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Do selected drugs increase the risk of lupus? A matched case-control study

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WHAT IS ALREADY KNOWN ON THIS SUBJECT

- Numerous previous case reports have suggested that lupus can be induced by a range of prescription medications.
- Analytical studies quantifying risk of drug-induced lupus are lacking.

WHAT THIS STUDY ADDS

- This was the first large study to quantify risk of lupus associated with carbamazepine, hydralazine, and other prescription medicines suspected of inducing the disease.
- We confirmed some, but not all, associations that have been hypothesized in case reports.
- This study provides evidence that increased risks may be causal given the lack of an increased risk observed with deliberately selected 'comparison' drugs.

AIM

To investigate the association between risk of lupus and exposure to selected drugs implicated in risk of lupus in a number of case reports.

METHODS

In this matched nested case-control study we utilized primary care data from the UK General Practice Research Database recorded between 1987 and 2001. Cases with at least one medical code for systemic lupus erythematosus or drug-induced lupus in their computerized records were matched to controls without a medical code for lupus or any other autoimmune disorder. Using conditional logistic regression we computed odds ratios (OR) and 95% confidence intervals (CI) for risk of lupus associated with exposure to selected drugs.

RESULTS

There were 875 incident cases, of which 12% (n = 107) had evidence of a prescription for one or more of the suspected drugs, and 3632 matched controls. For some drugs, prescriptions were too uncommon to be able to estimate associated risk of lupus. Despite small numbers of exposed patients and low statistical precision we observed an increased risk of lupus for hydralazine (OR = 6.62, 95% CI 1.03, 42.74), minocycline (OR = 4.23, 95% CI 2.65, 6.75) and carbamazepine (OR = 1.88, 95% CI 1.09, 3.22). There was some indication that the effect of carbamazepine was restricted to women (P for interaction by gender = 0.047).

CONCLUSION

This study shows that even those drugs suggested by case reports as causing lupus cannot all be clearly shown to be associated, even in a very large population-based database. Our findings support causal relationships for carbamazepine, minocycline and possibly hydralazine. Overall, drugs do not seem to be a major cause of lupus.

Introduction

A wide range of prescription drugs has been linked to the induction of auto-antibodies and, to a lesser extent, clinically apparent autoimmune disease. The most extensively documented drug-induced autoimmune disease is drug-induced lupus (DIL). Prescription drugs from several therapeutic classes have been reported to lead to lupus [1, 2]. Convincing evidence exists for procainamide and hydralazine; 20% of procainamide users and 5 to 8% of hydralazine users are said to develop clinically apparent lupus within 1 year of use [3]. However, the majority of evidence for drugs and risk of lupus comes from case reports and case series, not quantitative analytical studies [4]. Risks associated with exposure to these drugs have therefore been defined based on the quantity of case reports published in the literature, with risk levels divided into 'high', 'medium', 'low' and 'very low' [4]. 'Very low' may be based on a single (and potentially false-positive) case report [3].

No clear diagnostic criteria exist for DIL [2]. Many case reports describe symptom resolution upon withdrawal of the suspected drug and occasionally re-challenge has resulted in re-appearance of symptoms, supporting a causal association between suspected drugs and risk of lupus [2, 4]. Since the clinical manifestations of the drug-induced and idiopathic forms of lupus overlap, and formal classification criteria for drug-induced lupus do not exist, distinguishing between the two entities would require data regarding the resolution and non-recurrence of symptoms following termination of treatment with the suspected medication. Laboratory and animal studies provide further evidence of causal associations between drugs and lupus [5].

The UK based General Practice Research Database (GPRD) is a large primary care database that is widely used for pharmaco-epidemiological studies [6]. It contains information on a representative sample of about 6% of the UK population. Because of its size the GPRD is especially useful for studying relatively uncommon diseases such as lupus. Here we report the results of a large population-based matched case-control study utilizing the GPRD to assess and quantify whether selected prescription drugs, implicated in risk of lupus, are associated with risk of disease.

