

## Angiotensin- converting-enzyme (ACE) inhibitors and psoriasis

### Introduction

Angiotensin-converting-enzyme (ACE) inhibitors are widely used for the treatment of hypertension and heart failure. The following ACE-inhibitors are registered in the Netherlands: benazepril (Cibacen®), captopril, enalapril (Renitec®), fosinopril, lisinopril (Zestril®), perindopril (Coversyl®), quinapril (Acupril®), ramipril (Tritace®), and zofenopril (Zofil®). Most ACE-inhibitors are also registered in combination with other antihypertensive drugs.

Psoriasis is a chronic inflammatory skin condition that is often associated with systemic manifestations. The etiology includes genetic and environmental factors. Diagnosis is based on the typical erythematous, scaly skin lesions, often with additional manifestations in the nails and joints. Plaque psoriasis is the most common form. Atypical forms include guttate, pustular, erythrodermic, and inverse psoriasis [1].

Several skin reactions are known adverse reactions of ACE-inhibitors, including (maculopapular) rash, urticaria, lichenoid exanthema, but also severe skin reactions, such as erythema multiforme, Stevens-Johnsons-syndrome, exfoliative dermatitis and toxic epidermal necrolysis. (Aggravation of) psoriasis or psoriasiform dermatitis is mentioned as adverse reaction in several literature reviews and in the product information of nearly half of the ACE-inhibitors, available on the Dutch market.

The current observation describes the association between ACE-inhibitors and psoriasis or aggravation of psoriasis as a class effect.

### Reports

Lareb received 25 reports of (aggravation of) psoriasis associated with the use of ACE-inhibitors captopril, enalapril, fosinopril, lisinopril, perindopril and ramipril in a period from July 18, 1996 till April 3, 2015. The reports are listed in Table 1.

Four patients (C,I,Q,U) were diagnosed with a new onset psoriasis, the other patients experienced a flare-up or aggravation of psoriasis. In most cases the latency varies between several days to several weeks, with an exception of a few reports in association with perindopril, where latencies of hours till one year were reported. In nine cases a positive de-challenge was observed and one patient (W) recovered with sequelae. Some of these patients received topical corticosteroid as treatment for psoriasis as well. In eleven reports the outcome was unknown. In four patients no improvement of symptoms was seen: In one patient (U) perindopril was still continued, in patient K enalapril was only discontinued at the day of reporting, patient X did not recover within four weeks after discontinuation of perindopril and in patient G enalapril was replaced by bisoprolol. Confounding might have been caused by stress (patient B) or medication. Beta-blockers may cause or aggravate psoriasis [2]. In five patients (C,P, E, H, I) a beta-blocker was used. In two of these patients (C, I) also a calcium antagonist was used, which has occasionally been reported as a possible causative factor in psoriasis [2]. Patient I recovered after discontinuation of enalapril, while still using atenolol; for the four other patients, no course of the reaction was provided. Other concomitantly used drugs, which might play a role in psoriasis are digoxin (patient C), fluoxetine (F), amiodarone (M=Y) and ranitidine (N) [2]. All these medications have been continuously used, making a causative role in psoriasis in these patients less feasible.

Table 1. Reports of (aggravation of) psoriasis associated with the use of ACE-inhibitors

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 4060 F, 51 – 60 years General Practitioner	captopril, 50mg bid	coal tar / levomethol shampoo	psoriasis aggravated	1 month discontinued not reported
B 9745 F, 41 – 50 years	captopril, 12,5mg bid primary hypertension		psoriasis aggravated	3 weeks no change not reported

