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Psoriasis associated with ACE inhibitors: an analysis of the FAERS database

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Many case reports have been published concerning the development or exacerbation of psoriasis after administration of angiotensin-converting enzyme (ACE) inhibitors. The aim of the present study was to investigate the association between psoriasis and ACE inhibitors using the US Food and Drug Administration Adverse Event Reporting System (FAERS) data. After excluding patients with psoriasis-related primary diseases, the association of psoriasis with 14 ACE inhibitors was examined using disproportional analyses reporting odds ratio (ROR) and information component (IC). Signals were detected for all 14 ACE inhibitors combined (ROR: 1.25, 95% confidence interval [CI]: 1.14–1.37; IC: 0.31, 95% CI: 0.17–0.44) and individually for lisinopril (ROR: 1.20, 95% CI: 1.05–1.37; IC: 0.25, 95% CI: 0.06–0.45), perindopril (ROR: 1.86, 95% CI: 1.38–2.52; IC: 0.86, 95% CI: 0.43–1.30), and ramipril (ROR: 1.63, 95% CI: 1.36–1.96; IC: 0.69, 95% CI: 0.42–0.96). ACE inhibitors are widely used in patients with hypertension, heart failure, and diabetes mellitus, which are considered comorbidities of psoriasis. Our results suggest that the involvement of ACE inhibitors should be considered in patients on ACE inhibitor therapy who have developed (or show exacerbated) psoriasis.

1. Introduction

Psoriasis is a chronic, noncommunicable, painful, disfiguring and disabling disease. Moreover, because no cure is available for psoriasis, the negative impact on a patients' quality of life is substantial and life-long. Although there is evidence for the existence of a genetic predisposition (Harden et al. 2015), the etiology of psoriasis is still poorly understood. Although it has been proposed that psoriasis may be an autoimmune disease, the causative autoantigens have not been definitively identified. Psoriasis may be triggered by external and internal triggers such as mild trauma, infection, gene, stress, and systemic drugs (Baumgarth et al. 2007; Boehncke et al. 2015).

Angiotensin-converting enzyme (ACE) inhibitors are used for the treatment of hypertension, congestive heart failure, diabetic nephropathy, and other renal diseases (Halkin et al. 2002). They inhibit the production of angiotensin II in the renin-angiotensin system and the degradation of bradykinin, a vasodilator peptide that is a product of the kallikrein-kinin system. In addition to their effect on bradykinin, ACE inhibitors also increase substance P (SP), one of the major neuropeptides responsible for reactions characterized by erythema, pain, and swelling. Amongst its various actions, SP has been shown to participate in or modulate skin hypersensitivity reactions. Many authors have reported the development or exacerbation of psoriasis following the use of ACE inhibitors, such as captopril (Hamlet et al. 1987: Wolf et al. 1987, 1990; Gilleaudeau et al. 1993), enalapril (Wolf et al. 1990; Stavropoulos et al. 2003; Antonov et al. 2006), lisinopril (Gilleaudeau et al. 1993), and ramipril (Thakor et al. 2010).

Associations between psoriasis and various comorbidities such as hypertension, diabetes mellitus, and dyslipidemia have been reported (Osier et al. 2017; Sultana et al. 2019). In addition, antihypertensive drugs, especially beta-blockers, have been reported to be strongly associated with psoriasis (Waqar et al. 2009; Basavaraj et al. 2010; Milavec-Puretić et al. 2011; Wu et al. 2014; Balak et al. 2017). In the present study, we performed a disproportionality analysis using the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database, one of the largest databases in the world, to clarify the association between ACE inhibitors and psoriasis using various different algorithms.

2. Investigations and results

In total, 8,449 cases included one (or more) of the psoriasis-related preferred term (PT)s. The results of the statistical analyses of psoriasis-associated ACE inhibitors are presented for ROR and IC in Table 1. According to both signal scores (95% confidence intervals; CIs), signal was detected in all the ACE inhibitors (ROR:

Table 1: Association between individual ACE inhibitors and psoriasis in the FAERS