Methods

The GPRD

In the UK, over 98% of the population is registered with the National Health Service (NHS). NHS practices contributing to the GPRD are broadly representative of all UK practices in terms of age and sex distribution of patients, and geographical distribution and size of practices [7]. Data from the GPRD contain patient demographics, clinical data with codes for diagnoses and symptoms and corresponding consultation dates (including outcomes of specialist referrals and hospitalizations), prescription data with corresponding dates, dosages and methods of administration and limited laboratory data. GPRD data are entered by practice staff. Prior to central collection in the database, data are anonymized and their quality is checked. If certain quality criteria are met a practice is said to be 'up-to-standard' (UTS) [8]. Various independent studies have reported high quality and completeness of GPRD morbidity data [8]. For prescription data, high agreement with national data from the prescription pricing authority has been observed [9]. Drug prescriptions are generated by computer, irrespective of UTS status of a practice. We observed no missing or incomplete date values in combination with the prescription data for exposures of interest. Because of the high quality and completeness of the prescription data, we included prescriptions from outside the UTS period in the analyses. This enabled us to investigate exposures occurring over a longer time period than would have otherwise been possible.

Study period and base population

The base population consisted of the cohort of all individuals who were registered during 1987 to December 2001, with a practice that contributed UTS data to the GPRD. This study was part of a larger study of individuals with and without autoimmune diseases, who were selected from this base population.

Identification of incident lupus cases

We captured all individuals with diagnostic codes for systemic lupus erythematosus (SLE) (available on request) which were compiled from a coding dictionary by four investigators (ES, ST, LS, AH), and verified by a rheumatologist whose subspecialty is lupus (W.J. McCune). Codes for cutaneous forms of lupus were not included, except for subacute cutaneous lupus (SCLE) since a high proportion of patients with SCLE develop SLE [10]. The GPRD medical dictionary contains one code for drug-induced lupus, cases of which were also included in our case population. Patients with at least one occurrence of a lupus code in their medical records were identified from the GPRD. The earliest occurrence of a lupus code corresponded to a patient's diagnosis date.

Incident lupus cases with a diagnosis date during the study period and at least 12 months after the start of the UTS period were included. This 12-month period was chosen based on a method developed by Lewis *et al.* [11] and described in further detail for lupus by Somers *et al.* [10]. Cases which had a diagnosis recorded within 12 months of the start of the UTS period, and those with a missing calendar date corresponding to a lupus diagnostic code could potentially have had the disease for some time and had their diagnosis recorded retrospectively (i.e. be prevalent cases). These cases were excluded from the analyses because it would not have been possible to ensure that drug exposures had taken place before lupus

diagnosis. Cases with coexisting autoimmune conditions were also excluded, consistent with criteria used for controls (described below).

Controls

Control subjects had no medical code for any known autoimmune disease, and were eligible if there was at least 1 year between patient registration and occurrence of the index date (i.e. date of lupus diagnosis for the matched case). Up to five controls were matched to each case based on sex, age and practice. Controls had to be registered with their practice at the calendar date on which the matched case was diagnosed with lupus. If no suitable control of the same age was available, the window for matching was extended by 1 year increments up to a maximum age difference of 9 years. Controls not showing any activity in medical, therapy or prevention records in the 3 years before index date were assumed to be inactive and excluded from further analyses.

Exposure definition

Drugs of interest, which have been hypothesized to induce lupus, are listed in Table 1. We investigated drugs which are thought to be associated with a low, moderate or high risk of inducing lupus, based on the number of published case reports [4]. Drugs with an assigned risk level of 'very low' were not included in this study to limit the number of comparisons undertaken and because of the very weak evidence for such associations. We included a selection of drugs that are not known to be linked to risk of lupus to investigate whether effects were specific to the drugs hypothesized to be associated with risk of lupus and to check whether associations were therapeutic class specific. We chose the following frequently used drugs to ensure sufficient statistical power: doxycycline (a tetracycline antibiotic, as is the lupus-inducing drug minocycline), salbutamol (an asthma drug) and diazepam (an anxiolytic). We did not investigate drugs which have been reported to exacerbate pre-existing lupus or to initiate flares [3], because exacerbations of existing disease are difficult to assess reliably using clinical data from the GPRD. Risk of lupus associated with penicillamine and sulfasalazine could not be investigated because cases and controls did not have any autoimmune disease other than lupus, and were thus unlikely to be exposed to these two drugs for the autoimmune disease rheumatoid arthritis. If a study subject received a prescription for a lupus-inducing or 'comparison' drug 1 week or longer before diagnosis (index) date, this subject was considered to be exposed. No maximum time limit between prescription and diagnosis was set to ensure that all potential exposures were included. For drugs to which more than 10 cases and controls were exposed, we grouped number of prescriptions (as a proxy for cumulative dose) into tertiles (based on their distribution among controls) with non-exposed individuals serving as the reference group. This method of categorization ensured that each exposure group contained sufficient cases and controls to carry out investigation of risk of lupus with increasing cumulative dose.

