

# Alendronate: new formulations of an old and effective drug to improve adherence avoiding upper gastrointestinal side effects

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**Abstract. – OBJECTIVE:** Alendronate is a second generation bisphosphonate which has been widely used in medical practice for two decades to treat osteoporosis and prevent fragility fractures both in elderly people and in younger patients.

**METHODS:** Since many papers have been recently published and new formulations or dosages have been developed, our aim was to review the most significant medical literature addressing the issues of efficacy, safety, posology and formulations of the treatment with alendronate in osteoporotic patients.

**RESULTS:** The efficacy of alendronate in reducing the risk of vertebral and non-vertebral fractures has been demonstrated in several studies. Despite favourable data coming from clinical trials, tolerability of alendronate represented a critical issue since its introduction into real clinical practice, possibly leading to early discontinuation of the therapy, especially when combined with lack of motivation of the patient. For this reason, new dosages and formulations of alendronate have been developed, alone or in combination with vitamin D, which have shown to reduce the impact of gastro-oesophageal adverse events, and minimize discomfort due to the need of adopting unfavourable postural positions every day, fasting for at least one hour.

**CONCLUSIONS:** Alendronate is the most frequently used antifracture therapy among those currently available. The increasing use of the 70 mg weekly dosages and newest formulations of this drug are expected to reduce adverse events and increase adherence to the antifracture therapy, thus resulting in better clinical outcomes when treating osteoporotic patients.

*Key Words:*

Alendronate, New formulations, Efficacy, Safety, Compliance.

## Introduction

The World Health Organization (WHO) considers osteoporosis to be second only to cardiovascular diseases as a critical health problem<sup>1</sup>. Hip fractures suffered by elderly people because of underlying osteoporosis have shown incidence and costs comparable to those of acute myocardial infarction and strokes in our previous studies<sup>2-4</sup>. Hip fractures have a 5% acute mortality rate and a 15-25% 1 year-mortality<sup>5-7</sup>. Furthermore, once hip fracture has occurred, the ability to walk is completely lost in 20% of cases, and only 30-40% of patients recover a degree of autonomy comparable to the period before the fracture, with a high risk of long term disability<sup>8-11</sup>. Despite that, osteoporosis has been a neglected disease for many decades. Only the big clinical trials on the efficacy of alendronate<sup>12</sup> and other antifracture drugs<sup>13-17</sup>, carried out in the last 15 years, have definitely contributed to a full recognition of the disease and its fracture complications. In this frame, the scientific community has agreed on a comprehensive definition of osteoporosis (addressing both demineralization and bone quality/deterioration issues)<sup>18</sup>, while novel drugs or other therapeutical strategies were specifically developed for the treatment of the disease<sup>19-25</sup>. However, alendronate remains the most frequently used antifracture drug all over the world, mostly due to its favourable cost-efficacy profile<sup>23</sup>. The British National Institute for Clinical Excellence (NICE) indicates alendronate as first choice treatment in secondary prevention of post-menopausal osteoporosis (as measured by bone mineral density (BMD) values < -2.5 SD by Dual Energy X-ray Densio-Absorptiometry, DXA), as the annual cost of the therapy is estimated to remain always below the social ac-

ceptability threshold of 30,000 pounds per QUALY gained<sup>23</sup>, a threshold conventionally fixed by British health care authorities. Therefore, alendronate is considered by the NICE as a reference for all the other antifracture drugs, which can be prescribed only in patients with low tolerability to alendronate or/and in case of severe osteoporosis<sup>23</sup>. Due to its wide use in general population, data have been published about long-term efficacy of alendronate<sup>24</sup>. At the same time, new formulations (i.e. vitamin-D added alendronate and the effervescent drinkable solution ones) or dosages (passed from 10 mg per day to 70 mg per week) have been developed to reduce tolerability problems, especially gastro-oesophageal adverse events<sup>24,26-28</sup>. Our aim was to review the most significant medical literature addressing the issues of efficacy, safety and posology of alendronate treatment in osteoporotic patients, paying specific attention to the newest formulations of the drug such as effervescent alendronate or drinkable solution<sup>26-28</sup>.

