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INVESTIGATIVE REPORT

Drug Exposure and Psoriasis Vulgaris: Case-Control and Case-Crossover Studies

Arnon D. COHEN[1,2,3,4,5], Dan Y. BONNEH[2,3,5], Haim REUVENI[2,5], Daniel A. VARDY[2,5], Lechaim NAGGAN[3,4,5] and Sima HALEVY[1,5]

[1]*Department of Dermatology, Soroka University Medical Center,* [2]*Clalit Health Services, Southern District,* [3]*Siaal Research Center for Family Medicine and Primary Care,* [4]*Epidemiology and Health Services Evaluation Department, and* [5]*Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel*

Intake of drugs is considered a risk factor for psoriasis. The aim of this study was to investigate the association between drugs and psoriasis. A case-control study including 110 patients who were hospitalized for extensive psoriasis was performed. A control group (n=515) was defined as patients who had undergone elective surgery. A case-crossover study included 98 patients with psoriasis. Exposure to drugs was assessed during a hazard period (3 months before hospitalization) and compared to a control period in the patient's past. Data on drug sales were extracted by data mining techniques. Multivariate analyses were performed by logistic regression and conditional logistic regression. In the case-control study, psoriasis was associated with benzodiazepines (OR 6.9), organic nitrates (OR 5.0), angiotensin-converting enzyme (ACE) inhibitors (OR 4.0) and non-steriodal anti-inflammatory drugs (NSAIDs) (OR 3.7). In the case-crossover study, psoriasis was associated with ACE inhibitors (OR 9.9), beta-blockers (OR 9.9), dipyrone (OR 4.9) and NSAIDs (OR 2.1). Extensive psoriasis may be associated with intake of ACE inhibitors, NSAIDs or beta-blockers. ***Key words: psoriasis vulgaris; drug reactions; angiotensin-converting enzyme inhibitors; beta-blockers; non-steroidal anti-inflammatory drugs.***

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Dr. Arnon D. Cohen, 25 Tzeela St, POB 1076, Omer, 84965, Israel. E-mail: arcohen@clalit.org.il

Drugs are considered potential risk factors for psoriasis. Drugs may precipitate new-onset psoriasis (either in one of the defined forms of psoriasis or as a psoriasiform eruption) or may cause an exacerbation of pre-existing disease. Drugs which have been reported to induce or exacerbate psoriasis include lithium, antimalarial agents, beta-blocking agents, angiotensin-converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) and gold (1–4).

As drugs are considered to be potential risk factors for psoriasis, the identification of drugs which trigger or exacerbate psoriasis should enable withdrawal of these drugs, resulting in disease remission (secondary prevention). In susceptible individuals, drugs which are strongly associated with psoriasis should be avoided (primary prevention).

Despite the potential benefit for primary or secondary prevention of psoriasis, most of the current knowledge on the topic of drug-induced or drug-triggered psoriasis is based on case reports and uncontrolled case series. We have recently published a case-control study which demonstrated an association between intake of calcium channel blockers and plaque-type psoriasis (5). However, as drug exposure to numerous drugs was assessed in elderly patients, there were inherent recall and data biases. These biases may be treated using medical information systems which record drug prescriptions for administrative purposes.

In the current study, the computerized resources of Soroka University Medical Center and Clalit Health Services were used to investigate the association between intake of certain drugs and extensive psoriasis vulgaris.

PATIENTS AND METHODS

Case-control study

One hundred and ten consecutive patients (63 men and 47 women; mean age 49.6 years; SD 17.2) hospitalized for extensive plaque-type psoriasis vulgaris in the department of dermatology at the Soroka University Medical Center, between 1 January 1996 and 12 November 2001 were included in the case-control study. Patients who were hospitalized more than once for psoriasis were included only at the first admission. Psoriasis was defined on a clinical basis, as a chronic, relapsing-remitting papulo-squamous eruption with typical localization on the extensor surfaces such as the elbows and knees, which may also involve the scalp, genitalia or nails, as well as other sites. Excluded from the study were patients for whom a diagnosis of psoriasis was not definite (e.g. patients with psoriasiform eruptions). Exposure to drugs was assessed during the 3 months preceding the hospitalization for each patient.

Control patients were randomly sampled from a list of the patients who had undergone elective surgery (hernioplasty, cataract extraction or cholecystectomy) between 1 January 1996 and 12 November 2001, group-matched to the cases for age and gender (within 10-year periods). This control group is presumed to represent drug intake in the general population. Exposure to drugs in all control patients was

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assessed during the first year quartile in 2000. As some patients in the control group had psoriasis, they were excluded, without replacement, to avoid crossover between the case and control groups.