Statistical analysis

Conditional logistic regression was performed to model risk of lupus associated with drug exposures of interest. odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using Stata Software (Version 9, StataCorp, Texas). We investigated whether risk of lupus increased with increasing number of prescriptions by means of a test for trend based on number of prescriptions. Two additional covariates were added to the model based on *a priori* considerations: number of years of available prescription data between registration with the GP practice and lupus diagnosis date (index date for the controls), were included because a study subject with a longer time period of GPRD data is more likely to receive a prescription for a drug of

Table 1

Drugs of interest implicated in risk of lupus, with their estimated risk levels. Reprinted from *Toxicology*, Volume 209 (Issue 2), Robert L. Rubin, Drug-induced lupus, page 13, Copyright (2005), with permission from Elsevier

Drug name	Indication	Drug class	Risk*
Procainamide	Arrhythmias	Anti-arrhythmic	High
Hydralazine	Hypertension	Vasodilator	High
Quinidine	Drug for acute malaria and to treat arrhythmias	Anti-arrhythmic	Moderate
Isoniazid	Anti-tuberculosis drug	Hydrazide	Low
Minocycline	Bacterial infection; primarily used to treat acne	Antibacterials for systemic use; tetracycline	Low
Carbamazepine	Epilepsy	Anti-convulsant; carboxamide derivative	Low
Acebutolol	Hypertension, angina and arrhythmias	Antihypertensive; beta-adrenoreceptor blocker	Low
Captopril	Hypertension	Antihypertensive; angiotensin-converting enzyme (ACE) inhibitor	Low
Methyldopa	Hypertension	Antihypertensive; centrally acting anti-adrenergic agent	Low
Chlorpromazine	Schizophrenia and other psychoses	Psycholeptic; antipsychotic	Low
Prophylthiouracil	Hyperthyroidism	Systemic hormonal preparations; thyroid therapy	Low

*Due to a lack of analytical studies, risks are currently assigned based on number of case reports published in the literature [3].

interest as well as more likely to be diagnosed with lupus. Number of consultations in the year preceding diagnosis date (index date for the controls), was included because a subject with more consultations is more likely to receive a prescription for any drug (including drugs potentially associated with risk of lupus) and more likely to be diagnosed with lupus.

A potentially effect-modifying role of sex and age at diagnosis (index) date, factors on which cases and controls were individually matched, was investigated by computing stratum-specific ORs for men and women, and for younger or older age at diagnosis as defined by the median age at diagnosis. Interaction by sex or age was assessed by adding an interaction term in the regression model. To identify whether DIL can be distinguished from idiopathic lupus by means of its age- and sex distribution, we compared age- and sex distributions of exposed cases with those of unexposed cases. For age, Wilcoxon rank-sum tests were performed to compare median age in exposed *vs*. unexposed cases. A chi-squared test (or Fisher's exact for expected values <5) was performed to investigate if the male : female ratios differed between exposed and unexposed cases.

A Scientific and Ethical Advisory Group (SEAG) reviews all study proposals wishing to utilize GPRD data. We obtained ethics approval from SEAG and from the ethics committee of the London School of Hygiene and Tropical Medicine for this study.

Results

A total of 1375 incident cases of lupus were identified from the GPRD, of whom 875 had no co-morbid autoimmune disease and at least one available matched control, with 3632 matched controls in total (Table 2). 82.8% of the cases were female. Median age at lupus diagnosis was 44.7 years (SD 15.1); male cases were on average 7.4 years older than females at diagnosis (median age 50.7 *vs*. 43.2 years, Wilcoxon $P < 0.0001$). The observation period from study entry to index date was longer for cases than controls (Table 2), the mean for cases being 5.5 years and for controls being 4.9 years. Cases contacted their general practitioners more frequently in the year prior to the index date, with a median of 30 consultations (interquartile range (IQR) 16–53), compared with a median of 13 (IQR 5–28) consultations among controls.

