

Appropriate use of anabolic treatment for severe osteoporosis

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Summary

Osteoporotic fractures remain a major public health problem for their correlated morbidity and mortality. The primary aim of therapy must be the prevention of the first fragility fracture and avoiding subsequent fractures in patients who already have an existing fracture. There are evidences from randomized controlled trials (RCTs) about the efficacy of antiresorptives, such as bisphosphonates in reducing the risk of fracture, but none of these agents completely abolish the fracture risk.

The reduction of RRR by different therapies in RCTs is relatively constant but it is important to note that the proportion of inadequate-responders (i.e.: patients fracturing despite adequate pharmacological treatment) is increasing with the severity of the disease: the higher the risk of fracture the higher the proportion of inadequate-responders. Thus, the proportion of non responders across different trials is directly related to the fracture incidence observed in the control group of RCTs which is the most proximate indicator of osteoporosis severity.

Teriparatide (TPTD) demonstrate a real increases of both trabecular and cortical bone volume, which are associated with a true reduction of fracture risk, as many RCTs confirm.

The beneficial effect of introducing a treatment with antiresorptives after the treatment course with TPTD has been clearly demonstrated with the prevention of the reabsorption of the new bone tissue built during TPTD therapy and rapidly lowers cortical porosity, which leads to further increases in BMD. For these re-

sults, the introduction of an anti-resorptive after the treatment course with TPTD is strongly recommended and taken into account.

In Italy TPTD is fully reimbursed in patients incurring in a new vertebral or hip fracture while on chronic treatment with antiresorptive or in naive patients with 3 or more vertebral or hip fractures. In conclusion, since patients with severe osteoporosis are at very high risk of new fractures with worsening of quality of life and life expectancy, antiresorptives represent a sub-optimal treatment in these patients, whereas, since TPTD demonstrated real and substantial improvements in bone mass and reduction of fracture risk independently of initial risk, TPTD represents the only therapeutic option able to reverse at least in part this disabling disease.

KEY WORDS: *severe osteoporosis, antiresorptives, teriparatide, fractures, cost effectiveness.*

Introduction

Osteoporotic fractures remain a major public health problem, causing substantial morbidity and mortality (1-3).

The primary aims of therapeutic intervention in osteoporosis are to prevent the first fragility fracture and to avoid subsequent fractures in those patients who already have an existing fracture (4,5). There is a strong evidence from large randomized controlled trials (RCTs) of the efficacy of antiresorptives such as bisphosphonates in reducing the risk of fracture in patients with osteoporosis (5). The fracture risk reduction for osteoporosis medication is ranging from 30 to 70% for vertebral fractures and from 5 to 25% for non-vertebral fractures (6). Thus, none of these agents completely abolish the fracture risk, and a proportion of patients with existing fractures will sustain new fractures in a relatively short period while on treatment; similar considerations apply to strontium ranelate (Fig. 1) (7-14).

The reduction of the relative risk (RRR) by different therapies in clinical trials is relatively constant over a wide range of risk. Thus, the proportion of inadequate-responders (i.e.: proportion of patients suffering from new fractures while on active treatment) (18) is increasing with the severity of the disease: the higher the risk of fracture the higher the proportion of inadequate-responders. The number of prevalent fractures is by far the strongest risk factor for new incident fractures(15) (Fig. 2). For example, in the FIT Trial the proportion of non responders was 2.1% in patients without prevalent fractures and this proportion rose to 5.2% in patients with 1 prevalent vertebral fractures and to 12.8-18.7% in those with 2-5 prevalent fractures (16). Similar observations were provided by other pivotal trials (10, 13). Thus, the proportion of non responders across different trials is directly related with the fracture incidence observed in the control group of RCTs (Table I) which is the most proximate indicator of osteoporosis severity.

