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Adjunctive effect of neridronate in non-surgical periodontal therapy: a randomized clinical trial

Effetti aggiuntivi del neridronato alla terapia parodontale non chirurgica: clinical trial randomizzato

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Summary

An adjunctive course of intramuscular neridronate did not provide any additional clinical benefits as compared to scaling and root planing alone 6 months after periodontal treatment (3 months after the completion of BPs treatment).

Riassunto

L'utilizzo di neridronato intramuscolare non determina alcun beneficio clinico se comparato al solo scaling and root planing 6 mesi dopo terapia parodontale (ossia 3 mesi dopo la conclusione della terapia farmacologica).

Introduction

Anti-inflammatory and host-response modulators may be added to conventional periodontal treatment to further improve the effects of therapy (Salvi & Lang 2005). Among host modulators, Bisphosphonates (BPs) may be used as adjunctive treatment due to their action on bone metabolism and their ability to inhibit matrix-metalloproteinases (MMPs) (Giannobile 2008).

The aim of this randomized controlled trial conducted in patients with advanced generalized chronic periodontal disease was to evaluate whether 3 months of therapy with neridronate in association with non-surgical periodontal treatment would provide additional clinical improvements as compared to the ones obtained with conventional treatment alone.

Material and Methods

Experimental design and Patient Selection

This study was an open label randomized, parallel design, masked clinical trial with a 6-month follow up on periodontally affected subjects. Eligible patients were identified from the population referred to the Oral Surgery clinic of the University of Pisa, Italy. Ethical approval was obtained from the local Ethics Committee. A complete periodontal examination consisting of full mouth periodontal probing on six-sites per tooth was taken. O'Leary's full mouth plaque score (FMPS) and Ainamo & Bay full mouth bleeding score (FMBS) were calculated. Full mouth probing pocket depth (PPD) and recession of the gingival margin (REC) were recorded at the same time. Clinical Attachment Level (CAL) was calculated as PPD plus REC. A radiographic examination was also undertaken. Subjects who met the study inclusion criteria were invited to participate in the study. The trial included subjects with generalized advanced chronic periodontitis. Subjects were excluded from the study if they suffered from any systemic diseases, conditions such as pregnancy or if they were taking any medications. Informed consent was obtained from all the subjects to before starting the study.

Sample size calculation, randomization procedures and allocation concealment

Twenty-four subjects per treatment arm would be needed to detect a difference of 1.0 mm between test and control in PPD reductionin pockets ≥ 7mm as the primary outcome variable assuming that the common standard deviation is 1.0 mm. Thus, a convenience sample of 60 subjects, 30 per arm were recruited. Subjects were randomly assigned by a computer-generated table to receive one of the two treatments. The randomization table was saved by a research fellow not directly involved in the experimentation. Thirty plastic bags containing 12 ampoules of 12,5 mg/2 ml neridronic acid were matched with the treatment assignment number. Allocation to the treatment was concealed to the therapist and the examiner.

Treatment Procedures

A standard cycle of periodontal therapy consisting of oral hygiene instructions, supra and subgingival scaling and root planing was performed by a certified therapist using both ultrasonic and hand instruments. Both groups received this treatment in four different appointments within a period of 2 weeks. Test subjects received an adjunctive course of systemic bisphosphonates consisting of 12,5 mg of neridronate i.m. once a week for 12 weeks, while control subjects did not receive any medication. Neridronate was self-administered by the subjects.

Examinations and follow-up

Complete periodontal examinations were performed at baseline, at the end of the BPs treatment (i.e. 3 months after the first session of periodontal treatment) and 6 months after the first session of treatment (i.e. 3 months after the end of BPs therapy) by a masked calibrated examiner. The number of not administered ampoules were documented based on each subject's self report.