Crude and adjusted ORs for the association between risk of lupus and selected drugs are shown in Table 3. None of the prescription dates for any of the drugs of interest had a missing value. No cases and controls were exposed to procainamide, propylthiouracil or acebutolol andtherefore risk associated with these drugs could not be estimated. Only cases were exposed to isoniazid. Very few subjects were exposed to a further five drugs of interest, resulting in wide confidence intervals (e.g. OR hydralazine 6.62, 95% CI 1.03, 42.7). For three drugs of interest more than 10 cases and controls were exposed. Large numbers of both cases and controls were exposed to the 'comparison' drugs.

The crude ORs for all drugs suspected of inducing lupus were greater than 2.0 and statistically significant apart from quinidine (3.94, 95% CI 0.55, 28.17) and methyldopa (1.39, 95% CI 0.29, 6.70). Adjustment for confounders generally reduced the ORs but a more than four-fold increased risk remained or hydralazine and minocycline and a statistically significantly increased risk for carbamazepine.

In general, crude ORs for the 'comparison' drugs showed an increased risk of lupus of less than 2.0. After adjustment for confounding factors, including use of lupus-inducing drugs, these associations were no longer apparent.

Table 2

Demographic characteristics and univariable odds ratios (ORs) with 95% confidence intervals (CIs) for the association between selected variables and risk of lupus

		Study subjects (%) Case (n = 875)	Control (n = 3632)	OR* (95% CI)
Sex†	Female	721 (82.4%)	3012 (82.9%)	
Age at diagnosis (years)†	Age (SD)	45.4 (15.1)	45.3 (15.1)	
	Range	4.5–85.5	4.5–88.4	
Time in database (years)‡	1–3	209 (23.9)	1112 (30.6)	1.00 (reference)
	3–4.5	165 (18.9)	770 (21.2)	1.37 (1.03, 1.83)
	4.5–7	246 (28.1)	950 (26.2)	2.43 (1.79, 3.30)
	>7	255 (29.1)	800 (22.0)	4.27 (3.03, 6.02)
				$P < 0.001$
Consultation rate§	0–6	55 (6.29)	1060 (29.19)	1.00 (reference)
	7–12	105 (12.00)	672 (18.50)	4.27 (2.95, 6.18)
	13–24	194 (22.17)	826 (22.74)	8.51 (5.95, 12.2)
	>24	521 (59.54)	1074 (29.57)	28.2 (19.4, 40.8)
				$P < 0.001$

*Univariable odds ratio for risk of lupus. †Variable used to match cases and controls, therefore univariable OR is not reported. ‡Time (in years) in database before diagnosis. §Number of consultations per year in the year preceding diagnosis date (index date for the controls).

Table 3

Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between lupus and exposure to selected drugs before diagnosis or index date

Drug name	Study subjects Case (n = 875)	Control (n = 3632)	Unadjusted OR* (95% CI)	Adjusted OR*†‡ (95% CI)
Drugs suspected of inducing lupus§				
Hydralazine	4	2	8.91 (1.62, 48.94)	6.62 (1.03, 42.74)
Minocycline	50	49	4.35 (2.90, 6.52)	4.23 (2.65, 6.75)
Carbamazepine	28	49	2.39 (1.48, 3.85)	1.88 (1.09, 3.22)
Quinidine	2	2	3.94 (0.55, 28.17)	1.41 (0.17, 11.95)
Methyldopa	2	7	1.39 (0.29, 6.70)	1.40 (0.28, 7.11)
Captopril	11	24	1.97 (0.95, 4.09)	1.30 (0.57, 2.96)
Chlorpromazine	7	16	1.95 (0.78, 4.87)	0.86 (0.32, 2.33)
Procainamide	0	0	–	–
Propylthiouracil	0	0	–	–
Acebutolol	0	0	–	–
Isoniazid	3	0	–	–
'Comparison' drugs not suspected of inducing lupus				
Doxycycline	123	299	2.05 (1.61, 2.61)	1.21 (0.92, 1.59)
Diazepam	86	228	1.66 (1.26, 2.18)	0.92 (0.68, 1.26)
Salbutamol	135	411	1.44 (1.16, 1.79)	0.96 (0.76, 1.22)