Excluded from the study were also patients with missing data, leaving a total of 515 patients in the control group (305 men and 210 women; $n=515$; mean age 53.4 years, SD 17.0).

Case-crossover study

A case-crossover study was conducted in 98 patients from the case-control study for whom longitudinal data were available. A case-crossover design is used to assess certain exposures during different time intervals in a subject's life (6–9). In the current study, the hazard period was defined as an interval of 3 months, which preceded the hospitalization for psoriasis. The control period was defined as the first 3 months of each calendar year during which there was no hospitalization for psoriasis. The case-crossover design permits the assessment of change in the risk of psoriasis during a hazard period just before the hospitalization, as compared with control periods in the patient's past. To increase the power of the case-crossover study, for each patient (with one hazard period), one to five control periods were included. As drugs which supposedly trigger or exacerbate psoriasis may be withdrawn after hospitalization for psoriasis, control periods were taken only before the first hospitalization for psoriasis. For these 98 patients with psoriasis, 98 hazard periods and 434 control periods were used, one to five control periods for each patient.

Drug exposure

Drug sales were used as an estimate for drug exposure, as there are no presumable differences between the proportions of drug sales or drug intake between the case and the control groups. Drugs were grouped on the basis of similar chemical structure or pharmacological effect using the Anatomical Therapeutic Chemical Classification System (ATC). The unit of measurement for drug exposure was defined as at least one prescription bought during a period of a year quartile, which was categorized into a dichotomous variable.

Sample size calculation

A calculation assuming 10% exposure to a certain drug group in patients and 1% exposure in controls showed that a target sample size of 121 cases and 121 controls would give 80% chance to reject the null hypothesis, at $p=0.05$ level of significance. However, some drugs that may be associated with psoriasis had lower exposure in case patients. To increase the power of the study, assuming 6% exposure to a certain drug in patients and 1% exposure in controls, a 1:5 patients: controls ratio was used. With these values, 119 patients and 595 unmatched controls are needed to reject the null hypothesis.

Data mining

Clalit Health Services is the largest organization for management of care in Israel. In the southern district of Israel, Clalit Health Services covers a population of approximately 450 000 people. Since 1 January 1996, Clalit Health Services had computerized all its pharmacies, and created a database which may be used for assessment of drug intake using data mining techniques. All drugs which are bought by the members of Clalit Health Services, with mandatory fixed co-payment, are entered into the database. Data on drug sales in cases and controls were retrieved from the database of Clalit Health Services by queries using Business Object software, to create files of approximately 60 000–100 000 lines on drug exposure for case or control patients during the study period (between 1 January 1996 and 12 November 2001). From these files, data were extracted using Microsoft Access software or Visual Basic, as needed, to generate the final files for statistical analysis. In the case-crossover study only patients for whom longitudinal data were available were included.

Statistical analyses

Statistical analyses were performed to compare sales of drugs by patients, as compared to controls (case-control study), or to control periods within the patients' past (case-crossover study). SPSS software was used in the case-control study, and STATA software was used in the case-crossover study.

In the case-control study logistic regression was used for multivariate analyses. The best fitting model was chosen using the –2 log likelihood statistic. In the case-crossover study, matched multivariate analyses were used using conditional logistic regression.

RESULTS

Case-control study

Benzodiazepines, organic nitrates[1], ACE inhibitors and NSAIDs were associated with psoriasis in the multivariate analyses (Table I). As age was identified as a major confounder, the cohort was stratified into two strata (age <50 years, and age $\geqslant 50$ years). In patients $\geqslant 50$ years the following drugs were associated with psoriasis: benzodiazepines (OR 5.0, 95% CI 1.7–14.8), organic nitrates (OR 4.1, 95% CI 1.3–13.1), NSAIDs (OR 3.4, 95% CI 1.3–9.0), ACE inhibitors (OR 3.2, 95% CI 1.4–7.6) and calcium channel blockers (OR 3.1, 95% CI 1.0–7.6). In patients aged <50 years macrolides (OR 21.9, 95% CI 2.4–192.3) and penicillins (OR 4.0, 95% CI 1.4–11.0) were associated with psoriasis.

