Lareb

Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Alopecia caused by alendronate and risedronate

Introduction

The bisphosphonates alendronate and risedronate are indicated for *the prevention and treatment of postmenopausal osteoporosis in women, the prevention and treatment of osteoporosis caused by glucocorticosteroid treatment in women and men and treatment of osteoporosis in men*. Alopecia is not listed in the section of adverse events of the SmPC of alendronate or risedronate.[1,2]

Reports

Until March 5, 2008, the Netherlands Pharmacovigilance Centre Lareb received 53 reports of alopecia associated with the treatment with bisphosphonates. Only 4 of these reports concerned males. The majority of reports concern alendronate (*n*= 32) and risedronate (*n*=14).
Eighteen of the reports on alendronate concern the formulation of 70 mg/week. All of these reports concern women with a mean average age of 67 years (range: 54 – 78) and a mean time to onset of 13 weeks after start of treatment with alendronate. All but one of the 14 reports on the 10 mg/day formulation of alendronate concern women with an mean age of 60 years (range: 25 – 89) and an average latency of 9 weeks.
Ten of the 14 reports on risedronate concern the formulation of 35 mg/week. All but one of these reports concern women with average mean age of 59 years (range: 31 - 81) and a mean time to onset of 17 weeks (range 1 day – 1 year). The reports on risedronate 5 mg/day concern 3 women and one man with a mean age of 58 years (range; 46 – 71) with a time to onset of 4 – 5 weeks.
Alopecia is a medical condition with a multitude of possible causes including postmenopausal hormonal changes and chemotherapy or radiotherapy for the treatment of cancer. Confounding may be present in a number of reports and hampers the causality assessment. In nine reports a positive dechallenge was mentioned, which supports a causal relationship. These reports are listed in Table 1.

Table 1. Individual reports of alopecia associated with the use of bisphosphonates

patient, sex, age	dose indication for use	Concomitant medication	time to onset after last dose, outcome
A F, 66 22128	alendronate 10 mg/day osteoporosis	oxazepam, temazepam, paracetamol, diclofenac/misoprostol.	52 days, drug withdrawn, patient recovered
B M, 25 28365	alendronate 10 mg/day osteoporosis	salbutamol, cromoglycate, beclometason, cetirizine	3 months, drug withdrawn, patient recovered after 1 year
C F, 54 31485	alendronate 10 mg/day osteoporosis	none reported	unknown, drug withdrawn, patient recovered
D F, 76 38064	alendronate 70 mg/week osteoporosis	prednisolon, furosemide, hydrochlorothiazide/valsartan*	3.5 months, drug withdrawn, patient recovered within 1 month
E F, 79 42232	alendronate 70 mg/week osteoporosis	vitamin d, calcium, (paracetamol/codein when needed)	2 months, drug withdrawn, patient recovered

patient, sex, age	dose indication for use	Concomitant medication	time to onset after last dose, outcome
F F, 72 47974	alendronate 70 mgweek osteoporosis	none reported	unknown, drug withdrawn, patient recovered
G F, unk 55469	alendronate 10 mg/day osteoporosis	none reported	31 days, drug withdrawn, patient recovered
H F, 53 61225	risedronate 35 mg/week osteoporosis	none reported	1.5 years, drug withdrawn, patient recovered
I M, 54 71860	risedronate 5 mg/day osteoporosis	none reported	days, drug withdrawn, patient recovered

Alendronate and risedronate are available in formulations for daily and weekly administration. Higher peak plasma levels in the formulation for weekly dosage might influence the occurrence of alopecia. Although both daily and weekly formulations are involved, the distribution does not allow conclusions on the relevance of the formulation of alendronate or risedronate for the occurrence of alopecia.

Other sources of information

SmPC

In the Dutch SmPC of etidronate disodium 400mg with calcium carbonate 1250 mg (Didrokit®) alopecia is listed as a rarely occurring side effect. [3] Of products containing ibandronate alopecia is listed as a rarely occurring side effect in the SmPC of Bondronat® but not in the SmPC of Bonviva® or Bondenza®. [4 – 6] Alopecia is not listed in the Dutch SmPCs of any of other the bisphosphonate containing products.[7-9] In the US SmPCs of etidronate disodium (Didronel®) [10], of pamidronate (Aredia®) [11] and of zoledronate (Zometa®) [12] alopecia is mentioned as an adverse reaction.

Literature

Scarce reports on alopecia caused by bisphosphonates could be retrieved from Medline. In a Czech report 2 cases of transient alopecia during treatment with pamidronate are described. [13]

Mechanism

The exact mechanism of bisphosphonate induced alopecia is unknown. A hypothetical mechanism can possibly be deduced from the enzymatic pathway with which the majority of bisphosphonates interfere by blocking an enzyme.
Cholesterol is a structural constituent of human scalp hair. This cholesterol is partly absorbed and partly synthetised in hair follicles through the HmG-CoA-reductase pathway, which is also known as the mevalonate pathway.[14] Nitrogenous bisphosphonates [alendronate, risedronate, ibandronate, pamidronate, zoledronate] act on bone metabolism by binding and blocking the enzyme farnesyl diphosphate synthase (FPPS) in this HMG-CoA reductase pathway. [15] Statins are another class of drugs that inhibit the HMG-CoA reductase pathway by inhibiting HMG-CoA. Alopecia is an adverse drug reaction which is labeled for all statins.