The anti-fracture efficacy of treatment with antiresorptive agents documented in RCTs is generally extended to routine practice if treatment is associated with an adequate adherence (17). However, in ICARO, a large Italian study (with both cross-sectional and prospective phases) (18,19) in patients eligible for antosteoporotic treatment according to Italian reimbursability criteria (20), the incidence of fractures during treatment with antiresorptives was

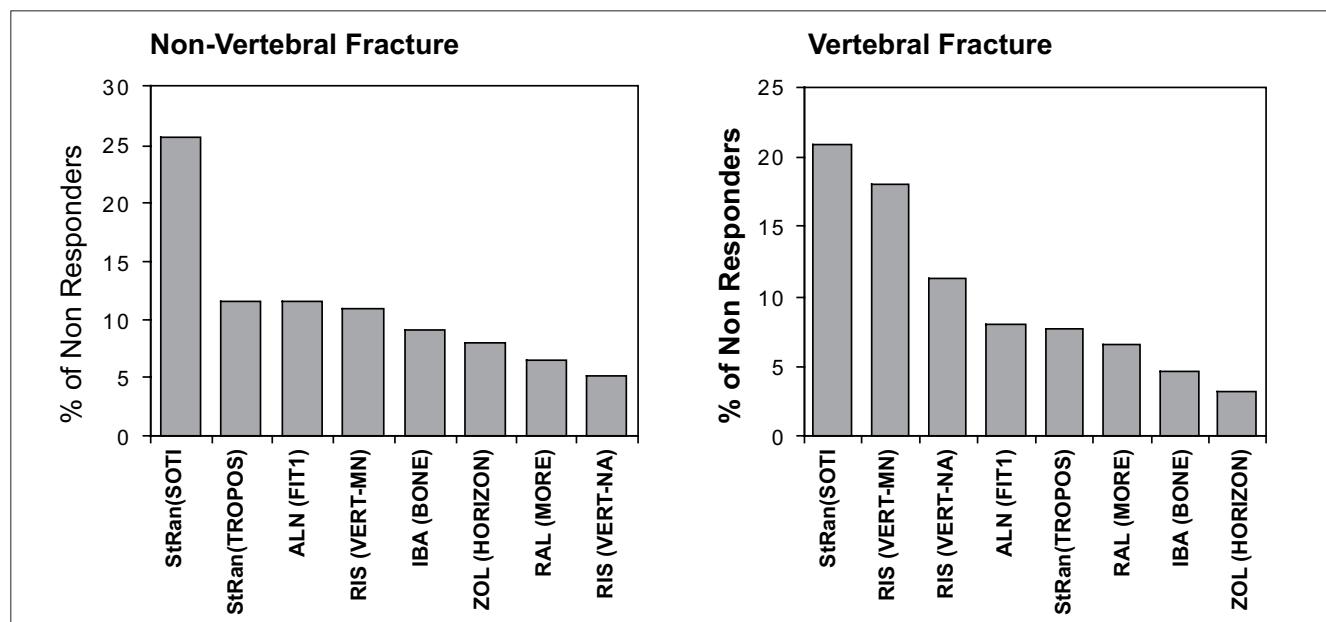


Figure 1 - Proportion of non-responders in the treatment arm of the pivotal trials (7-14).

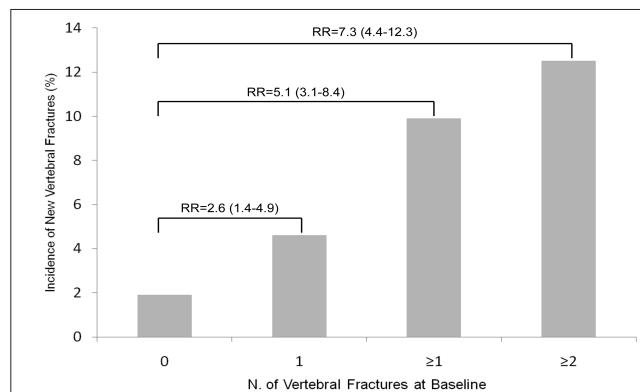


Figure 2 - Effect of prevalent vertebral fractures on risk of subsequent vertebral fractures in 12 months observation on 2725 postmenopausal women (15).

considerably higher than that observed in randomized clinical trials, even though only patients with adequate treatment adherence (>70%) were included in the analysis. This is likely due to the severity of osteoporosis identified by Nota 79 bis as inclusion criteria for post-menopausal osteoporosis: history of at least one vertebral or hip fragility fracture or a hip BMD < -3.0 T-score (20). The results of both the retrospective and prospective phases of the ICARO study indicate that about 8% of women with severe osteoporosis (as engulfed by the Nota 79) experience a new fragility fracture every year despite treatment with bisphosphonates (18,19). The consequences in terms of morbidity and quality of life of inadequate response to antiresorptives and strontium ranelate is depending on the initial conditions. In patients without prevalent vertebral or hip fractures, a new incident fracture is generally (but not invariably) not associated with irreversible deterioration of the quality of life. However, in the typical patients eligible to treatment reimbursability in Italy with a prevalent vertebral or hip fractures, the impact of a new fracture is most often dramatic (see Appendix A, for the Italian situation on fractures).