General Practitioner				
C 17825 M, 51 – 60 years General practitioner	captopril, 25mg tid bisoprolol, 5mg od	digoxine bumetanide amlodipine	psoriasis on the hand	weeks no change not reported
D 26908 F, 61 – 70 years General Practitioner	captopril, 25mg bid primary hypertension	triamterene / hydrochlorothiazide	psoriasis aggravated	5 months discontinued recovering after 1 week
E 4320 F, 51 – 60 years General Practitioner	enalapril, 10mg od	metoprolol dihydralazine mefruside	psoriasis aggravated, nausea, vision abnormal	unknown unknown not reported
F 20091 F, 61 – 70 years General Practitioner	enalapril, 10mg od primary hypertension	fluoxetine	psoriasis aggravated	1 week discontinued recovering
G 29723 M, 51 – 60 years Pharmacist	enalapril, 10mg od	atorvastatin clobetasol acetyl salicylic acid	psoriasis aggravated	months discontinued not recovered
H 31246 F, 71 years and older Pharmacist	enalapril, 10mg bid	timolol eye drops insulin glucophage chlorothiazide cisapride omeprazole psyllium	psoriasis aggravated	6 weeks no change unknown
I 79722 M, 61 – 70 years General Practitioner	enalapril, 5mg od hypertension and decreased renal function	spironolacton carbasalate calcium metformin nitrendipin atenolol	psoriasis vulgaris	1 week discontinued recovering
J 110680 F, 41 – 50 years Specialist doctor	enalapril, 20mg hypertension		psoriasis flare- up	17 day discontinued unknown
K 170554 M, 51 – 60 years General Practitioner	enalapril, 10 mg od hypertension	hydrochlorothiazide	psoriasis aggravated	5 days discontinued not yet recovered (day of reporting)
L 23486 F, 41 – 50 years Specialist doctor	fosinopril 20mg od primary hypertension		psoriasis aggravated	3 month unknown not reported
M 29869 M, 71 years and older Specialist doctor	fosinopril 10mg od heart failure	furosemide acenocoumarol amiodaron spironolacton allopurinol	psoriasis aggravated	days discontinued recovered
*N 29912 M, 51 – 60	lisinopril, 10 mg od primary hypertension	ranitidine omeprazole	psoriasis aggravated	weeks discontinued

years Pharmacist			(back, chest, limbs)	recovering
*O 45044 F, 51 – 60 years Consumer	lisinopril, 20 mg od myocardial infarction		psoriasis aggravated	weeks discontinued recovering
*P 54033 M, 41 – 50 years Pharmacist	lisinopril 10 mg od hypertension metoprolol hypertension	nitroglycerin esomeprazole simvastatin	psoriasis aggravated	2 days discontinued unknown
*Q 86931 F, 71 years and older General practitioner	lisinopril 10 mg od hypertension	metformin carbasalate calcium dipyridamol glimepiride	psoriasis	3 days discontinued recovering
R 14083 F, 51 – 60 years Specialist doctor	perindopril, 4 mg od primary hypertension		psoriasis aggravated	1 year discontinued not reported
S 14084 M, 61 – 70 years Specialist doctor	perindopril 4mg od primary hypertension		psoriasis aggravated	1 month discontinued not reported
T 77671 M, 61 – 70 years Pharmacist	perindopril 2mg od hypertension	carbasalate calcium clobetasol paracetamol /codein simvastatin isosorbidedinitrate metronidazole (topical)	psoriasis aggravated	hours no change unknown
U 87853 M, 31 – 40 years Consumer	perindopril 8mg essential hypertension	simvastatin levocetirizin	psoriasis	8 month no change not recovered
V 90625 M, 71 years and older Pharmacist	perindopril 4mg od hypertension	metformin atorvastatin insulin	psoriasis aggravated	1 month discontinued recovering
W 177970 F, 61 – 70 years Physician	perindopril 4 mg od hypertension	citalopram	psoriasis aggravated	5 months discontinued recovered with sequel
X 180849 M, 51 – 60 years Pharmacist	perindopril 2 mg od clarithromycin 500 mg atorvastatin 40 mg	clopidogrel pantoprazole tamsulosin acetyl salicylic acid	psoriasis flare- up	4 months discontinued not recovered
*Y 29870 M, 71 years and older Specialist doctor	ramipril 10 mg od heart failure	allopurinol amiodaron spironolactone furosemide acenocoumarol	psoriasis aggravated	days discontinued recovered

\* (aggravation of) psoriasis already mentioned in SmPC

Underneath additional data on reports, if available, are described in detail.

#### Patient B

Stress was mentioned as a possible other factor. Patient was treated with topical betamethasone.

Patient C

Patient started bisoprolol, followed by captopril in the following month. A few weeks hereafter, psoriasis on the hand was diagnosed. Two months later, bisoprolol was discontinued and replaced by carvedilol. It is not mentioned if the psoriasis complaints altered. Calipotriol and clobetasol were used as treatment of the psoriasis.

Patient F

One week after starting enalapril psoriasis aggravated. Usually patient reacted well on light therapy, but during the use of enalapril psoriasis seemed resistant to this light therapy. After discontinuation of enalapril, light therapy resulted in improvement of the psoriasis again.

Patient G

Patient used enalapril and experienced an aggravation of his psoriasis. Enalapril was discontinued and replaced by bisoprolol, but the psoriasis did not improve.

Patient H

Patient reported an aggravation of psoriasis on the scalp, arms and neck, six weeks after the start with enalapril. She had used timolol eye drops for a long time without experiencing problems.