Data management and statistical analysis

Subject-level analysis was performed. Numerical data were summarized as means and 95% confidence intervals, categorical data were summarized as frequency distribution and the percentage-based measures (e.g. FMPS) were summarized as the median of the percentage and interquartile range. Significance of differences between test and control groups in terms of numerical data was evaluated using the independent samples *t*-test. Likewise, significance of difference within each group before and after treatment was evaluated with the paired samples *t*-test. Categorical data were analyzed with the Chi-Squared test, and the percentage data between the two groups were compared with the Mann-Whitney test while the within group percentage changes were evaluated with the Wilcoxon signed rank test. The significance of the treatment option (test or control) on the dependent variables PPD reduction and CAL gain at different initial PPD categories was estimated by analysis of covariance (ANCOVA). The models were adjusted for baseline values and controlled for smoking. The primary outcome measure of the study was PPD reduction in sites with initial PPD ≥7mm. An intention-to-treat, last observation carried forward analysis was performed. An "on-drug" analysis excluding data from subjects who incurred in a protocol violation (non-adherent to test medication) was also performed. In addition, the statistician was masked to the treatment group.

Results

Subject accountability

Flow of patients is depicted in Fig. 1. Sixty subjects were randomly allocated to participate in the study. All participants received the allocated intervention. Five subjects from the test and 4 subjects group were lost throughout the 6-month follow-up. All participants were included in the intent to treat analysis.

Subject characteristics at baseline

Baseline characteristics of the 60 participants are displayed in table 1. None of the demographic parameters showed a statistically significant difference between groups.

Values for clinical parameters

Mean and median values for clinical parameters and the differences between baseline and 3 months and baseline-6 months are displayed in table 2. At baseline there were no significant differences between test and control. All parameters showed highly statistically significant differences between baseline and follow-up time points. On the contrary, no statistically significant differences were detected between test and control groups in any of the variables at any time point.

There were no significant treatment effects for any of the clinical variables included in the ANCOVA models (Table 3). In addition, smoking proved to be a significant factor on PPD reduction and CAL gain.

Percentage of sites with clinically relevant changes

A subset analysis was carried out to test the changes of some clinically relevant parameters at 3 and 6 months (Table 4). All the median values (interquartile range) showed no statistically significant differences. In particular, the percentage of pockets that converted from ≥ 4mm at baseline to ≤ 3mm also failed to show a statistically significant difference at 3 (P=0.438) and at 6 months (P=0.953).

Adverse events, concomitant medication and compliance

During the first three weeks of treatment, 8 subjects (26.7%) in the test group and 2 subjects (6.7%) in the control reported adverse events. Four subjects in the test group complained of muscolo-skeletal pain. One subject experienced a large edema at the injection sites. Nine subjects (5 in the test group and 4 in the control group) had a tooth extraction each between baseline visit and the 6 months visit. Concomitant medication during the study period was recorded. Two subjects in the test group and 2 in the control group took amoxicillin capsules for periodontal abscesses.Two subjects (6%) did not complete the treatment as indicated due to 1 edema at the injection site and 1 subject reported severe muscolo-skeletal pain. These 2 subjects missed 91% and 66% of the whole number of ampoules respectively.

Secondary "on-drug" analysis did not report differences from the overall results (data not shown).

Discussion

This was the first trial designed to assess the effect of neridronate as an adjunctive treatment of conventional non-surgical therapy of generalized advanced chronic periodontitis. Neridronate was chosen for its effects on bone metabolism and its safety. Our data indicate that neridronate did not add any clinically significant benefit to scaling and root planing in otherwise systemically healthy patients.

Our results disagree with other reports showing significant clinical improvement adding alendronate to conventional periodontal treatment (Rocha et al. 2001, Rocha et al. 2004). Their findings indicate that in subjects with diabetes or osteoporosis, thus showing higher susceptibility to periodontal disease and impaired wound healing, the added benefit of using bisphosphonate were clinically small but significant.

One of the possible reasons for the lack of clinical effects 3 months after the end of drug intake could be related to the molecular action of the drug. Neridronate has not been tested on matrix metalloproteinases. Moreover, neridronate may either enhance or decrease human osteoblasts biosynthetic activity according to the dosage and the metabolic stage of the cell (Corrado et al. 2005). Therefore, it could be also speculated that the dosage used in our study was not sufficient to expect an effective action on the osseous metabolism of the alveolar bone. However, the same dosage is routinely used for the osteoporosis treatment (Adami et al. 2008).