Case-crossover study

ACE inhibitors, beta-blockers, dipyrone[2] and NSAIDs were all found to be associated with psoriasis in the multivariate analyses (Table II). To allow for comparison between the case-control study and the case-crossover study, the same strata (patients less than or above 50 years) were used in the case-crossover study. In patients <50 years the following drugs were associated with psoriasis: ACE inhibitors (OR 21.7, 95% CI 2.6–178.3), beta-blockers (OR 17.0, 95% CI 1.9–155.7) and dipyrone (OR 2.5, 95% CI 1.4–16.9). In patients younger than 50 years the following NSAIDs were associated with psoriasis: acetic acid derivatives (e.g. diclofenac, indomethacin) and proprionic acid derivatives (e.g. ibuprofen, naproxen) (OR 3.1, 95% CI 1.3–7.05).

[1] Organic nitrates are indicated for e.g. angma pectoris.

[2] Dipyrone is indicated in Israel for fever reduction and relief of moderate to severe pain.

Table I. *Case-control study: univariate and multivariate (footnotes) logistic regression analyses of drug risk factors for psoriasis vulgaris*

Drug group	Cases	Controls	OR	95% CI
Paracetamol	18	29	3.3	1.6–6.4
Dipyrone	10	15	3.3	1.3–8.2
Benzodiazepines	14	8	9.2	3.5–26.0[a]
NSAIDs				
Entire group	25	24	6.0	3.1–11.5[b]
Acetic acid deriv.	14	13	5.6	2.4–13.4
Proprionic acid deriv.	14	11	6.7	2.7–16.7
Antibiotics				
Penicillins	14	17	4.3	1.9–9.5
Cephalosporins	9	12	3.7	1.3–9.9
Sulfonamides	1	2	2.4	0.4–45.5
Fluoroquinolones	2	3	3.2	0.3–27.9
Macrolides	6	5	5.9	1.5–24.8
Tetracyclines	2	4	2.4	0.2–16.7
Cardiovascular drugs				
ACE inhibitors	18	22	4.4	2.1–8.9[c]
Beta-blockers	9	15	3.0	1.1–7.5
Aldosterone antag.	1	0	–	
Adrenergic blockers	3	4	3.6	0.5–21.4
Ca channel blockers	10	9	5.6	2.0–16.0
Organic nitrates	9	9	5.0	1.7–14.6[d]
Thiazides	3	6	2.4	0.4–11.3
Lithium	1	0	–	
Antimalarial agents	0	0	–	

Odds ratio (OR) and 95% confidence intervals (CI). Multivariate analyses for special cases: OR, 95% CI: [a]6.9, 2.6–18.7, [b]3.7, 1.9–7.1, [c]4.0, 1.8–9.0, [d]5.0, 1.6–15.2.

Table II. *Case-crossover study: univariate and multivariate (footnotes) logistic regression analyses of drug risk factors for psoriasis vulgaris*

	Period (*n*)		Univariate analysis	
Drug group	Hazard	Control	OR	95% CI
Paracetamol	17	54	1.5	0.8–2.7
Dipyrone	9	9	4.8	1.6–13.9[a]
Benzodiazepines	13	41	1.5	0.7–2.9
NSAIDs				
Entire group	23	57	2.0	1.1–3.6[b]
Acetic acid deriv.	12	37	1.5	0.7–3.1
Proprionic acid deriv.	13	25	2.5	1.1–5.3
Antibiotics				
Penicillins	12	41	1.3	0.6–2.7
Cephalosporins	8	16	2.3	0.8–5.9
Sulfonamides	1	2	2.2	0.0–43.1
Fluoroquinolones	2	3	3.0	0.2–26.4
Macrolides	6	13	2.1	0.6–6.1
Tetracyclines	2	4	2.2	0.2–15.8
Cardiovascular drugs				
ACE inhibitors	18	48	1.8	0.9–3.4[c]
Beta-blockers	9	18	2.3	0.9–5.7[d]
Aldosterone antag.	1	0	–	
Adrenergic blockers	3	5	2.7	0.4–14.1
Ca channel blockers	10	42	1.1	0.5–2.3
Organic nitrates	9	33	1.2	0.5–2.7
Thiazides	3	3	4.5	0.6–34.3
Lithium	0	0	–	
Antimalarial agents	0	0	–	

Odds ratio (OR) and 95% confidence intervals (CI). Multivariate analyses for special cases: OR, 95% CI: [a]4.9, 1.7–4.3, [b]2.1, 1.0–4.2, [c]9.9, 2.0–47.6, [d]9.9, 1.9–47.6.

DISCUSSION

In the current study the association between intake of drugs and psoriasis was investigated using a combined case-control and case-crossover methodology for patients who were hospitalized for extensive psoriasis vulgaris.