*Reference category is the unexposed group for each drug. †ORs adjusted for time (in years) in database before diagnosis, and number of consultations in the year preceding diagnosis or index date. ‡Control drugs additionally adjusted for exposure to lupus-inducing drug. §Drugs are reported to have high, moderate or low risk, based on number of case reports published in the literature [3].

Table 4

Sex-specific adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between lupus and exposure to selected drugs before diagnosis or index date

Drug name	Women Case (n = 721)	Control (n = 3012)	OR (95% CI)*†‡	Men Case (n = 154)	Control (n = 620)	OR (95% CI)*†‡	P value for interaction
Drugs suspected of inducing lupus§							
Hydralazine	2	1	2.87 (0.26, 31.71)	2	1	13.1 (1.04, 166)	0.387
Minocycline	45	44	4.29 (2.61, 7.06)	5	5	4.47 (1.08, 18.58)	0.885
Carbamazepine	25	39	2.47 (1.37, 4.48)	3	10	0.60 (0.15, 2.38)	0.047
Quinidine	2	2	1.36 (0.16, 11.65)	0	0	–	–
Methyldopa	2	7	1.43 (0.28, 7.26)	0	0	–	–
Captopril	9	16	1.84 (0.71, 4.76)	2	8	0.53 (0.09, 3.21)	0.203
Chlorpromazine	3	12	0.51 (0.12, 2.15)	4	4	1.75 (0.40, 7.69)	0.301
'Comparison' drugs not suspected of inducing lupus							
Doxycycline	110	275	1.17 (0.88, 1.56)	13	24	1.62 (0.66, 3.97)	0.608
Diazepam	73	203	0.87 (0.62, 1.21)	13	25	1.34 (0.59, 3.03)	0.437
Salbutamol	105	335	0.88 (0.68, 1.15)	30	76	1.29 (0.75, 2.22)	0.199

*Reference category is the unexposed group for each drug. †ORs adjusted for time (in years) in database before diagnosis, and number of consultations in the year preceding diagnosis or index date. ‡Control drugs additionally adjusted for exposure to lupus-inducing drug. §Drugs are reported to have high, moderate or low risk, based on number of case reports published in the literature [3].

Gender-specific estimates are shown in Table 4. Very few men were diagnosed with lupus as well as exposed to a suspected drug. However, some evidence for effect modification by sex was seen for carbamazepine; only women appeared to have an increased risk (P for interaction 0.047). The male : female ratio for chlorpromazine-exposed cases was significantly different from the ratio among unexposed cases (ratio exposed 1:0.77, ratio unexposed 1:4.7, Fisher's exact $P = 0.021$), suggesting that men are proportionately more affected with chlorpromazine-induced lupus than women, in contrast to idiopathic lupus. There was no clear evidence of effect modification by sex or differing male : female ratios by exposure for any of the 'comparison' drugs. Stratum-specific estimates for younger and older age at diagnosis could not be obtained for drugs where no cases or controls were exposed (mostly among

Table 5

Odds ratios (ORs) and 95% confidence intervals (CIs) for number of prescriptions and risk of lupus

