Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

AT_1-receptor antagonists and psoriasis

Introduction

Angiotensin II type 1 (AT_1) receptor antagonists are widely used for the treatment of essential hypertension and heart failure. The SPC's of the AT_1-antagonists describe rash, angioedema and urticaria as rare skin reactions [1-6]. However psoriasis or exacerbation of psoriasis is not mentioned.

Reports

On December 1, 2005 the database of the Netherlands Pharmacovigilance Centre contained 7 reports concerning (aggravated) psoriasis associated with the use of losartan, valsartan and irbesartan (table 1). Patient B,C E and F recovered after withdrawal or dose reduction of the suspect drug. Patient D and G had no history of psoriasis, for the other patients the psoriasis was in remission. Case D was reported by the MAH.

Table 1. (aggravated) psoriasis in combination with an AT_1-antagonist reported to Lareb

patient	sex, age	symptoms	Suspect drug	concomitant medication	time to onset	remarks
A	F, 72	exacerbation psoriasis after dose increase	losartan	isradipine	several months after dose increase	
B	M, 42	exacerbation psoriasis after dose increase	losartan	none	several days after dose increase	pos. dechallenge
C	M, 32	exacerbation psoriasis	valsartan	none	several days	pos. dechallenge
D	F, 64	psoriasis	valsartan	none	unknown	
E	F, 58	exacerbation psoriasis	losartan	amlodipine, atenolol, metformin, tolbutamide, calcipotriene	2 weeks	pos. dechallenge
F	F, 61	exacerbation psoriasis	losartan	oxazepam	2 weeks	pos. dechallenge
G	F, 82	psoriasis	irbesartan	temazepam	1 week	

Other sources of information

Literature

Psoriasiform eruptions in relation with antihypertensive drugs have been described for β-adrenergic blocking agents, calcium channel blocker and angiotensin converting enzyme (ACE) inhibitors [8-10].

A literature search reveals also two publications for AT_1-antagonists. Kawamura et al. describe a 67-year-old woman with generalized pustular psoriasis 4½ months after initiation of candesartan [10]. She had no (family) history of psoriasis. Marquart-Elbaz et al. report nine patients in whom psoriasis was induced (5 patients) or exacerbated (4 patients) by AT_1-antagonist treatment [11]. They describe predominated lesions in the sun exposed areas in four patients and severe ungual involvement in three patients. Suspected drugs were valsartan, candesartan, losartan and irbesartan.

Databases

On December 1, 2005 the database of the Netherlands Pharmacovigilance Centre contained 5 reports on an AT_1-antagonist concerning aggravated psoriasis and 2 concerning a *de novo* psoriasis. The database of the WHO Uppsala monitoring centre contains 21 reports of psoriasis and 21 reports of aggravated psoriasis in association with AT_1-antagonists.

Table 2. Overview of data of case/non-case approach of Lareb and WHO database

Database	n reports AT_1 antagonist with (aggravated) psoriasis	ROR (95% CI)
Lareb	7	2.8 (1.3 – 6.0)
WHO	42	4.6 (3.4 – 6.2)

Mechanism

The mechanism of AT_1-antagonist induced psoriasis is not fully understood. Marquart-Elbaz *et al.* suggest an increased keratinocyte proliferation as a result of elevated angiotensin II serum levels [11]. Another hypothesis, postulated by Kawamura *et al.* suggests a role for bradykinin [10]. ACE-inhibitor induced psoriasis is caused by increased bradykinin levels in skin [8,9]. Although it is generally believed that AT_1-antagonists have not the same effect on bradykinin levels as ACE-inhibitors, they might have some potency as up-regulators for bradykinin.

Prescription data

Table 3. Number of prescriptions of AT_1-antagonists per year since 2000
(Source: GIP College voor Zorgverzekeringen, Diemen).

	2000	2001	2002	2003	2004
Losartan (Cozaar®)	410.740	423.860	509.960	595.170	653.540
Eprosartan (Teveten®)	6.116	14.885	16.420	23.467	34.793
Valsartan (Diovan®)	141.470	177.670	223.670	273.460	316.470
Irbesartan (Aprovel®)	117.390	156.160	211.530	262.680	326.040
Candesartan (Atacand®)	112.020	129.190	154.780	176.680	191.920
Telmisartan (Micardis®)	11.540	23.403	27.251	52.903	79.757
Olmesartan (Olmetec®)	.	.	.	.	11.775
Total	**799.276**	**925.168**	**1.143.611**	**1.384.360**	**1.614.295**

Conclusion

Lareb received 7 reports of (aggravated) psoriasis in association with AT_1-antagonists. Although psoriasis is a disease with spontaneous exacerbation and remission, in the reported cases of aggravated psoriasis, the time relationship and positive dechallenge are supportive for a causal relationship.
Aggravated / *de novo* psoriasis is disproportionally present in both the WHO and Lareb databases. Several case-reports described in literature support the association. The fact that psoriasis is reported for most of the AT_1-antagonists suggests a group effect with a direct pharmacological action as underlying mechanism. Psoriasis is mentioned in none of the SPC's of the AT_1-antagonists.

References

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2. Dutch SPC (version date 09-11-2004) Cozaar® http://www.cbg-meb.nl/IB-teksten/17617-26791.pdf
3. Dutch SPC (version date 03-08-2005) Diovan® http://www.cbg-meb.nl/IB-teksten/26939-26940.pdf
4. Dutch SPC (version date 17-01-2005) Aprovel® http://www.emea.eu.int/humandocs/PDFs/EPAR/Aprovel/H-141-PI-nl.pdf
5. European SPC (version date 17-01-2005) Micardis® http://www.emea.eu.int/humandocs/PDFs/EPAR/Micardis/H-209-PI-nl.pdf
6. Dutch SPC (version date 19-07-2004) Olmetec® http://www.cbg-meb.nl/IB-teksten/28782-28783-28784.pdf
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