### **Long Term Efficacy**

The Fracture Intervention Trial (FIT) demonstrated that a 3-year treatment with alendronate – in a cohort of both fractured and non-fractured osteoporotic patients – results in an overall significant reduction of fracture risk: 53% for hip fractures, 45% for clinical vertebral fractures and 30% for wrist fractures<sup>29</sup>. Moreover, a reduction of 48%, 30% and 27% in the risk of radiologic vertebral fractures (which decreased up to 87% for multiple fractures), any clinical fracture and any non-vertebral clinical fracture were observed, respectively<sup>29</sup>. Evidence of statistically significant fracture risk reduction was already present at the end of the first treatment year for any type of clinical fracture in the FIT trial, with a 59% reduction in the risk of clinical vertebral fractures by month 12<sup>29</sup>. By month 18, the risk of developing any clinical fracture or hip fracture was reduced by 27% and 63%, respectively. At month 24, non-vertebral fracture risk decreased by 26%, while the risk of wrist fractures was reduced by 34% at month 30<sup>29</sup>. Number Needed to Treat (NNT) to prevent vertebral fractures in the FIT population was very favourable: NNT=8 and NNT=29 in patients with or without previous vertebral fractures, respectively<sup>29</sup>. A 4-year treatment with alendronate has specifically been shown to reduce the risk of first vertebral deformity in post-menopausal women with osteoporosis (as measured by BMD values < -2.5 SD by

femoral neck DXA) but without vertebral fractures, over a 4-year period<sup>26</sup>. An overall 36% and 44% risk reduction was observed for clinical and radiographic vertebral fractures, respectively. A significant decrease in the risk of developing a first radiographic vertebral fracture was shown in osteopenic women too (BMD values between -2.0 and -2.5 SD)<sup>26</sup>. However, in these latter patients it has been recorded a higher value of NNT=59, compared to a NNT=35 observed in osteoporotic patients (BMD values below -2.5 SD)<sup>26</sup>. In post hoc analyses, a 4-year treatment with alendronate confirmed to reduce hip fracture risk by 56% (NNT=81) in osteoporotic women (femoral neck BMD values below -2.5 SD)<sup>26,30</sup>. In other words, alendronate is effective in reducing the risk of osteoporotic fractures in people with osteoporosis and/or prevalent vertebral fractures<sup>29,30</sup>. Data about efficacy of alendronate are available up to 5 years of continuous treatment in the FIT cohort<sup>26,30</sup> and for additional 5 years in the FLEX extension study (1099 postmenopausal women already treated for 5 years in the FIT study)<sup>30</sup>. According to the currently available evidence, the possibility to continue the treatment with alendronate for more than 5 years should be considered only in postmenopausal women with osteoporosis, as documented by T-score values -2.5 SD at femoral neck (DXA), and in those with at least one vertebral fracture and higher values of bone mineral density (below -2.0 SD at femoral neck by DXA)<sup>31</sup>. Finally, the efficacy of sequential treatment strategies with alendronate and other antifracture drugs (i.e. parathyroid hormone, PTH) has also been positively explored<sup>32</sup>.

### **Safety Concerns and Compliance Issues as Rationale for New Drug Formulations**

Safety and gastro-oesophageal tolerability of alendronate has been specifically investigated in the FIT II cohort, showing favorable data: discontinuations due to adverse events (AEs) were similar in the treatment and placebo groups (any AE leading to discontinuation: 9.9 vs. 10.2; gastro-oesophageal AEs: 47.5 vs. 47.2; abdominal pain: 14.5 vs. 14.7; oesophagitis: 0.9 vs. 0.5; oesophageal ulcer: 0.2 vs. 0.2; other oesophageal AEs: 2.0 vs. 1.8; acid regurgitation: 9.2 vs. 8.7)<sup>30,31</sup>. The occurrence of AEs resulting in hospitalizations were also similar between the two groups (29.1 vs. 26.9), as well as the number of people who died during the study period for any cause (1.7 vs. 1.8)<sup>30</sup>. Despite that, safety con-