Drug name	Number of prescriptions*	Study subjects Case (n = 875)	Control (n = 3632)	Unadjusted OR (95% CI)	Adjusted OR†‡ (95% CI)
Drugs suspected of inducing lupus§					
Minocycline	Unexposed	825	3583	1.00 (Reference)	1.00 (Reference)
	1	17	22	3.43 (1.81, 6.51)	3.03 (1.49, 6.17)
	2–3	13	12	4.31 (1.94, 9.60)	6.10 (2.20, 16.93)
	≥4	20	15	5.67 (2.88, 11.14)	5.00 (2.37, 10.51)
				P < 0.001	P < 0.001
Carbamazepine	Unexposed	847	3583	1.00 (Reference)	1.00 (Reference)
	1	9	16	2.39 (1.05, 5.45)	1.55 (0.62, 3.84)
	2–6	4	17	0.96 (0.32, 2.89)	0.94 (0.27, 3.25)
	≥7	15	16	3.83 (1.88, 7.80)	3.04 (1.34, 6.85)
				P < 0.001	P = 0.011
Captopril	Unexposed	864	3608	1.00 (Reference)	1.00 (Reference)
	1–13 Rx	8	13	2.58 (1.06, 6.26)	2.13 (0.79, 5.73)
	≥14 Rx	3	11	1.20 (0.32, 4.40)	0.56 (0.14, 2.29)
				P = 0.180	P = 0.970
Chlorpromazine	Unexposed	868	3616	1.00 (Reference)	1.00 (Reference)
	1 Rx	4	11	1.60 (0.49, 5.27)	0.63 (0.17, 2.26)
	≥2 Rx	3	5	2.65 (0.63, 11.2)	1.48 (0.29, 7.42)
				P = 0.124	P = 0.987
'Comparison' drugs not suspected of inducing lupus					
Doxycycline	Unexposed	752	3333	1.00 (Reference)	1.00 (Reference)
	1 Rx	69	208	1.64 (1.22, 2.20)	1.05 (0.75, 1.45)
	2–3 Rx	43	71	3.30 (2.18, 4.99)	1.60 (1.01, 2.54)
	≥4 Rx	11	20	2.80 (1.29, 6.05)	1.56 (0.68, 3.55)
				P < 0.001	P = 0.054
Diazepam	Unexposed	789	3404	1.00 (Reference)	1.00 (Reference)
	1	50	118	1.85 (1.30, 2.62	1.10 (0.74, 1.63)
	2–3	19	53	1.64 (0.96, 2.81)	0.79 (0.44, 1.42)
	≥4	17	57	1.28 (0.74, 2.23)	0.73 (0.40, 1.33)
				P = 0.009	P = 0.297
Salbutamol	unexposed	740	3221	1.00 (Reference)	1.00 (Reference)
	1 Rx	40	161	1.08 (0.75, 1.56)	0.85 (0.57, 1.26)
	2–6 Rx	52	126	1.85 (1.31, 2.59)	1.23 (0.84, 1.79)
	≥7 Rx	43	124	1.49 (1.04, 2.15)	0.83 (0.55, 1.25)
				P < 0.001	P = 0.744

*Categorization number of prescriptions based on distribution in controls. †Adjusted for years in database before diagnosis and number of consultations in year prior diagnosis. ‡Drugs not known to induce lupus additionally adjusted for use of lupus drug yes/no. §Drugs are reported to have high, moderate or low risk, based on number of case reports published in the literature [3]. Rx prescription.

those aged younger than 45 years). Risks which could be estimated were similar to the overall estimates (data not shown). However, risk of minocycline-induced lupus appeared to be lower at younger age (<45 years; 34 cases and 41 controls exposed; OR = 3.38 (95% CI 1.94, 5.90)) compared with older age (≥45 years, 16 cases and 8 controls exposed, OR = 7.93, 95% CI 3.12, 20.17). This difference was not statistically significant (P for interaction 0.117). Comparing median age of exposed *vs*. unexposed cases revealed that cases with a history of exposure to minocycline were on average 8.5 years younger than minocycline-unexposed cases (Wilcoxon test P = 0.004). Exposed cases were substantially older than unexposed cases for hydralazine (24.6 years older, P = 0.009), quinidine (17.8 years older, P = 0.094) and captopril (12.1 years older, P = 0.004).

For minocycline there was a clear trend of increasing risk of DIL with increasing number of prescriptions (adjusted OR per 10 prescriptions 3.10, 95% CI 2.10, 4.55, P for trend < 0.001) (Table 5) and some evidence was found for carbamazepine (adjusted OR per 10 prescriptions 1.27, 95% CI 1.04, 1.57, P for trend = 0.011). No clear associations were observed for chlorpromazine and captopril. Among the 'comparison' drugs, only doxycycline showed weak evidence of a trend of increasing risk with increasing number of prescription (P = 0.054), however this could not be verified with the adjusted OR per 10 prescriptions 1.15, 95% CI 0.90, 1.49.