Furthermore, in this study neridronate was used in a cohort of systemically healthy patients showing no pathologies altering the susceptibility to periodontal disease. Interestingly, another trial conducted on systemically healthy patients showed that alendronate and risendronate did not present additional clinical benefit versus conventional treatment after 6 months but only after 12 months (Lane et al. 2005). According to the authors the effect of scaling and root planning would mask the adjunctive benefit of the drug during the first 6 months. Indeed, in our study periodontal treatment was successfully conducted in both groups as mean pocket probing depth reduction and clinical attachment gain were higher than the average standard of therapy as seen in table 2 (Cobb 1996, Van der Weijden & Timmerman 2002). Thus, trials evaluating the possible effects of the bisphosphonate during maintenance are advocated.

An open label study design with no placebo was chosen for practical convenience and not to expose patients to multiple injections with no benefit. Nonetheless, the authors are aware that this may represent a limitation to the conclusion that can be drawn. However, in order to compensate the absence of a placebo, a masked examiner was chosen (Day & Altman 2000).

On the basis of our findings, neridronate did not appear to add significant benefits to conventional periodontal treatment 3 months after the completion of the adjunctive therapy. However, longer observation periods are needed in order to evaluate a possible long-term action of this adjunctive medication.

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Figure 1. Flow of patients throughout the study

