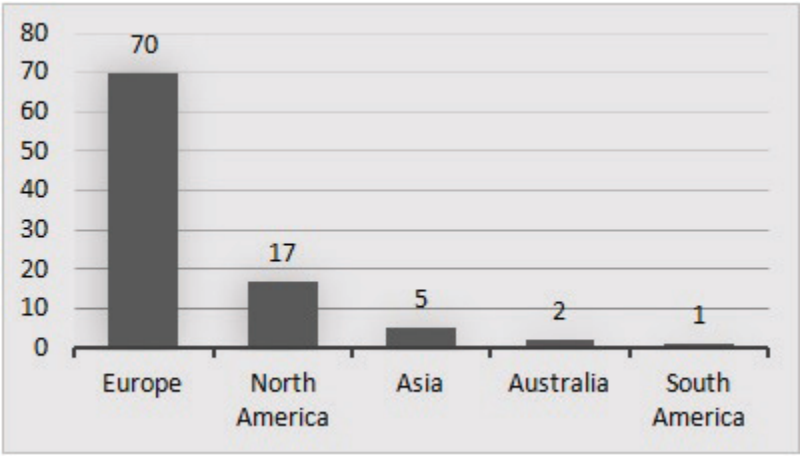

Figure 2. *DI-SCLE reports by continent since August 2009*

biologic immunomodulator classes. Of note, proton pump inhibitors are being increasingly used among US ambulatory centers [7]. In addition, the protein pump inhibitor omeprazole was made available in the United States to the public without a prescription in 2002. Tumor necrosis factor inhibitor use is also growing and in earlier levels of disease activity [8].

The ongoing introduction of newly approved pharmacotherapies may also be contributing as well as other factors such as changes in cost, provider preference, disease rate, or level of healthcare access.

Why might differences exist in the number of DI-SCLE reports geographically?

Since August 2009, nearly three quarters of the cases reported have come from authors in European countries. This could be related to the fact that SCLE has been associated with certain susceptibility genes found in a number of Europeans. Several genes have been associated with the development of idiopathic SCLE, including the HLA-A1-B8-DR3 haplotype (HLA 8.1), C2 and C4 deficiency, TNF-alpha-308A polymorphism, and C1q deficiency [4]. An estimated 10% of Northern Europeans carry the HLA 8.1 haplotype, and the haplotype is much less common in other parts of the world. This could certainly contribute to the differences in reporting rates compared with the rest of the world.

There may also be an increased number of case reports from countries with more highly developed healthcare systems. Among others, Europe and North America combine to contribute 92% of the total cases reported in the literature since August, 2009.

Which drugs should clinicians consider most imputable to DI-SCLE?

Hydrochlorothiazide and terbinafine have been widely recognized as two of the most frequently associated drugs with DI-SCLE in the literature. However, our review of the literature from August, 2009 to present identified only three additional reports of DI-SCLE between the two. Is the frequency of reports over time the correct approach to determine risk? Is it safe to assume that drugs with a paucity in reports as having low risk? It is difficult to accurately predict drug imputability using information largely from case reports in the literature alone.

In 2012, Gronhagen et al. published a population-based matched case-control study examining the relationship between the previously reported drugs in the literature and incident SCLE cases in Sweden [5]. From 234 cases and 2,311 matched controls, the authors examined drug exposures 0-6 months prior to SCLE development. Of all drugs previously associated with DI-SCLE in the literature, the relative risk estimates were highest for terbinafine (OR 52.9, 95% CI 6.6-∞), and tumor necrosis factor inhibitors (OR 8.0, 95% CI 1.6-37.2) [5]. Antiepileptics (OR 3.4, 95% CI 1.9-5.8), proton pump inhibitors (OR 2.9, 95% CI 2.0-4.0), thrombocyte inhibitors (OR 2.2, 95% CI 1.5-3.2), and nonsteroidal anti-inflammatory drugs (OR 1.7, 95% CI 1.1-2.7) all were also observed to have significantly increased relative risk for SCLE onset [5]. Although 160 of the 234 cases had taken at least one antihypertensive medication in the 6 months prior to SCLE diagnosis, only ACE-inhibitors showed a significant association with SCLE onset when matched with controls (OR 1.7, 95% CI 1.1-2.7) [5]. Patients taking thiazides were not observed to have a significantly associated risk for the development of SCLE. This is curious since hydrochlorothiazide was the first drug reported to be a trigger for SCLE [1]. These observations would suggest that while thiazide diuretics were the first drug class recognized to be capable of inducing SCLE, the association between thiazides and SCLE might not be any more significant than that of other drug triggers reported subsequently.

The Gronhagen et al. [5] study gives further understanding of which drugs carry risk of DI-SCLE.

There is no apparent association between the total number of reports for a drug over time and the statistically significant associations identified by Gronhagen et al. This study was the first of its kind, and we believe additional studies by this design are warranted to further reveal which drugs can be considered as truly causative. It is possible that additional results may vary between regions with changes in genetic predispositions and medication popularity. Though limited, recent pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database supports a signal of a similar association in the United States between SCLE and proton pump inhibitors [9].