Patient I

Patient was not known with skin problems. After she started enalapril 5 mg daily she was diagnosed with psoriasis. After a dose increase to 10 mg daily, psoriasis symptoms worsened. Enalapril was discontinued after almost three weeks and patient was treated with topical corticosteroids, followed by a referral to the dermatologist and received small spectrum UVB. Patient was recovering at the moment of reporting.

Patient J

Reporter is an allergist. Patient was known with mild psoriasis on extensor side of elbows. In the past she experienced a rash on metoprolol. Seventeen days after starting enalapril, she developed a severe generalized psoriasis exacerbation. Patient was treated with corticosteroids and antihistamines, enalapril was discontinued after 4 weeks. Outcome is unknown.

Patient L

A dermatologist reported an aggravation of psoriasis, 3 months after starting fosinopril. The psoriasis on patient's scalp became resistant to her regular treatment and psoriasis guttate was induced on pressure (Kobner phenomena). Local treatment was intensified and the general practitioner was advised to prescribe an alternative antihypertensive drug.

Patient M

The reports of psoriasis in patient M and Y concern the same patient.

A dermatologist reported a severe exacerbation of psoriasis days after starting fosinopril 10 mg daily. Fosinopril was stopped and one week later ramipril was started (see patient Y), which gave no relief. Only one to two weeks after discontinuation of ramipril, symptoms gradually diminished.

Patient O

Patient had slight symptoms of psoriasis on the shin of her left leg. Several weeks after switching from Zestril® to Lisinopril, she experienced a severe exacerbation of psoriasis, which could not be treated well. Eight weeks hereafter she returned to Zestril again, which resulted in improvement of her psoriasis symptoms.

Patient P

Patient started lisinopril 20 mg daily and metoprolol 200 mg daily for hypertension as secondary prevention after a myocardial infarction. After several days an exacerbation of psoriasis developed. The dose of metoprolol was reduced and lisinopril was switched to valsartan. Outcome is unknown.

Patient Q

A general practitioner reported itchy desquamation due to psoriasis confined to the scalp following administration of lisinopril for hypertension with a latency of 3 days after start. Use of lisinopril has been suspended. A topical corticosteroid (betamethasone) was applied. The patient was recovering

after one week. Patient's medical history included COPD, hypertension, CVA, diabetes and allergy to cow's milk and fungi.

Patient R.

An specialist in internal medicine reported two cases (R and S). In patient R an exacerbation of psoriasis one year after starting perindopril 4 mg daily was reported. Perindopril was discontinued and patient was treated with acitretine. Outcome is unknown.

Patient U

No family history of psoriasis. Treatment with clobetasol.

Patient V

After the exacerbation of psoriasis, patient received betamethasone/calcipotriole, which did not help sufficiently. Patient discontinued perindopril 8 months after the aggravation of symptoms, which resulted in a substantial improvement.

Patient W

Patient experienced an aggravation of her psoriasis, 5 months after starting perindopril 4 mg daily for hypertension. Perindopril was discontinued immediately and treatment with calcipotriol cream was started. Patient recovered with sequel.

Patient X

A psoriasis flare-up was observed, three days after the start of clarithromycin, 4 months after the start of perindopril and atorvastatin. The course of clarithromycin ended after 1 week. Because the psoriasis symptoms worsened, both perindopril and atorvastatin were discontinued several weeks later. Patient had not yet recovered at the moment of reporting, which was four weeks later.

## Other sources of information

### SmPC

(Aggravation of) psoriasis is not mentioned in the SmPCs of benazepril (Cibacen®), captopril, enalapril (Renitec®), fosinopril and perindopril (Coversyl®). The SmPCs of lisinopril (Zestril®), quinapril (Acupril®), ramipril (Tritace®), and zofenopril (Zofil®) mention (aggravation of) psoriasis or psoriasiform dermatitis as adverse reaction [3-11].

### Literature

ACE-inhibitors as a group are mentioned as causative drugs in (exacerbation of) psoriasis in several publications [2,12-15]. In a case control study including 110 patients hospitalized for extensive psoriasis and a case-crossover study in 98 patients, the multivariate logistic regression analysis showed that ACE-inhibitors were associated with psoriasis (OR 4.0 (1.8 -9.0 respectively OR 9.9 (2.0-47.6) [12]. The observation was observed in the entire group as well as in patients aged > 50 years. Case reports of (aggravation of) psoriasis have been described in association with several ACE-inhibitors. The times of onset of eruptions varied between one week and five months. Resolution of symptoms occurred in most cases between one and four months.

Coulter et al describes a series of 7 patients, six women and one man, who experienced psoriasiform eruptions or exacerbation of existing psoriasis (one patient), in most cases a few months after starting captopril, enalapril or lisinopril. In five cases the scalp was involved, in one case the face and in one case the back and buttocks. In two cases the outcome was known, showing a resolution of symptoms within one and four months [16].