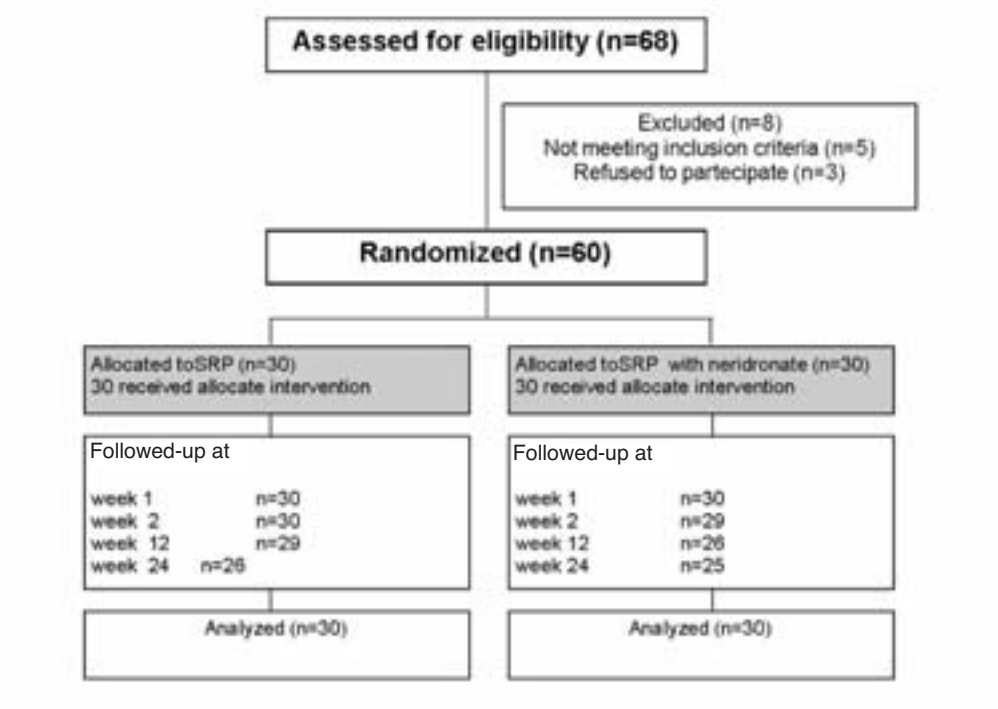

Table 1. Subject and clinical characteristics at baseline

Parameter	Test group N=30	Control group N=30	P-value
Age Mean (95% C.I.)	44.7 (42.2, 47.3)	42.2 (38.7, 45.7)	0.233 N/S *t*-test
Females (percentage)	19 (63.3%)	20 (66.7%)	0.787 N/S Chi-squared
Smokers (percentage)	10 (33.3%)	9 (30 %)	0.781 N/S Chi-squared
Body Mass Mean (95% C.I)	23.9 (22.3, 25.4)	24.2 (23.1, 25.2)	0.750 N/S *t*-test
Teeth at baseline Mean (95% C.I.)	25.0 (23.7, 27.0)	25.0 (24.0, 28.0)	0.268 N/S Mann-Whitney
% of pockets ≥ 5 mm Median (I.Q.)	21.9 (14.4, 33.5)	26.1 (11.0, 36.8)	0.865 N/S Mann-Whitney
Number of pockets ≥ 5 mm Mean (95% C.I.)	37.0 (28.3, 45.7)	38.4 (29.0, 47.8)	0.824 N/S *t*-test
% of pockets ≥ 7mm Median (I.Q.)	3.3 (1.1, 8.4)	4.2 (1.2, 10.5)	0.836 N/S Mann-Whitney
Number of pockets ≥ 7mm Mean (95% C.I.)	8.3 (4.7, 11.9)	9.6 (5.7, 13.5)	0.608 *t*-test N/S
Full-mouth plaque score Median (I.Q.)	76.5 (59.7, 82.0)	66.0 (45.7, 77.5)	0.129 N/S Mann-Whitney
Full-mouth bleeding score Median (I.Q.)	31.5 (17.7, 42.0)	29.7 (20.0, 49.4)	0.631 N/S Mann-Whitney

(C.I.: Confidence interval; I.Q: Interquartile range)
N/S non significant

Table 2. Clinical outcome variables at baseline and differences between baseline – 3 months and baseline - 6 months

Clinical Outcomes	Group	Baseline	Difference between Baseline and 3 months	Difference between Baseline and 6 months	P value	
					Difference Baseline 1-Baseline 2	Difference Baseline 1-Baseline 2
Full-mouth mean PPD Mean (95% C.I.)	Control	3.5 (3.2, 3.7)	0.7 (0.5, 0.9)	0.7 (0.5,0.9)	<0.001 Paired *t*-test	<0.001 Paired *t*-test
	Test	3.4 (3.2, 3.7)	0.8 (0.6, 0.1)	0.7 (0.8,0.9)	<0.001 Paired *t*-test	<0.001 Paired *t*-test
Mean PPD at pockets ≥ 7 mm Mean (95% C.I.)	Control	7.6 (7.4, 7.8)	3.0 (2.4, 3.6)	3.2 (2.7, 3.9)	<0.001 Paired *t*-test	<0.001 Paired *t*-test
	Test	7.6 (7.3, 7.9)	2.7 (2.0, 3.4)	3.0 (2.3, 3.8)	<0.001 Paired *t*-test	<0.001 Paired *t*-test
Full-mouth mean CAL Mean (95% C.I.)	Control	4.1 (3.6, 4.6)	0.5 (0.3, 0.8)	0.6 (0.3, 0.9)	<0.001 Paired *t*-test	<0.001 Paired *t*-test
	Test	4.2 (3.9, 4.6)	0.6 (0.3, 0.8)	0.5 (0.2, 0.8)	<0.001 Paired *t*-test	<0.001 Paired *t*-test
Mean CAL at sites with initial pockets ≥ 7mm Mean (95% C.I.)	Control	8.3 (7.9, 8.8)	2.8 (2.2, 3.4)	3.1 (2.5, 3.7)	<0.001 Paired *t*-test	<0.001 Paired *t*-test
	Test	8.4 (7.8, 8.9)	2,2 (1.5, 2.9)	2.6 (1.8, 3.4)	<0.001 Paired *t*-test	<0.001 Paired *t*-test
Percentage of pockets ≥ 5 mm Median of percentage (I.Q.)	Control	26.1 (11.1, 36.8)	12.8 (3.7, 22.8)	12.6 (4.7, 27.4)	<0.001 Wilcoxon	<0.001 Wilcoxon
	Test	21.9 (14.5, 33.5)	13.1 (8.6, 19.9)	13.8 (7.4, 19.1)	<0.001 Wilcoxon	<0.001 Wilcoxon
Percentage of pockets ≥ 7 mm Median of percentage (I.Q.)	Control	4.2 (1.2, 10.5)	1.5 (0.0, 8.6)	2.6 (0.6, 9.3)	<0.001 Wilcoxon	<0.001 Wilcoxon
	Test	3.3 (1.1, 8.4)	1.4 (0.5, 4.2)	1.4 (0.6, 5.3)	<0.001 Wilcoxon	<0.001 Wilcoxon
Full-mouth plaque score (%) Median (I.Q.)	Control	66.0 (45.7, 77.5)	43.5 (28.5, 60.2)	40.5 (26.0, 48.0)	<0.001 Wilcoxon	<0.001 Wilcoxon
	Test	76.5 (59.7, 82.0)	51.5 (29.0, 60.5)	50.0 (21.0, 63.2)	<0.001 Wilcoxon	<0.001 Wilcoxon
Full-mouth bleeding score (%) Median (I.Q.)	Control	29.7 (20.0, 49.4)	18.3 (9.7, 26.5)	14.9 (5.9, 25.6)	<0.001 Wilcoxon	<0.001 Wilcoxon
	Test	31.5 (17.7, 42.0)	15.4 (5.1, 23.9)	11.4 (0.3, 21.3)	<0.001 Wilcoxon	<0.001 Wilcoxon