In conclusion, this article represents an updated review of the literature and a measurement of the observed change in causative drugs over time. It also serves as a reminder to readers evaluating DI-SCLE imputability to be aware of possible influences from bias. We acknowledge that this retrospective analysis has its limitations, including variables related to case identification. This report did not include cases reported in foreign languages, as translation resources for inclusion of additional reports were not available to us. However, our analysis of the literature reveals a previously unknown change in the drugs reported to cause DI-SCLE in favor of newly developed agents or those previously undescribed.

To best assess which drugs hold a high risk for the development of DI-SCLE, the information should be evaluated with the presence of a large prospective study and not from case reporting information alone. We recommend using results from articles similar to Gronhagen et al. [5] to confirm suspicions for associated DI-SCLE. Further studies of this nature are warranted in populations with increased DI-SCLE occurrence.

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Supplement

Table 1. Drugs identified as causative of drug-induced SCLE in this report

	Lowe et al. [2]	Aug 2009 - present
Antihypertensives	40/117 cases: 34.2%	5/95 cases: 5.3%
Calcium channel blockers		
Diltiazem	6 cases	
Verapamil	5 cases	
Nifedipine	3 cases	1 case [9]
Nitrendipine	1 case	1 case [10]
Amlodipine		1 case [11]
Diuretics		
Hydrochlorothiazide	10 cases	
Hydrochlorothiazide + triamterene	3 cases	
Chlorothiazide	2 cases	
Beta blockers		
Oxprenolol	4 cases	
Acebutolol	1 case	
ACE - inhibitors		
Enalapril	2 cases	1 case [10]
Lisinopril	1 case	
Captopril	1 case	
Cilazapril	1 case	
Ramipril		1 case [10]
Antifungals	30/117 cases: 25.6%	3/95 cases: 3.2%
Terbinafine	29 cases	3 cases [12, 13]
Griseofulvin	1 case	
Chemotherapeutics	10/117 cases: 8.5%	20/95 cases: 21.1%
Docetaxel	3 cases	4 cases [14-17]
Paclitaxel	3 cases	1 case [18]
Tamoxifen	2 cases	
Capecitabine	2 cases	4 cases [19-22]
Doxorubicin		1 case [23]
Doxorubicin + Cyclophosphamide		4 cases [24, 25]
Gemcitabine		2 cases [26, 27]
Pazopanib		1 case [28]

Table 1. Drugs identified as causative of drug-induced SCLE in this report		
Mitotane		1 case [29]
Pemetrexed and/or Carboplatin		1 case [30]
Fluorouracil		1 case [31]
Antihistamines	9/117 cases: 7.7%	0/95 cases: 0.0%
Ranitidine	7 cases	
Bromopheniramine	1 case	
Cinnarizine + thiethylperazine	1 case	
Immunomodulators	8/117 cases: 6.8%	8/95 cases: 8.4%
Leflunomide	5 cases	1 case [10]
Intereron α and β	3 cases	3 cases [32-34]
Hydroxychloroquine		2 cases [10]
Imiquimod		2 cases [35, 36]
Antiepileptics	3/117 cases: 2.6%	2/95 cases: 2.1%
Carbamazepine	2 cases	1 case [10]
Phenytoin	1 case	
Lamotrigine		1 case [37]
Statins	3/117 cases: 2.6%	1/95 cases: 1.1%
Simvastatin	2 cases	1 case [38]
Pravastatin	1 case	
Biologics	2/117 cases: 1.7%	12/95 cases: 12.8%
Etanercept	1 case	3 cases [10, 39, 40]
Efalizumab	1 case	
Adalimumab		2 cases [40, 41]
Golimumab		2 cases [42, 43]
Ranibizumab		1 case [44]
Bevacizumab		1 case [45]
Infliximab		2 cases [40]
Rituximab		1 case [46]
Proton pump inhibitors	2/117 cases: 1.7%	34/95 cases: 35.8%
Lansoprazole	2 cases	15 cases [47-51]
Omeprazole		11 cases [51-55]
Pantoprazole		3 cases [51, 53]
Esomeprazole		5 cases [51, 53, 56]
Nonsteroidal anti-inflammatory drugs	2/117 cases: 1.7%	1/95 cases: 1.1%

Table 1. Drugs identified as causative of drug-induced SCLE in this report		
Naproxen	1 case	
Piroxicam	1 case	1 case [10]
Hormone-altering drugs	2/117 cases: 1.7%	0/95 cases: 0.0%
Leuprorelin	1 case	
Anastrozole	1 case	
Ultraviolet therapy	2/117 cases: 1.7%	0/95 cases: 0.0%
PUVA	1 case	
PUVA and UVB	1 case	
Antibiotics		5/95 cases: 5.3%
Minocycline		1 case [57]
Doxycycline		1 case [58]
Norfloxacin		1 case [59]
Amoxicillin + clavulanic acid		1 case [10]
Nitrofurantoin		1 case [60]
Others	4/117 cases: 3.4%	4/95 cases: 4.2%
Bupropion	1 case	
Tiotropium	1 case	
Ticlopidine	1 case	
Hay with fertilizer	1 case	
Citalopram		1 case [61]
Allopurinol		1 case [10]
Iodine-131		1 case [62]
Amiodarone, Torasemide, Losartan, Phenprocoumone*		1 case [63]

Abbreviations: ACE-I, angiotensin converting enzyme. PUVA, psoralen plus ultraviolet (UV) A. SCLE, subacute cutaneous lupus erythematosus.
*Reported in combination without known causative agent(s).