Wolf presents two cases of palmoplantar psoriasis. The first one is an induction of psoriasis in a 68-year old man, two months after captopril 12.5 mg twice daily. He used several other drugs on a continuous basis for cardiovascular disease. Patient was resistant to treatment with topical steroid ointments, therefore a drug was considered as causative agent. The indirect mast cell degranulation (MCD) test only showed a positive result for captopril. Captopril was discontinued and within days the skin began to improve, despite discontinuation of topical treatment. A second patient, a 62-year old woman, was known with a few hyperkeratotic patches of feet and hands, which could be well controlled by topical steroid ointment. She used atenolol, furosemide, diltiazem and nitroglycerin as needed, theophylline and salbutamol. She experienced a flare up, two weeks after the introduction of

enalapril, which replaced atenolol. The MCD test was only positive for atenolol. Still, the lesions subsided after discontinuation of enalapril [17].

Gilleaudeau describes two patients with a flare-up of psoriasis. A 80-year old man had suffered from psoriasis on the upper -and lower extremities for years, which responded well to topical betamethasone. Four months after the start of captopril pruritic red psoriatic lesions developed on the posterior aspect of his left calf and left arm, confirmed by a biopsy. Within four weeks after discontinuation of captopril and treatment with topical triamcinolone, a total resolution was observed. The second patient, a 50-year old man, with psoriasis since more than 30 years, experienced a generalized flare, one week after starting lisinopril, diagnosed by biopsy as a psoriasiform drug eruption. He was treated with wet dressings, coal tar, UV and lisinopril was replaced by verapamil. Soon, his psoriasis had almost healed [18].

Two different ACE-inhibitors were involved in the following case. A volar pustulosis was seen six weeks after starting captopril. Substitution of captopril by perindopril and a short course of systemic steroids resulted in disappearance of the eruptions five months later. One month later similar symptoms emerged. Perindopril was withdrawn and two months later, eruptions had disappeared [19].

More recently, three remarkable psoriatic flare-ups were published. The first one was a co-existence of pemphigus foliaceus (confirmed by biopsy) with psoriasis two months after starting enalapril and lacidipine in a 70-year old man, who had a history of plaque psoriasis for 35 years. It was resistant to treatment with systemic steroids and it cleared completely within three months of discontinuation of enalapril and treatment with topical betamethasone [20].

A 59-year old man with a 35 year personal history of psoriasis had a flare of his psoriasis, five weeks after the start of enalapril 10 mg twice daily, which developed into a generalized psoriatic erythroderma, in the following week. This was accompanied with psoriatic arthritis and a chronic tubulointerstitial nephritis. Patient was treated with allopurinol, diet, methotrexate and discontinuation of enalapril. Gradually symptoms improved to his pre-eruptive chronic plaques (5 % of body surface area) [21].

A case of generalized pustular psoriasis, after recently started ramipril, was observed in a 67-year old woman with a history of psoriatic arthritis and rheumatoid arthritis, for which she used adalimumab. Patient was treated with prednisone, which resulted in a marked improvement. Ramipril was replaced by hydrochlorothiazide [22].

### Databases

Table 2. Reports of psoriasis with ACE-inhibitors in the databases of the Netherlands Pharmacovigilance Centre Lareb, the WHO- and Eudravigilance (EMA) database [23]

Database	Preferred Terms	Number of reports	ROR (95% CI)
Lareb	Psoriasis	25	3.4 (2.3 - 5.1)
WHO	Psoriasis	201	0.52 (0.46-0.60)
Eudravigilance	Psoriasis	62	0.44 (0.34-0.56)

### Prescription data

Table 3. Number of patients using ACE-inhibitors in the Netherlands between 2009 and 2013 [24]

Drug	2009	2010	2011	2012	2013
Benazepril	331	294	263	247	215
Captopril	33,712	30,215	26,853	21,141	21,428
Enalapril	293,740	299,180	301,710	306,510	301,830
Fosinopril	60,707	59,679	58,958	60,756	57,486
Lisinopril	176,770	190,600	201,650	214,600	225,910
Perindopril	214,810	232,840	245,980	262,190	274,070

Drug	2009	2010	2011	2012	2013
Quinapril	36,608	34,583	32,380	30,399	28,057
Ramipril	52,504	54,293	55,614	57,120	56,930
Zofenopril	4,935	5,159	4,970	4,529	4,079
Cilazapril*	496	458	419	388	196
Trandolapril*	659	132	.	.	.
<b>Total</b>	<b>861,960</b>	<b>894,130</b>	<b>916,740</b>	<b>949,650</b>	<b>959,430</b>

