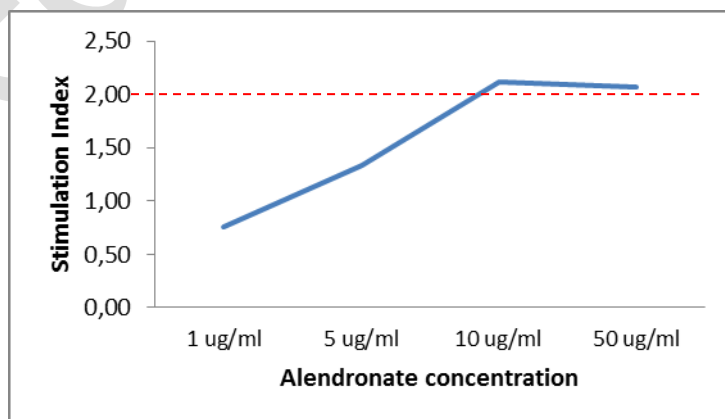


Appendix A. Skin biopsy of the left calf taken during flare-up shows a slight epidermic atrophy with a lymphocytary infiltrate. Moreover, a mixed infiltrate with perivascular lymphocytes and abundant dermic eosinophils can be observed. In the center of the biopsy a subcorneal pustule constituted by polymorphonuclears, eosinophils and neutrophils can be seen (Hematoxylin-Eosin stain; original magnification x10, x40 respectively).

Alendronate concentration	Stimulation Index
50 ug/ml	2,07
10 ug/ml	2,12
5 ug/ml	1,33
1 ug/ml	0,75
0,5 ug/ml	0,90
0,1 ug/ml	0,89
50 ng/ml	1,83
10 ng/ml	0,97

Appendix B



Appendix C

Table 1. Reported non-immediate reactions due to alendronate with allergological study.

Author(s)	Sex, age	Clinical presentation	Latency period	Allergological study with alendronate
Kimura et al. [1]	F, 72	Red papules and petechiae	10 days	Patch test 20%, 10%, 1%, 0.1% pet. - Negative Scratch patch tests 1%, 0.1% pet. - Negative Scratch patch tests 20%, 10% pet. - Positive LTT – Positive
Brinkmeier et al. [2]	F, 60	Maculopapular skin lesions	4 months	Patch test (scratch-chamber) 50% pet., wat. -Positive* Open test (rub, prick, scratch) - Negative OCT - Positive
Barrantes et al. [3]	CASE 1 M, 70	Erythematous rash	-	Patch test 1% pet. - Positive Patch test 1%, 0.1% wat. - Positive
	CASE 2 F, 78	Desquamative bilateral rash on the eyelids	-	Patch tests - Negative Delayed-reading ID 0.1% wat. - Positive
Pet. – Petrolatum; Wat. – water; OCT – Oral challenge test; ID – intradermal test *patch tests showed weak positive skin reactions on 10 healthy subjects.				

References

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2. Brinkmeier T, Kügler K, Lepoittevin JP, Frosch PJ. Adverse cutaneous drug reaction to alendronate. *Contact Dermatitis*. 2007; 57(2):123-5.
3. Barrantes-González M, Espona-Quer M, Salas E, Giménez-Arnau AM. Bisphosphonate-induced cutaneous adverse events: the difficulty of assessing imputability through patch testing. *Dermatology*. 2014; 229(3):163-8.