Current use of minocycline or chlorpromazine was associated with a four-fold increased risk of lupus (OR = 4.05, 95% CI 1.04, 15.76) and two-fold increased risk (OR = 2.27, 95% CI 0.27, 19.02), respectively. Increasing time since cessation of drug use was associated with a decreased risk of lupus for minocycline and chlorpromazine, which was confirmed by a test for trend (minocycline P = 0.009, chlorpromazine P = 0.031). Time since cessation of use of carbamazepine, captopril and all of the 'comparison' drugs

was not clearly associated with risk of lupus (data not shown).

Discussion

In this large matched case-control study we found an increased risk of lupus among individuals who were exposed to hydralazine, minocycline and carbamazepine. For the latter two drugs, risk increased with increasing cumulative dose. Although the number of individuals exposed to carbamazepine was small, the association appeared stronger among women than men.

To our knowledge this was the first large study to quantify risk of lupus associated with carbamazepine, hydralazine, and other prescription medicines suspected of inducing the disease. We confirmed some, but not all, associations that have been hypothesized in case reports [3]. Given the relatively low incidence of lupus [10] and infrequent use of many of the suspected drugs, the number of patients who are newly diagnosed with a drug-induced form of lupus is likely to be low. Twelve per cent of the 875 incident lupus cases in this study had evidence of a prescription for one or more of the suspected drugs, leaving the vast majority of lupus cases with unexplained aetiology of their disease.

One previous GPRD study investigating minocycline-induced lupus among acne patients [12] identified a clear association between exposure to minocycline and risk of lupus among 29 cases with lupus-like syndrome who were aged 15–29 years. Margolis *et al*. [13] also investigated risk of lupus among acne patients utilizing a UK database (The Health Improvement Network) similar to the GPRD. In their study, an association with risk of lupus was found for minocycline but not for other tetracyclines, among acne patients aged 15–35 years.

In our study, the power to detect moderately increased risks or to perform relevant subgroup analyses was limited, even in the largest population-based data set available to date. For some drugs, prescriptions were too uncommon to be able to estimate associated risk of lupus. Despite small numbers of exposed patients and low statistical precision of some of our risk estimates, the magnitude of the risks observed for hydralazine and minocycline as well as the observed increased risk with increasing number of prescriptions for minocycline and carbamazepine provide evidence to support a causal relationship.

Evidence for a causal association between drugs and risk of lupus has previously been demonstrated by disappearance of symptoms after withdrawal of a suspected drug [14]. In addition, re-challenge with the suspected drug has been reported to result in re-appearance of symptoms [15, 16]. Neither formal criteria nor International Classification of Diseases (ICD) codes exist for the classification and coding of DIL. Thus the distinction between DIL and idiopathic SLE relies on the resolution and non-recurrence of symptoms following medication termination. Because the GPRD does not contain codes for recovery from disease we were not able to investigate directly causality or distinguish between DIL and SLE cases in this manner. We were also not able to distinguish SLE from DIL based on the computerized medical codes recorded by the GP. Of the 107 cases with evidence of exposure to a lupus-inducing drug before their diagnosis, only one had a code with a qualifier for drug-induced. All other patients had a recorded diagnosis of SLE. It has been hypothesized that DIL patients are generally older and more likely to be male than cases with idiopathic SLE [2]. We found some evidence for a male preponderance of chlorpromazine-induced lupus, but not for other drugs. The older median ages observed among DIL cases exposed to hydralazine, quinidine and captopril compared with unexposed SLE cases are as expected since these drugs are indicated for conditions generally diagnosed at older age (Table 1).

In order to assess whether an association is causal, it is important to ensure that drug exposure took place prior to onset of disease. We defined lupus diagnosis date as the date on which the first medical code for lupus was recorded in a patient's medical file. Accurately assessing the lupus diagnosis date based on computerized medical information is a complex task, since the first occurrence of a code for lupus may not necessarily reflect the date on which symptoms of the disease first appeared. In theory, an alternative approach may be to define the lupus diagnosis date as the date on which the first prescription for a lupus-specific treatment was issued, or on which symptoms first became apparent. In practice this approach would also result in inaccurate assessment of diagnosis dates since many treatments and symptoms for lupus are non-specific and seen in a wide range of other diseases.