\* in 2015 cilazapril and trandolapril are not registered anymore in the Netherlands

### Mechanism

The mechanism of ACE-inhibitors associated or aggravated psoriasis is unknown. Already in the eighties Wilkin et al proposed a logical mechanism for this reaction. ACE- inhibitors not only inhibit the production of angiotensin II, but also inhibit the catabolism of kinins. As a result, the ACE- inhibitors potentiate the activity of kinins and thus may cause exacerbation of kinin-associated skin disorders [25]. A decade later Coulter also postulated that the dermatosis is related to blockade of bradykinin inactivation, leading to elevated concentrations of inflammatory mediators [16].

Bradykinin elevates the cytosolic-free calcium concentration ( $[Ca^{2+}]_c$ ) in normal keratinocytes via phospholipase C and inositol triphosphate production. Potentiation of the  $[Ca^{2+}]_c$  response is linked to an increase in proliferation. Therefore, it is hypothesized that bradykinin, which is involved in the inflammatory response in the skin and is present in wounds, may increase the inflammation leading to accelerated proliferation above that of normal epidermal homeostasis, particularly during wound healing and may be a mechanism for hyperproliferation in skin disorders such as psoriasis [26].

Wolf proposed two possible mechanisms: an allergic immune-dependent reaction and a pharmacologic dose-dependent response. In the first option, he observed circumstantial evidence: A psoriatic eruption emerged after introduction of an ACE-inhibitor, was resistant to potent steroid ointment and showed improvement only after discontinuation of the ACE-inhibitor. This was supported by a positive result of the mast cell degranulation test for the ACE-inhibitor. The second option suggests an exacerbation of psoriasis by an ACE-inhibitor; the initial lesions of psoriasis were caused by another drug, i.e. beta-blocker, with a positive macrophage migration inhibition test only for this other drug and not for the ACE-inhibitor [17].

### Discussion and conclusion

Lareb has received 25 reports of (aggravation of) psoriasis with ACE-inhibitors. In twenty of these reports psoriasis is yet not mentioned in the SmPC. Although in some of these patients concomitant medication was used, which might have played a role in the (worsening of) psoriatic symptoms, in nine of these reports, patients recovered after discontinuation of the involved ACE-inhibitor. Other known possible risk factors of psoriasis are stress, bacterial and viral infections, smoking, obesity and alcohol [1]. In one of the patients, stress was mentioned as a factor, but in none of the patients signs of infections or treatment of infections had been reported.

In the literature several publications upon the association of (aggravation of) psoriasis in relation to ACE-inhibitors can be found. Psoriasis is a common disease, affecting 2-3 % of the population in northern Europe and therefore it is possible that some of the reports of the association between a drug and psoriasis is a chance finding [15]. Also a coincidental recovery after discontinuation of the ACE-inhibitor in a fluctuating illness as psoriasis cannot be ruled out. However, differences in histology can be observed between drug related psoriasis (spongiosis) and early eruptive psoriasis (hyperkeratosis) [2].

Beside ACE-inhibitors, angiotensin II-antagonists have been associated with psoriasis. A common mechanism might be shared with a role of bradykinin [27].

Remarkably, a complex relation between ACE and psoriasis is described in several publications. It is known that a genetic factor might play a role in psoriasis. The angiotensin-converting enzyme (ACE) gene carries a 287-base pair insertion/deletion (I/D) gene polymorphism, which is associated

with plasmaconcentrations of bradykinin-degrading ACE. It was shown that homozygosity for the ACE I allele may affect susceptibility to early-onset psoriasis [28].

In another study Cheng provided study results with genetic evidence that psoriasis might share common mechanisms with hypertension and diabetes [29].

Of further interest are the results of Huskic, who observed a significant increase in tissue ACE activity in patients with psoriasis in comparison to healthy individuals. After appropriate therapy, serum ACE activity was significantly decreased [30]. It is not clear this finding reflects a causal relation or merely shows only a correlation.

Although it is not easy to establish an evident drug-relationship in a fluctuating disease like psoriasis, it is still of importance to acknowledge the possible role of ACE-inhibitors in (exacerbation of) this disease. (Aggravation of) psoriasis or psoriasiform dermatitis is already mentioned in the SmPCs of four out of nine marketed ACE-inhibitors in the Netherlands. As a class effect is presumed, (aggravation of) psoriasis should be mentioned in the SmPCs of all ACE-inhibitors.

- (aggravation of) Psoriasis should be mentioned in the SmPC of all ACE-inhibitors

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