cerns and complaining issues about the use of alendronate have been perceived both by physicians and patients as a possible critical issue in real clinical practice since the introduction of the drug into the market at the dosage of 10 mg per day. Unfavorable postural restrictions when assuming the drug were prescribed by the manufacturers, with the patient standing up and fasting for at least 1 hour (and possibly not taking other concomitant drugs in the meanwhile). Side effects, especially gastro-oesophageal AEs, and lack of motivation have been recognized as the main cause of permanent discontinuation of the therapy, thus, resulting in possible fractures for the patients and waste of money for healthcare systems or insurances<sup>34</sup>. Initial effects in terms of fracture risk reduction have been associated with compliance rates to bisphosphonates no lower than 50%, with more acceptable and pronounced effects being reached for compliance rates of 75% and higher<sup>35,36</sup>. This suggests that optimal adherence to therapy might improve clinical outcomes in the treatment of osteoporotic patients<sup>35,36</sup>. Specifically, compliance rates of about 45% have been associated to half of the antifracture effect observed in clinical trials, while a compliance rate of 80% is needed to reach a full effect of the drug (comparable to that reported in registrative studies)<sup>35</sup>. Since compliance to therapy is so crucial for the antifracture effect of bisphosphonates, different dosages (i.e. alendronate 70 mg once a week instead of 10 mg per day) and formulations (i.e. the liquid and the newest effervescent ones) of alendronate have been developed to overcome the risk of early discontinuation of medication<sup>37,38</sup>. In huge studies on institutional database, 1-year compliance was between 14% and 40%<sup>38-40</sup>. Population studies confirmed the lowest estimations (17% compliance to antifracture drugs at 1 year)<sup>41</sup>, while clinical studies were associated to much higher compliance rates<sup>34</sup>. Daily oral bisphosphonates were associated to lower compliance compared to weekly regimens<sup>34,39-42</sup>. Also in sub-populations at very high risk of fracture (or re-fracture) such as patients with a previous hip fracture<sup>43</sup>, the compliance to the therapy is acceptable for a very small proportion of patients<sup>44</sup>, and even the prescription of antifracture drugs after the fracture is very uncommon<sup>45</sup>. Interestingly, it is still controversial whether monthly-administered bisphosphonates (i.e. ibandronate) are associated to higher compliance rates than weekly dosages or not<sup>38,39</sup>. Despite that, type of drug and dose regimen seem to

be the most important factor influencing compliance to antifracture treatment, in addition to patients concerns about adverse events (especially those affecting gastro-oesophageal tract)<sup>38</sup>. These tolerability concerns leading to lower compliance rates – and consequently to lower efficacy of the treatment – have risen up even more frequently after the introduction of “generic” alendronate (non-branded drugs with bioequivalent properties)<sup>46,47</sup>. Some authors have also suggested that drug efficacy might result not only from a higher rate of discontinuation due to side effects, thus questioning the bioequivalency itself of generic vs. branded alendronate<sup>48</sup>. However, the reduced antifracture treatment efficacy of generic vs. branded alendronate is well documented, as well as a higher rate of adverse events, especially affecting gastro-oesophageal tract<sup>49-51</sup>. The higher appearance of gastro-oesophageal complications due to the use of generic alendronate seem to be associated to a faster disintegration time that may cause lesions to the oesophageal mucosa<sup>47-53</sup>. *In vitro* data on six different generic bisphosphonates confirmed this hypothesis<sup>54</sup>. Obviously, differences between all the different generic bisphosphonates commercially available should also be taken into account, as many traditional and new manufacturers have started to produce and market this drug. The possibility of higher gastro-oesophageal side effects are of particular concern because bisphosphonates had already been associated with oesophagitis and gastric ulcerations, or with more rare but serious complications such as oesophageal strictures and cancer<sup>55-57</sup>. The more frequent early discontinuation of treatments and the higher occurrence rates of adverse events associated to generic alendronate have been investigated in specific pharmaco-economic studies, which questioned the supposed cost-savings that would come from the switching from branded to generic formulations of bisphosphonates<sup>58</sup>. In this frame two new alendronate formulations have been introduced in the market. The first one is a novel effervescent formulation – with a high buffering capacity – that has been recently developed to improve gastric and oesophageal tolerance.

In a clinical study, Hodges et al<sup>59</sup> evaluated gastric emptying and gastric pH after administration of alendronate tablets and this novel effervescent ALN formulation with a high buffering capacity. Gastric pH was monitored by nasogastric probes. Gastric emptying was determined simultaneously by scintigraphic imaging of