When studying the association between exposures and risk of disease, it is important to ensure only true cases are included in the study. In clinical practice, the classification of SLE is based on criteria formulated by the American College of Rheumatology [17, 18]. Laboratory test results for anti-nuclear antibody (ANA) or anti-DNA antibody positivity were not available for the majority of our cases and we did not validate a diagnosis of SLE for each case individually. We believe this did not result in incorrectly including many non-SLE patients as cases in our study, since incidence rates based on our data were consistent with other published estimates [10]. Criteria for diagnosis of DIL are less strict than those for diagnosis of idiopathic lupus [3, 15]. The set of diagnostic codes we included in our definition may have excluded codes that were preferred by GPs to describe the symptoms of DIL.

Bias in recording exposure to suspected drugs was virtually non-existent in our study, because all prescription information was recorded in a prospective manner prior to the diagnosis (index) date. A potential source of bias in this study may have been protopathic bias, i.e. when early

symptoms of a disease influence the likelihood of being exposed to a certain drug [19]. For example, skin problems which may have been an early presentation of the typical butterfly-shaped rash seen in idiopathic lupus may have been misdiagnosed as acne and treated with minocycline or doxycycline. Protopathic bias is therefore a possible explanation for the marginally increased point estimates observed for doxycycline. For minocycline, however, the strongly increased point estimates and confidence limits cannot be fully explained by protopathic bias and suggest a causal, drug-specific association with risk of lupus. Ethnicity is a known risk factor for lupus but little, if any, evidence exists that the relevant drug prescribing patterns are associated with ethnicity in a systematic way. Thus ethnicity is unlikely to be a strong confounding factor in our study, as it would need to be associated with both drug exposure and outcome.

Consultation behaviour was included as a confounding factor in our models, even though one could argue it is on the causal pathway between drug exposure and induction of lupus. We believe it was appropriate to adjust for consultation behaviour as after adjustment, the increased risk of lupus disappeared for the 'comparison' drugs, but not for the drugs thought to induce lupus. A GPRD-based study of minocycline-induced lupus in a population of acne patients reported an 8.5-fold increased risk of lupus for use of minocycline at the time of lupus diagnosis [12]. Excluding past users of minocycline from our study results in a similar unadjusted 8-fold increased risk. Adjustment for confounders reduced this risk to 4, highlighting the potential influence of consultation behaviour and length of therapy on risk estimates of lupus.

Numerous case reports have suggested that lupus can be induced by a range of prescription medications but these have not been investigated in sufficiently large observational studies. The present study used the largest population-based database available to date and still lacked statistical power to reliably confirm or exclude an effect for a number of the suspected drugs. We did observe a substantially increased risk of lupus associated with exposure to hydralazine and minocycline and moderately increased risk for carbamazepine. These observed increased risks may be causal given the lack of an increased risk observed with deliberately selected 'comparison' drugs. Our results are based on a representative sample of UK individuals, and as such these findings are likely to be generalizable.

Although the majority of selected drugs investigated in our study are not used commonly, a possible diagnosis of lupus should always be considered given that potentially serious symptoms of the drug-induced form are thought to be reversible [2]. Recently, newer drugs such as anti-tumour necrosis factor (TNF) inhibitors have also been linked to induction of lupus [20]. These biologicals are not routinely administered in primary care and were not approved for widespread use in the UK during the study period, so it was not be possible to quantify their risk of inducing lupus in our study. However, in the current age of computerized medical records it is possible that other (and larger) sources will become available in the near future, perhaps through pooling of national data and linkage of several data sources [21]. Such large databases are needed to evaluate signals of DIL and to assess causality of these rare but serious events associated with uncommonly used prescription medicines.

Competing interests

Potential conflicts of interest

WMS and JK are currently employees of Amgen Ltd, a company which is investigating a compound in a phase I clinical development programme but does not have any marketed products for the treatment of SLE. At the time of carrying out the research described in the manuscript, they worked at the London School of Hygiene and Tropical Medicine. WMS had PhD studentship funded by GlaxoSmith Kline. The other authors have no competing interests to declare.

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