Any new fracture doubles the risk of an additional fracture, with an exponential worsening of quality of life (15, 21-24). In patients with more than one vertebral deformity, the life expectancy is also severely reduced (1, 2, 15, 25-27).

Fundamental differences in the mechanism of action between teriparatide and antiresorptives

Bisphosphonates are the most commonly used antiresorptives for the osteoporosis treatment. These agents inhibit the activity of osteoclasts and lower the activation frequency, i.e.: the number of remodeling unit per unit bone volume. This results in a rapid (within 2-4 months) decrease in the remodeling space (i.e.: the bone volume undergoing remodeling processes) and a progressive ageing of the bone tissue which is associated with increased mineralization (secondary mineralization). Most of the BMD changes as measured by DXA during bisphosphonate therapy are explained by the increased mineralization of the existing bone tissue, without any relevant change in bone volume (27-29). The fracture risk reduction reported during RCTs of bisphosphonates is likely to be mostly related to the prevention of further bone losses, taking place in the control groups.

Thus, the antiresorptive agents are quite effective in preventing further worsening of osteoporosis, but they might have little effect on the actual fracture risk. The prevention of further bone loss is of value in patients with osteopaenia or with a mild form of osteoporosis, but it is inadequate in patients with severe osteoporosis. For example, in patients with one or more prevalent fractures, the risk of new fractures is so high that the prevention of further worsening is definitely a sub-optimal strategy (15, 16).

The anabolic agents, such as teriparatide (TPTD), increase bone formation, by making the bone balance within individual remodeling unit positive (i.e.: more bone is laid down by osteoblasts than that reabsorbed by osteoclasts) and at the same time by forming new bone tissue on the resting surfaces and possibly also on the periosteum (30, 31). TPTD administration is also associated with some later increases in activation frequency and then in remodeling space, which leads to transient increase in cortical porosity and decreased global mineralization of bone tissue (31, 32). However, the effect on bone remodeling does not offset the positive effects on bone mass and mechanical resistance (32, 33). The final effect of TPTD therapy translates in true increases of both trabecular and cortical bone volumes, which are expected to be associated with a *true* reduction of fracture risk (34,35). There are 3 evidences that TPTD decreases the fracture risk, rather than preventing the worsening of the risk:

A - The reduction in absolute risk of fracture is independent of the

Table 1 - Incidence of vertebral (A) and non-vertebral (B) fractures for placebo and active treatment arms in pivotal trials for antiresorptive agents available in Europe (7-14).

Table 1 - A. Vertebral fractures

antiresorptive agents	study and reference	vertebral fractures n/N (%)		p
		placebo	active treatment	
Alendronate	FIT	145/965	78/981	<.001
	Black, Lancet 1996	(15,0%)	(8,0%)	
Risedronate	VERT-NA	93/678	61/696	.003
	Harris, JAMA 1999	(16,3%)	(11,3%)	
Risedronate	VERT-MN	89/346	53/344	<.001
	Reginster, Osteoporosis Int. 2000	(29%)	(18,1%)	
Ibandronate	BONE	73/975	37/977	<.001
	Chesnut, JBMR 2004	(9,6%)	(4,7%)	
Zoledronate	HORIZON	310/2853	92/2822	<.001
	Black, NEJM 2007	(10,9%)	(3,3%)	
Raloxifene	MORE	231/2292	148/2259	<.05
	Ettinger, JAMA 1999	(10,1%)	(6,6%)	
Strontium Ranelate	SOTI	n.a./723‡	n.a./719‡	<.001
	Meunier, NEJM 2004	(32,8%)	(20,9%)	
Strontium Ranelate	TROPOS	n.a./637	n.a./587	
	Reginster, JCEM 2005	(31,5%)	(22,7%)	