ACE Inhibitor(s)	Cases (n)	Total (n)	ROR	95% CI	IC	95% CI
ALL	489	280,111	1.25	1.14–1.37	0.31	0.17–0.44
Alacepril	0	70	0	–	-0.14	-3.04–2.77
Benazepril	28	17,844	1.11	0.77–1.61	0.15	-0.39–0.68
Captopril	14	7,226	1.37	0.81–2.32	0.42	-0.33–1.17
Cilazapril	1	721	0.98	0.14–6.98	-0.01	-2.06–2.03
Delapril	0	85	0	–	-0.17	-3.07–2.74
Enalapril	53	36,533	1.03	0.78–1.35	0.04	-0.36–0.43
Fosinopril	8	5,175	1.09	0.55–2.19	0.12	-0.85–1.08
Imidapril	0	1,066	0	–	-1.33	-4.21–1.56
Lisinopril	224	133,242	1.20	1.05–1.37	0.25	0.06–0.45
Perindopril	43	16,402	1.86	1.38–2.52	0.86	0.43–1.30
Quinapril	15	10,576	1.00	0.61–1.67	0.01	-0.72–0.73
Ramipril	117	51,164	1.63	1.36–1.96	0.69	0.42–0.96
Temocapril	0	480	0	–	-0.75	-3.64–2.14
Trandolapril	2	3,529	0.40	0.10–1.60	-1.00	-2.66–0.67

ROR, reporting odds ratio; CI, confidence interval; IC, information component

1.25, 95% CI: 1.14–1.37; IC: 0.31, 95% CI: 0.17–0.44). While individual signals were detected for lisinopril (ROR: 1.20, 95% CI: 1.05–1.37; IC: 0.25, 95% CI: 0.06–0.45), perindopril (ROR: 1.86, 95% CI: 1.38–2.52; IC: 0.86, 95% CI: 0.43–1.30), and ramipril (ROR: 1.63, 95% CI: 1.36–1.96; IC: 0.69, 95% CI: 0.42–0.96), no signal was detected for the other ACE inhibitors.

3. Discussion

This study examined the association between psoriasis and ACE inhibitors using the FAERS. While psoriasis was associated with ACE inhibitors overall, it was specifically associated with lisinopril, perindopril, and ramipril.

Analyses of the national pharmacovigilance databases from different countries supported our results. While it is not easy to establish a causative drug-disease relationship in an unpredictable disease like psoriasis, the LAREB (Netherlands Pharmacovigilance Foundation) has warned of an association between ACE inhibitors and psoriasis, noting that 9 of 25 patients reported a recovery after discontinuation of ACE inhibitors (https://www.lareb.nl/en/news/ace-inhibitors-and-psoriasis). More recently, an analysis of 100 reports registered in the French national Pharmacovigilance Database has also detected a significant association (ROR: 2.40, 95% CI: 1.96–2.95) (Azzouz et al. 2019). However, in that study, captopril, trandolapril, and benazepril were also associated with psoriasis (not only lisinopril, perindopril, and ramipril). The difference between their result and our results may be attributed to a difference of magnitude in the database, the time period of extracted data, PTs used for the definition of psoriasis, and geographic region, *etc*.

Previous studies have reported that the prevalence of psoriasis varied according to geographic region and race. In particular, psoriasis appears to be most common in Northern European populations (Danielsen et al. 2013, Bø et al. 2008), and least common in East Asian populations (Chang et al. 2009; Ding et al. 2012; Kubota et al. 2015). Moreover, a study carried out from 2009 to 2010 in the United States revealed that the prevalence of psoriasis was 3.6%, 1.9%, 1.6%, and 1.4% for whites, blacks, Hispanics, and other races, respectively (Rachakonda et al. 2014). Therefore, further study is needed to understand whether our result can be generally adopted, especially given the low prevalence of psoriasis in East Asian populations.

The pathophysiology of psoriasis involves various complex inflammatory changes. A host of cytokines are reported to be involved in the inflammatory cascade, including tumor necrosis factor (TNF)-α, interleukin (IL)-12, IL-17, and IL-23, acting via T-helper (Th) 1 and Th 17 cells (Paust et al. 2009). However, not much is known regarding internal factors that can affect the behavior of psoriatic keratinocytes (Zhu et al. 2016). Nonetheless, substances modulated by ACE inhibitors in the nerve system may play a role in pathogenesis (Yu et al. 2010). In particular, SP, which is increased by ACE inhibitors, appears to have stimulatory effects on keratinocyte proliferation, while upregulating IL-1, Il-8, and TNFα (Scholzen et al. 1998). Additionally, vasoactive intestinal peptide (VIP), which is reported to be increased by lisinopril (Woie et al. 1987), stimulates proliferation and migration of human keratinocytes, thus implicating VIP in pathophysiological skin conditions such as psoriasis (Haegerstrand et al. 1989; Wollina et al. 1997).