It was observed that ACE inhibitors were associated with psoriasis in both the case-control and the case-crossover studies. The association was observed in the entire study group and in patients aged ≥ 50 years. This observation is concordant with previous case repots (10–14). Although the current study, as well as previous publications, does not prove a causal relationship, we consider ACE inhibitors to be possible triggering or exacerbating factors in patients with psoriasis. It is recommended that physicians should consider the possibility of withdrawing ACE inhibitors in patients with psoriasis, particularly in patients who are > 50 years.

Beta-blockers are considered a major factor in triggering or aggravating psoriasis (15–17). In both the case-control and the case-crossover studies, univariate analyses showed an association between intake of beta-blockers and psoriasis. However, when using multivariate models, it was found that beta-blockers were associated with psoriasis only in the case-crossover study. The lack of association between beta-blockers and psoriasis in the case-control study is unexplained. It is recommended that physicians taking care of patients with psoriasis should be aware of the possibility that beta-blockers may exacerbate the disease.

An association between psoriasis and intake of NSAIDs (in particular, proprionic acid derivatives) was demonstrated in the case-control and case-crossover analyses. These observations are in agreement with previous reports (18–21). However, as psoriasis may be associated with psoriatic arthritis, and in some patients the exacerbation of psoriasis and arthritis may occur simultaneously, there is a potential for bias of the observed associations.

Univariate analysis in the case-control study demonstrated an association between intake of calcium channel blockers and psoriasis. This association was only marginally significant in the multivariate case-control model in patients ≥ 50 years. In a recent publication (5), we reported on an association between calcium channel blockers and psoriasis, but apart from this study, no previous case reports or studies were found on this association. The lack of consistency between the case-control and case-crossover studies casts doubt on the association between intake of calcium channel blockers and psoriasis. It is suggested that the current study be repeated in additional populations before further conclusions are made.

In the case-control study, multivariate analyses demonstrated a possible association between intake of benzodiazepines and psoriasis; this is also supported by a single case report (22). However, it is possible that benzodiazepines were taken as a result of the severe exacerbation of the disfiguring disease, and not as an exacerbating factor.

Organic nitrates were associated with psoriasis in the case-control study, but not in previous reports. We suggest that the observation be repeated before further conclusions are drawn.

Macrolides and penicillins were associated with psoriasis in the multivariate case-control model in patients aged <50 years. Macrolides have not been reported to exacerbate psoriasis and reports of psoriasis exacerbated by penicillins are rare (23) and may actually represent acute generalized exanthematous pustulosis (24). Therefore, it is possible that the penicillins or macrolides were given as a treatment for a presumed streptococcal infection, which could have triggered the flare of psoriasis by itself (25), rather than being an independent exacerbating exposure.

A controlled design was used in the current study. Previous studies on the association between psoriasis and drugs were uncontrolled and relied mainly on temporal associations. As exposure to drugs is ubiquitous, a controlled approach is essential to confirm or refute these associations. Furthermore, the use of both a case-control and case-crossover design allowed for comparison of the results between the two methods studied. For example, the consistent association between intake of ACE inhibitors and psoriasis in both the case-control and the case-crossover analyses strengthens the validity of this observation.

Even when a case-control design is undertaken, assessment of drug exposure in patients with psoriasis is difficult to perform, particularly in elderly patients who take multiple drugs. As some patients take several drugs and exposure to drugs is assessed by an interview, drug exposure may be underestimated. A different approach was planned and undertaken in our study: using data mining techniques, the exact drugs that the patients bought were registered and therefore exposure was free of recall bias. The current study design, based on computerized data, has the advantage of being an objective assessment of drug exposure, assuming that most people took the drugs that they had bought, and if not, underestimates are likely to be similar in cases and controls.

Previous publications on the topic of drugs and psoriasis consisted mainly of case reports and cases series. However, although the current study provides some evidence for the assessment of the alleged association between intake of drugs and psoriasis, this does not prove causality. Further studies on this topic should be conducted prospectively on a wide population base, taking into account the limitations mentioned above.

In summary, it has been shown that extensive psoriasis vulgaris may be associated with intake of ACE inhibitors, NSAIDs or beta-blockers. It is recommended that physicians taking care of patients with extensive psoriasis should consider withdrawal of these drugs. For other drug groups such as calcium channel blockers, contradictory results were observed in the current study and the literature. Relying on previous uncontrolled experience, it is recommended that physicians should be aware of the possibility that other drugs such as lithium and antimalarials may also exacerbate psoriasis.

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