Table 1 - B. Non Vertebral fractures

antiresorptive agents	study and reference	non vertebral fractures n/N (%)		p
		placebo	active treatment	
Alendronate	FIT	148/1005	122/1022	n.s.
	Black, Lancet 1996	(14,7%)	(11,9%)	
Risedronate	VERT-NA	52/815	33/812	.02
	Harris, JAMA 1999	(8,4%)	(5,2%)	
Risedronate	VERT-MN	51/406	36/406	n.s.
	Reginster, Osteoporosis Int. 2000	(16,0%)	(10,9%)	
Ibandronate	BONE	n.a./n.a.	n.a./n.a.	n.s.
	Chesnut, JBMR 2004	(8,2%)	(9,1%)	
Zoledronate	HORIZON	388/2853	292/2822	<.001
	Black, NEJM 2007	(10,7%)	(8,0%)	
Raloxifene	MORE	240/2579	437/5129§	n.s.
	Ettinger, JAMA 1999	(9,3%)	(6,6%)	
Strontium Ranelate	SOTI	122/723	112/719	n.s.
	Meunier, NEJM 2004	(16,9%)	(25,6%)	
Strontium Ranelate	TROPOS	n.a./1633	n.a./1687	n.s.
	Reginster, JCEM 2005	(12,9%)	(12,9%)	

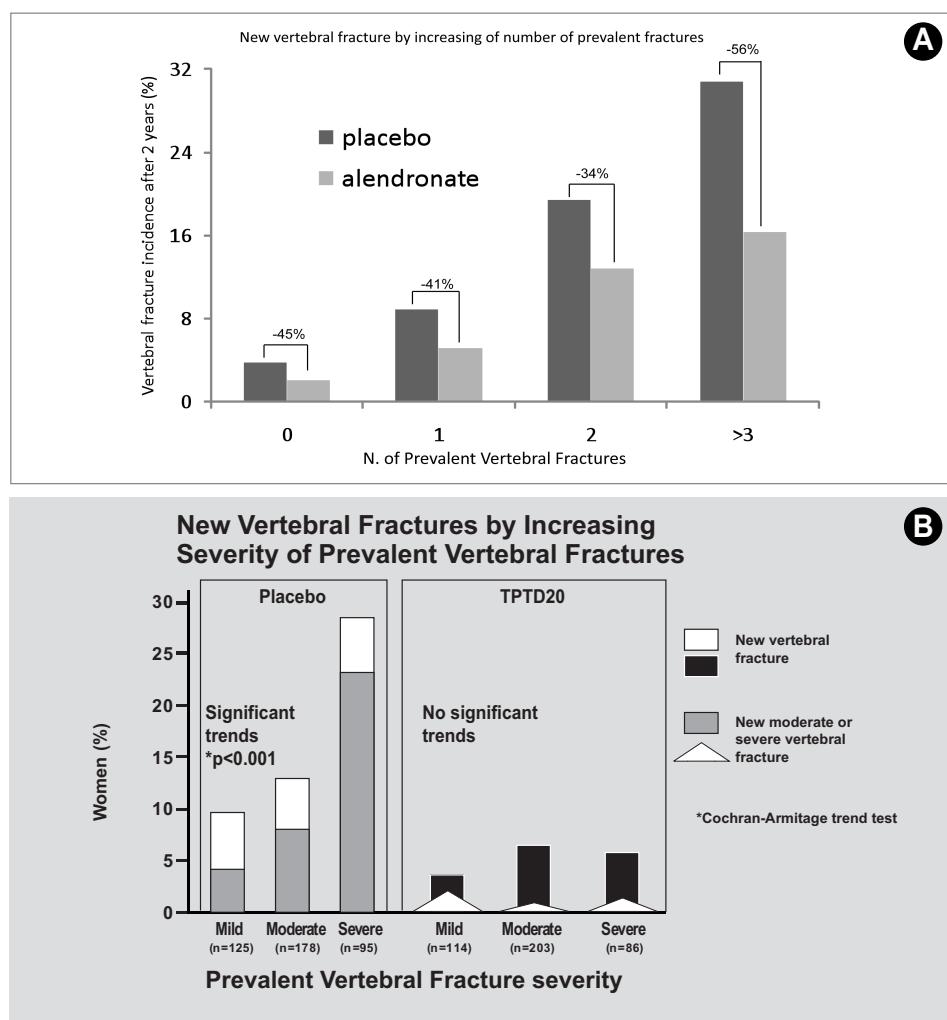
‡ incidence considered for patients with at least one prevalent vertebral fracture

§ pooled data from two raloxifene arms (120 mg/die and 60mg/die)

baseline risk. In other words, in contrast to bisphosphonates, the proportion of patients fracturing during treatment with TPTD is maintained very low regardless of baseline risk (36). For example during the FPT the incidence of new vertebral fracture was 9.6% and

28.4% in patients with prevalent mild or severe vertebral deformities, respectively. On the contrary in patients treated with Forsteo these proportions were very low (3.5-5.8%) and unrelated to baseline osteoporosis severity (Fig. 3).