Table 3. Analysis of covariance for PPD reduction and CAL gain at 3 and 6 months in different pockets categories

Multivariate "ANCOVA" analysis Models	Parameter	Difference Baseline-3 months		Difference Baseline – 6 months	
		Estimate (95% C.I.)	P. value	Estimate (95% C.I.)	P- value
Full mouth mean PPD reduction	Treatment group (test-control)	0.1 (-0.1, 0.3)	0.440	0.0 (-0.2, 0.2)	0.863
	Smoking (no-yes)	0.2 (-0.0. 0.4)	0.129	0.2 (-0.0. 0.5)	0.053
Mean PPD reduction in pockets ≥7 mm	Treatment group (test-control)	-0.3 (-1.2, 0.5)	0.414	-0.2 (-1.0, 0.5)	0.549
	Smoking (no-yes)	0.1 (-1.1, 0.8)	0.749	0.4 (-0.4, 1.3)	0.317
Full mouth mean CAL gain	Treatment Group (test-control)	0.0 (-0.3, 0.3)	0.902	-0.1 (-0.5, 0.2)	0.428
	Smoking (no-yes)	0.4 (0.0, 0.8)	0.022	0.4 (0.0, 0.8)	0.039
Mean CAL gain in sites with initial PPD ≥7mm	Treatment group (test-control)	- 0.6 (-1.4, 0.3)	0.210	-0.5 (-1.4, 0.5)	0.342
	Smoking (no-yes)	0.0 (-1.0, 1.0)	0.984	0.5 (-0.6, 1.6)	0.084

Table 4. Percentage of sites with clinically relevant changes in test and control groups at 3 and 6 months

	Difference Baseline- 3 months			Difference Baseline- 6 months		
Median of percentage (I.Q.)	Test group	Control group	P value Mann-Whitney test	Test group	Control group	P value Mann-Whitney test
% of sites with ≥ 2 mm of CAL gain after treatment	24.8 (19.2, 34.0)	18.7 (8.3, 29.7)	0.255	21.7 (13.4, 34.6)	18.4 (13.3, 36.0)	0.882
% of sites with ≥ 2mm of PPD reduction after treatment	24.8 (17.2, 34.0)	24.1 (9.5, 29.8)	0.620	25.2 (15.3, 30.7)	21.3 (12.0, 34.0)	0.988
% of sites with CAL loss ≥ 2 mm after treatment	7.3 (2.9, 11.3)	5.1 (3.2, 10.7)	0.847	5.1 (2.3, 16.0)	5.0 (1.8, 14.1)	0.965
% of pockets converting from ≥5mm at baseline to ≤4 mm after treatment	76.3 (63.0, 88.8)	70.4 (53.8, 85.7)	0.407	75.3 (65.9, 88.9)	74.4 (62.5, 92.0)	0.780
% of pockets converting from ≥4mm at baseline to ≤3 mm after treatment	66.6 (45.9, 76.1)	57.0 (48.2, 69.2)	0.438	66.4 (48.4, 80.0)	63.1 (51.6, 75.3)	0.953