Several limitations of this study should be acknowledged. It is possible that ACE inhibitors such as alacepril, cilazapril, imidapril, and temocapril, could not be fully validated because they were relatively infrequently prescribed in the United States; reflecting a tendency for different drugs to be prescribed in different countries or regions. In addition, cases may be underreported, because spontaneously reported cases are actually only a fraction of the cases with suspected adverse events. Reporting biases may also distort data, including the release of safety information from regulatory agencies and media coverage. It is also important to note the lack of detailed clinical information and the lack of a denominator to calculate the incidence of adverse events, which makes it impossible to quantify the risk against a control group.

In summary, our result demonstrated an association between psoriasis and ACE inhibitors using the FAERS. It is suggested that the involvement of ACE inhibitors should be considered if a patient who has developed psoriasis (or demonstrated exacerbated psoriasis) is on ACE inhibitor therapy, especially because ACE inhibitors are prescribed to patients with several diseases which are considered comorbidities of psoriasis.

4. Experimental

4.1. Data source

The FAERS data is available for downloading from the FDA website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). The FAERS database consists of the following seven datasets: patient demographic and administrative information (DEMO), drug/ biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), start and end dates of drug therapy (THER), and indications for use/ diagnosis (INDI). All drug names in the DRUG table were changed to their respective generic names using the drug databases Drugbank (https://www.drugbank.ca/) and Drugs.com (https://www.drugs.com), because the FAERS database contains both generic names and their respective brand names used in the reporting countries. The patients included in this study were extracted according to the flowchart described in the Fig. A summary of patient characteristics is reported in Table 2. The definitions of primary diseases used in the Table are based on a previous report (Ohyama et al. 2019).

Table 2: Overall patient characteristics

	Total number	%
Sex		
Female	3,370,751	56.4
Male	2,096,198	35.0
Unknown	516,436	8.6
Age		
<20	247,102	4.1
20 ≤ , < 40	600,284	10.0
40 ≤ , < 65	1,602,301	26.8
65 ≤	1,205,742	20.2
N/A	2,327,956	38.9
Primary disease		
Hypertension	194,580	3.3
Diabetes Mellitus	265,465	4.4
Dyslipidemia	143,124	2.4

Primary diseases are defined according to a previous report by Ohyama et al., 2019.

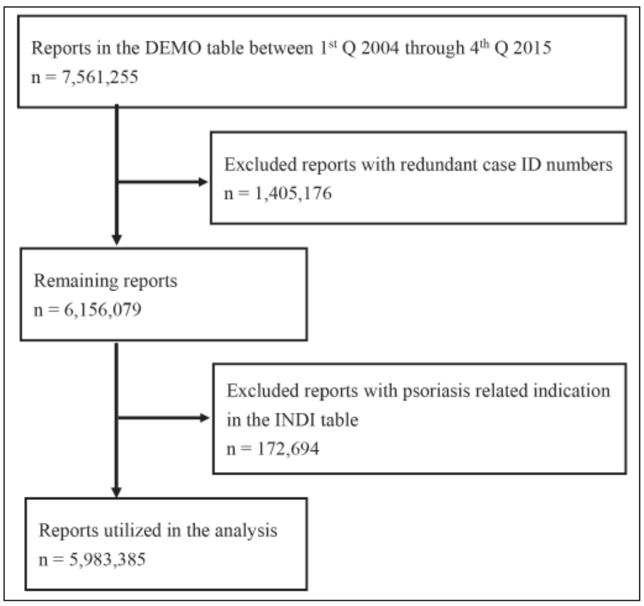

Fig.: Flowchart of patient extraction

4.2. Drugs of interest

The drugs of interest comprised the following 14 ACE inhibitors (including combined formulations) registered in the FAERS: alacepril; benazepril; captopril; cilazapril; delapril; enarapril; fosinopril; imidapril; lisinopril; perindopril; quinapril; ramipril; temocapril; and trandolapril.

4.3. Definitions of psoriasis

The indications for use/diagnosis in INDI and adverse events in REAC are coded using PTs from the Medical Dictionary for Regulatory Activities (MedDRA) terminology. We used erythrodermic psoriasis (PT: 10015278), guttate psoriasis (PT: 10018797), psoriasis (PT 10037153), and psoriatic arthropathy (PT: 10037162), to define 'psoriasis'.

4.4. Data analyses

The association between psoriasis and individual ACE inhibitors was evaluated using a case/ non-case method (Almenoff et al. 2007; Sakaeda et al. 2013; Takada et al. 2016) in the different algorithms; ROR values (van Puijenbroek et al. 2002; Ohyama et al. 2017) with the frequentist method and IC values (Bate et al. 1998; Takada et al. 2016) with the Bayesian method. Signal scores were subsequently calculated. The signal was defined when the lower limit of the 95% CI of ROR was > 1 and that of IC was > 0.

Conflicts of interest: None declared.

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