Figure 3 - Incidence of new vertebral fractures in patients treated with study drug or placebo; according to the number of prevalent vertebral fractures at baseline in the FIT trial (7) (A) and in the FPT trial (35) (B) (36).



B - In a head-to-head study in patients on glucocorticoid therapy, TPTD was shown to be superior to alendronate in decreasing vertebral fracture risk (6.1% vs. 0.6%, $p=0.004$). Significant, fewer new vertebral fractures occurred in the TPTD group compared to the alendronate group. TPTD was also associated with greater increases in bone mineral density at the spine and hip (37).

C - In pivotal RCTs for osteoporosis treatment the RRR of vertebral fracture relative to placebo tended to decrease (risedronate, alendronate and strontium ranelate) or to be maintained (zoledronate and ibandronate) from the first to the 2nd and 3rd year of treatment (7-14) (Table II).

This is not the case for TPTD. In the Fracture Prevention Trial (FPT), Neer et al. reported a decreased incidence of non-vertebral fractures over time in teriparatide treated patients compared to placebo (35). In a subsequent post-hoc analysis of the FPT Lindsay et al. found that TPTD 20 µg compared with placebo decreased the relative hazard for non-vertebral fragility fractures by 7.3% for each additional month of treatment and by 9.8% for major non-vertebral fractures (34). Similarly, in another post-hoc FPT analysis on clinical vertebral fractures Lindsay reported a correlation between increased duration of treatment and decreased incidence of clinical vertebral fractures (38). Eastell et al. reported a gradual decrease in clinical fragility fracture incidence over 24 months of teriparatide treatment in severe osteoporotic women in the EU-ROFOR study (39). Notably, there were 1.7% of patients who fractured during the 19-24 month period compared with 2.3% during the 13-18 month period.

In addition, the results from the European Forsteo Observational Study (EFOS) showed a similar relationship (40). Overall, the number of patients who had at least one fracture during TPTD treatment significantly decreased between the first 6-month period (4.6%) and the second 6-month period (3.5%), $p=0.036$, and between the first 6-month period and the last 6-month period on treatment (2.8%) ($p=0.004$). The fracture incidence per 10,000 patient-years of 1113 in the first six months decreased to 583 during the 12-18 month period. A relevant decline in the incidence of both clinical vertebral and non-vertebral fractures was observed during the study (40) (Fig. 4).

Extended benefits after treatment discontinuation (AR treatment, anabolic treatment)

Most of the BMD benefits from bisphosphonates are rapidly lost at the hip after treatment discontinuation, while their effect at the lumbar spine is maintained for a variable length of time depending on the duration of previous treatment and on the type of bisphosphonate (zoledronate > alendronate > risedronate) (41-43). The persistence of the anti-fracture efficacy has not been extensively investigated. In the FLEX study with alendronate it was reported that after 5 year of continuous treatment only the incidence of clinical vertebral fracture was significantly higher in patients who discontinued treatment as compared to that observed in patients who continued the treatment (42).

		RRR in vertebral fracture (%)				
		years				
		0-1	0-2	0-3	0-4	0-5
Alendronate 10mg daily	n.a.	62%	47%	n.a.	n.a.	
FIT Study			p<0.001			
Ibandronate 2.5mg daily	58%	61%	62%	n.a.	n.a.	
BONE study	p=0.0561	p<0.001	p<0.001			
Risedronate 5mg daily	65%	55%	41%	n.a.	n.a.	
VERT-NA study	p=0.001		p=0.003			
Risedronate 5mg daily	61%	59%	49%	n.a.	n.a.	
VERT-MN study	p=0.001		p=0.001			
Strontium ranelate 2g daily	49%	n.a.	41%	33%	n.a.	
SOTI Study	p<0.001		p<0.001	p<0.001		
Strontium ranelate 2g daily	45%	n.a.	39%	n.a.	24%	
TROPOS Study	p<0.001		p<0.001		p<0.001	
Zoledronic acid 5mg/year	60%	71%	70%	n.a.	n.a.	
HORIZON Study	p<0.001	p<0.001	p<0.001			
n.a.: not available; p values always vs. placebo						

Table II - Vertebral antifracture efficacy over time for alendronate (a), risedronate (b), strontium ranelate (c, d), ibandronate (e) and zoledronate (f) (7-14).