Databases

Alopecia is disproportionally associated with alendronate and risedronate in both the Lareb database and in the database of the WHO.

Table 2. Number of reports and RORs of alopecia associated with the use of bisphosphonates in the Lareb database

Bisphosphonates	Reports Lareb	RoR (CI min-max) Lareb
alendronate[1]	32	3.9 [2.7 - 5.7]
risedronate	14	6.9 [3.9 – 12.]
etidronate[2]	3	2.8 [0.9 - 8.8]
ibandronate	2	-[3]
pamidronate	1	-[3]
clonodrate	1	-[3]

[1] two reports on alendonate 70 mg with colecalciferol 2800 IE [16]
[2] all 3 reports on etidronate 400 mg with calcium [17]
[3] RoR was not estimated due to small numbers

Table 3. Number of reports of alopecia associated with the use of alendronate and risedronate in the WHO database

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
alendronate	**4**	**4**	**6**	**12**	**65**	**29**	**5**	**3**	**13**	**14**	**14**	**4**	**2**
risedronate	**0**	**0**	**0**	**0**	**0**	**0**	**6**	**0**	**4**	**2**	**5**	**2**	**0**

Prescription data

Table 4. Use of bisphosphonates in the Netherlands, number of consumers

	2002	2003	2004	2005	2006
clodronate	**3,820**	**3,868**	**3,550**	**3,340**	**3,417**
pamidronate	**3**	**4**	**.**	**.**	**.**
alendronate	**76,655**	**92,219**	**109,490**	**126,110**	**147,330**
tiludronate	**50**	**36**	**29**	**34**	**17**
ibandronate	**.**	**.**	**.**	**362**	**4,885**
zoledronate	**.**	**.**	**.**	**50**	**279**
risedronate	**14,635**	**29,823**	**46,577**	**52,856**	**60,089**

Discussion

Lareb received 53 reports of alopecia associated with the treatment with bisphosphonates. In the Lareb database alopecia is disproportionaly associated with alendronate and risedronate, the two most frequently prescribed bisphosphonates in the Netherlands. The majority of reports (n= 46) concern alendronate (*n*= 32) and risedronate (*n*=14). In 9 of the 53 reports a positive dechallenge was reported which supports a causal relationship independent of possible confounding. The reports to Lareb do not allow for qualitative differentiation in the occurrence of alopecia between the daily and weekly dosage formulations of alendronate or risedronate. In the Dutch SmPCs of etidronate (Didrokit®)

and ibandronate (Bondronat®) containing products alopecia is listed as rarely occurring side effect.

Conclusion

Lareb received 53 reports of alopecia associated with the treatment with bisphosphonates. In nine of the 46 reports on alopecia during treatment with alendronate and risedronate a causal relationship is supported by a positive dechallenge. Alopecia should be listed in the SmPC of alendronate and risedronate and listing of alopecia should be considered for all bisphosphonates

References

1. Dutch SmPC Fosamax. (version date 03-06-2005) http://db.cbg-meb.nl/IB-teksten/h18021-h22841.pdf
2. Dutch SmPC Actonel (version date 01-02-2007)http://db.cbg-meb.nl/IB-teksten/h28338.pdf
3. Dutch SmPC Didrokit (version date 10-03-1998) http://db.cbg-meb.nl/IB-teksten/h13739.pdf.
4. Dutch SmPC Bondronat. (version date 09-10-2007) http://www.emea.europa.eu/humandocs/PDFs/EPAR/Bondronat/H-101-PI-nl.pdf
5. Dutch SmPC Bonviva. (version date 11-10-2007) http://www.emea.europa.eu/humandocs/PDFs/EPAR/Bonviva/H-501-PI-nl.pdf
6. Dutch SmPC Bondenza. (version date 27-11-2007) http://www.emea.europa.eu/humandocs/PDFs/EPAR/bondenza/H-502-PI-nl.pdf
7. Dutch SmPC Pamipro (version date 11-10-2007) http://db.cbg-meb.nl/IB-teksten/h30311.pdf
8. Dutch SmPC Ostac. (version date 09-01-2008) http://db.cbg-meb.nl/IB-teksten/h13412.pdf
9. Dutch SmPC Zometa. (version date 07-11-2007) http://www.emea.europa.eu/humandocs/PDFs/EPAR/zometa/H-336-PI-nl.pdf
10. US SmPC Didronel. (version date May 2005) http://www.pgpharma.com/pi/US-Didronel.pdf
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16. Dutch SmPC Fosavance. (version date 28-01-2008) http://www.emea.europa.eu/humandocs/PDFs/EPAR/Fosavance/H-619-PI-nl.pdf
17. Dutch SmPC Actokit (version date 23-11-2007)http://db.cbg-meb.nl/IB-teksten/h31634.pdf

This signal has been raised on June 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).