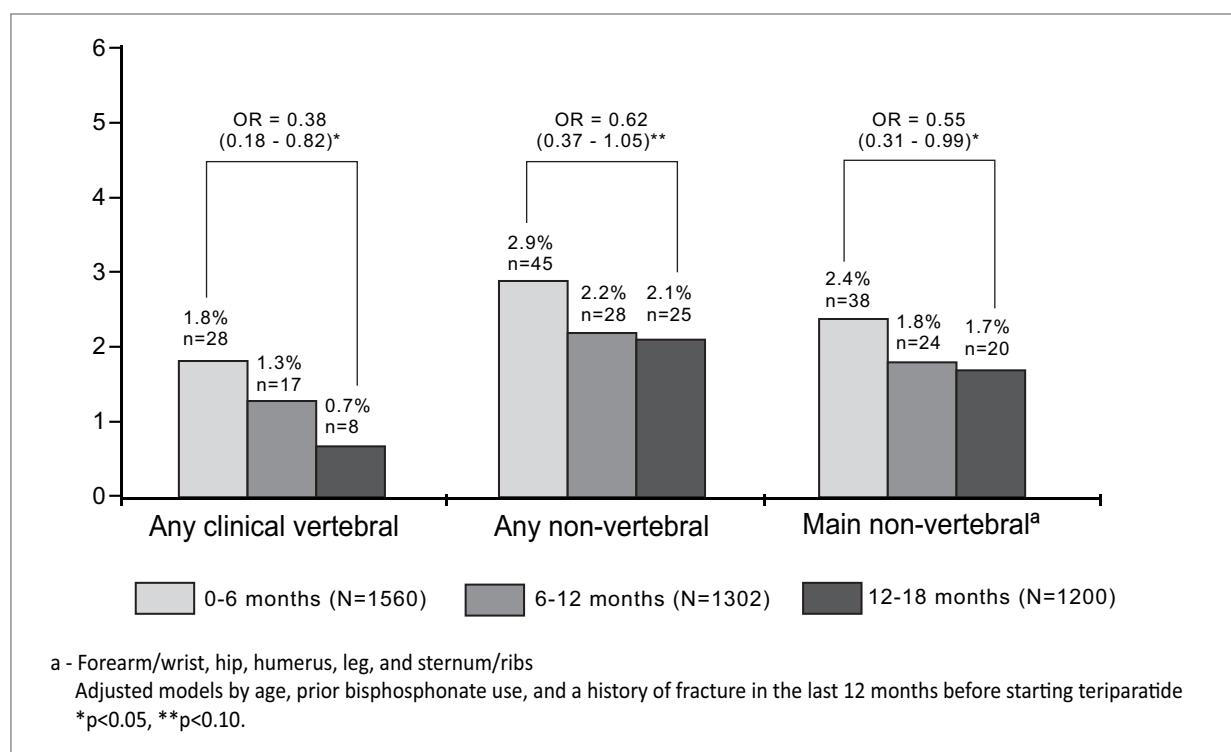


Figure 4 - Incident fractures by fracture type is reduced progressively during increasing duration of TPTD treatment (EFOS Study) (40).

Lumbar Spine BMD Following Treatment with TPTD20 mcg With or Without Antiresorptives

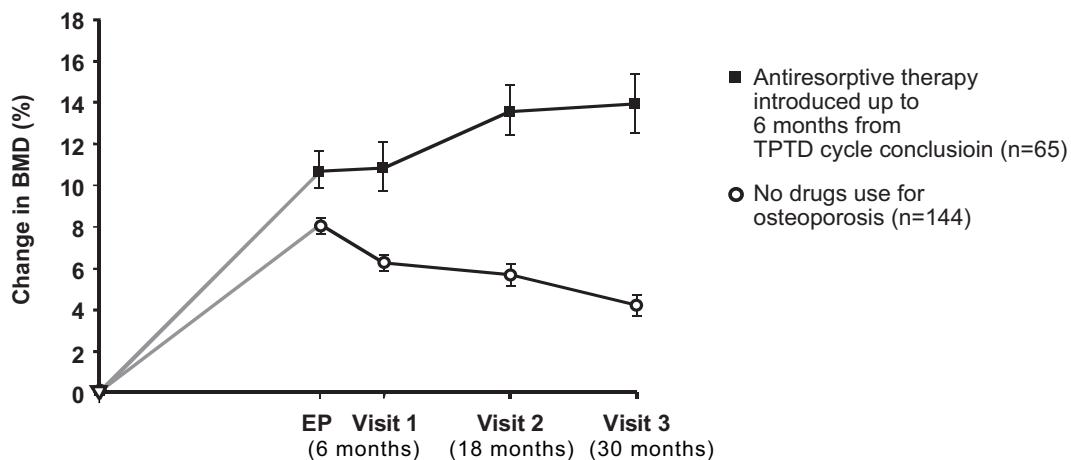


Figure 5 - Percentage change in DXA BMD from baseline at lumbar spine (34, 47).

Post-treatment follow-up examinations were obtained for a large proportion of patients participating in the FPT with TPTD. The cumulative incidence of clinical fracture in patients previously given TPTD continued to diverge when compared to patients who had been on placebo (34,47). The difference was even more striking among patients who were treated with bisphosphonates during the follow up (34, 47) (Fig. 5).

The beneficial effect of introducing a treatment with antiresorptives after the treatment course with TPTD or PTH has been demonstrated in other studies (39,48,49) and it is supported by a good rationale. TPTD increases bone mass but, at the same time, the new bone is less mineralized. The treatment with antiresorptives after TPTD prevents the reabsorption of the new bone tissue build during TPTD therapy increases mineralization and rapidly lowers cortical porosity; this leads to further increases in BMD. For these reasons the introduction of an anti-resorptive after the treatment course with TPTD is recommended and in the long term estimation of efficacy the complete scheme (e.g.: TPTD followed by a bisphosphonate) should be always taken into account.

Cost effectiveness of teriparatide treatment

The cost of TPTD treatment is considerably higher than that of antiresorptives. For this reason its use is indicated for patients with severe osteoporosis; for example in Italy TPTD is fully reimbursed in patients incurring in a new vertebral or hip fracture while on chronic treatment with antiresorptives or in patients never treated with AR, with 3 or more vertebral or hip fractures (20). From an analysis of the fracture incidence in sub-groups of the placebo arm of RCTs (Adami et al, in press) it can be estimated that the yearly incidence of clinical fractures is approximately 10% in the patients identified by "Nota 79". As described before, in these patients any additional new fracture is associated with dramatic worsening of quality of life, substantially increased mortality and huge costs.

The Number Needed to Treat (NNT) to prevent a given event is often used to assess the cost-effectiveness of any preventive therapy. TPTD is reimbursed for a treatment course of 18 months which ideally should be followed by an antiresorptive, in order to maintain the achieved benefits. Data on the anti-fracture efficacy of this therapeutic scheme are available (38,47) for a total period of 50 months (on average 19,3 months of treatment plus up to 30-months follow-up) for about half of the patients in the FPT study (both placebo and TPTD groups). Up to the completion of this time lag the fracture incidence for treated (TPTD followed by a bisphosphonate) and untreated (placebo followed by a bisphosphonate) patients was still diverging. At the end of the follow-up period, the relative risk of a non-vertebral fracture was reduced by 38% in the group originally treated with TPTD versus the placebo group. After the cumulative 37 months of observation, the initial 19-months teriparatide treatment at dose of 20 mcg daily s.c. was found to produce the final NNT of 7.75 for reduction of a new vertebral fracture (38); this is the lowest NNT obtained for osteoporosis treatment. It should be highlighted that the inclusion criterion in the TPTD registration trial was at least one prevalent vertebral fracture and the mean fracture number was 2.3 per person; on the other hand, the NOTA 79 allows reimbursement of TPTD treatment in patients with at least 2-3 severe fractures or non-responders to antiresorptives, that means in patients at higher fracture risk. Indeed, in the Italian observational study on severe osteoporosis, the mean number of vertebral fractures per patient was 3.6 at enrollment (Adami et al., in press). Assuming that this observational study mirrors the common Italian clinical practice, only patients at great fracture risk are treated with TPTD, in this "high risk" population the NNT can be estimated to be even lower than that one reported during the follow up of the registration trial by Lindsay et al. (38), i.e. 4.

This observation, together with the economic burden of osteoporotic fractures in this type of patients, should be kept into account while evaluating the cost effectiveness of TPTD in patients with severe osteoporosis as identified by the Italian Nota 79.

Conclusions

The major aim of osteoporosis treatment is the prevention of new fragility fractures. Patients with severe osteoporosis (i.e. with more than one prevalent vertebral or hip fracture) are at very high risk of new fractures and these new fractures are associated with dramatic worsening of quality of life and life expectancy. Treatment of osteoporosis with antiresorptives (e.g.: bisphosphonates) is not associated with true changes in bone mass and does not sufficiently reduce the fracture risk, especially in patients with prevalent fractures. Thus, antiresorptives are of great help in patients with mild-moderate osteoporosis but represent a sub-optimal treatment in patients with severe osteoporosis.

A treatment course with TPTD, particularly when followed by an antiresorptive is associated with real and substantial improvements in bone mass and with a reduction of fracture risk to an acceptable level, independently of the initial risk. In these patients TPTD treatment is the only therapeutic option able to revert at least in part this disabling disease.

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Appendix A

Fractures: the Italian situation

Fragility fractures compromise patients' Quality of Life and have a strong negative impact on direct and hospitalization costs (50). In detail, hip and femoral fractures have detrimental consequences in term of social costs: 40% of patients lost walking ability, 80% is unable to perform usual activities and 20% died within a year for fractures complications (51).

In fact, fracture complications have a great importance among the possible causes of disability in the elderly with dimensions comparable only to the Acute Myocardial Infarction (AMI) (51).

In Italy, in 2000 and in 2007, the national hospitalization database (SDO) maintained by the Italian Ministry of Health, recorded over 700,000 hospitalizations for femoral neck fractures (51).

In 2007 there was nearly 98,000 hospitalizations for femoral proximal fractures: 78% of these were in over 75 year patients (male/female ratio: 1:4).

Between 2000 and 2007, the incidence by range of age remain constant despite the increment of the absolute number of fractures due to the increased number of the elderly people (Table 1).

About other fractures of the skeleton, since hospitalization is not always necessary, we have an underestimated incidence. So, the 750,000 total hospitalizations in 2000-2007 for proximal humerus, distal radius, ankle and vertebrae fractures will be not a real data.

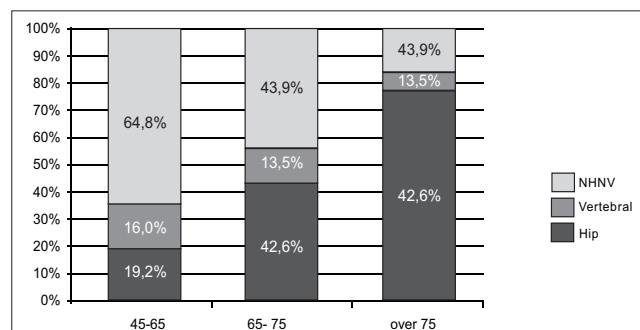


Figure 1 - Distribution of hip, vertebral and non-hip/non-vertebral (NHNV) fractures by age range in Italy (SDO 2007).

It could be estimated that ankle fractures are a third, humerus fractures a quarter and wrist a fifth of all those really happen. Different from these are vertebral fractures that are symptomatic in the 30% of the cases (and of this 30% only a third is recorded), and are asymptomatic in the 70%, despite their incidence is correctly estimated.

Fracture site distributions significantly changes on age basis: the patients older than 75 years have more frequently hip fractures (78% of the total), while younger patients have non-femoral and non-vertebral fractures (Figure 1).

Table 1 - Incidence (%) of femoral neck fractures by gender and age in Italy (SDO 2000-2007).

	Male				Female				Total
	45-64	65-75	> 75	total	45-64	65-75	> 75	total	
2000	3.32	12.00	77.86	15.42	4.16	25.92	165.30	42.40	30.12
2001	3.33	12.15	78.89	15.89	4.55	25.82	172.37	44.86	31.66
2002	3.24	11.94	78.58	15.97	4.29	26.28	173.13	45.54	32.05
2003	3.13	11.44	81.34	16.40	4.13	25.35	171.39	45.43	32.17
2004	3.38	12.37	78.03	16.49	4.59	26.51	168.23	45.71	32.33
2005	3.30	11.89	80.01	16.88	4.39	26.26	170.08	46.55	32.94
2006	3.24	11.93	79.62	16.98	4.37	25.62	168.03	46.18	32.78
2007	3.16	11.83	79.63	17.02	4.34	25.34	171.93	47.06	33.25
mean	3.26	11.94	79.24	16.38	4.35	25.89	170.06	45.47	32.16