<sup>99m</sup>Tc-DTPA labelled formulations. Both formulations tested rapidly cleared the oesophagus and there were no statistically significant or physiologically relevant differences in gastric emptying times. Mean pH at time to 50% gastric emptying of the radiolabel was significantly higher in effervescent formulation-treated subjects compared to those treated with tablets. At time to 90% gastric emptying of the radiolabel, mean pH values were comparable. Mucosal exposure to ALN at pH less than 3 is irritating to gastro-oesophageal tissue. Ingestion of tablets resulted in ALN being present in the stomach at a pH below 3 within minutes. The effervescent formulation minimised the possibility of exposing the oesophagus (in case of reflux) to acidified ALN. This study has indicated that new effervescent alendronate formulation has been shown to reduce the gastric mucosal exposure to alendronate at level of pH  $\leq$  3, which represents a risk factor for irritation of gastro-oesophageal mucosae. The other developed formulation is a water-soluble alendronate delivery system. Potential advantages of a drinkable formulation of alendronate are avoiding adherence of the tablet to the gastric mucosa, overcoming motility obstacles (i.e. hernia, spasm, the body position of the patient during transit), eliminating the variability in the tablet disintegration rate with consequent irritation or reflux of particles, and controlling the pH of the gastric fluid. Gomez Acotto et al<sup>60</sup> compared the transit time and bioequivalence of a drinkable solution of 70 mg/100 mL alendronate to reference tablets in 104 healthy volunteers. In order to characterize the oesophageal passage time of the two alendronate formulations, the authors performed a randomized, controlled study, in healthy subjects who took the formulations standing or lying down, by an X-ray video deglutition system. The results showed that when taken in the standing position, both formulations had equal mean transit times from mouth to stomach and tablet disintegration but data dispersion was significantly smaller with the liquid form. While when taken in lying position, drinkable alendronate had shorter and less variable median transit times compared to the tablets<sup>60</sup>. Therefore, the introduction into the market of these new formulations of alendronate is supposed to reduce the gastro-oesophageal adverse events compared to alendronate tablets, enhance persistence on therapy, and consequently the efficacy of the antifracture treatment.

## Discussion

One out seven postmenopausal women in the United States are estimated to have been treated with bisphosphonates in their life, with alendronate being the most used among this class of drugs<sup>31</sup>. Adherence to the therapy represents a major issue of antifracture treatments, as it directly affects the efficacy of the drug<sup>33,34,38</sup>. One-year unacceptable compliance rates are associated to significant increases of avoidable fracture and hospitalization rates (17% and 37%, respectively, as reported by Huybrechts et al), on top of higher medical costs sustained by healthcare services or insurances<sup>41</sup>. Most common reasons for discontinuing the therapy are known to be adverse events (often affecting stomach and oesophagus) and lack of motivation by the patient<sup>34</sup>. Apart from upper gastro-intestinal tolerability, bisphosphonates have been indicated as responsible for other rare side effects (recognized only when million people all over the world started taking the tablets), such as osteonecrosis of the jaw (ONJ) and atypical subtrochanteric femoral fractures<sup>31,61-64</sup>. While this latter very rare complication has almost exclusively been observed in case of prolonged use of the drug<sup>61</sup>, ONJ has become a "threatening" event in maxillofacial medicine, with many case reports published all over the world<sup>65-67</sup>.

Despite many of these cases could theoretically be ascribed to an improper use of the drug (i.e. osteoporotic patients assuming higher doses than those recommended), most of ONJs occur when bisphosphonates (i.e. intravenous zoledronate) are used in the oncological setting (for the prevention of bone metastatic disease), where significantly higher dosages are routinely administered than those used to treat osteoporosis<sup>68-71</sup>. The remaining ONJ cases, apart from those affecting oncological patients, are often described in people with underlying dental problems (i.e. peri/parodontitis, gingivitis, hidden dental infections)<sup>66,67</sup>. Nevertheless, atypical femoral fractures and ONJ have fostered a focused interest in the scientific community, so that the U.S. Food and Drug Administration (FDA) has recently re-evaluated the efficacy of continuing bisphosphonate therapy beyond 5 years<sup>60,72</sup>.

The need for overcoming gastro-oesophageal adverse events (which remain the most frequently reported adverse events in clinical practice)<sup>34,38,47</sup> and to minimize discomfort due to the instructions for the assumption of alen-

dronate (standing and fasting for at least one hour every day with the initial 10 mg/die dose) have pushed researchers and manufacturers to introduce new dosages (70 mg once a week) and new formulations, such as the newest effervescent alendronate and drinkable solutions. Actually, a change in dosing frequency has already been associated to positive effect on the compliance, with significant differences between drugs administered daily, weekly or monthly<sup>34,38,73-74</sup>. However, available data show that 1-year compliance rates remain usually below the threshold of clinical efficacy for all antifracture drugs at any dosage, with worst adherence being recorded for treatments administered every day (i.e. strontium ranelate 2 g/die or alendronate 10 mg/die) and for those drugs for which gastro-oesophageal adverse events are more frequently reported in clinical practice, including alendronate tablets 70 mg once a week<sup>38</sup>. Table I resumes compliance rates observed in large studies examining administrative databases of two entire Italian regions<sup>38,39</sup>. In such studies, patients on alendronate tablets 70 mg once a week were more frequently switched to other antifracture treatments than those assuming strontium ranelate<sup>38</sup>, thus, supporting the rationale for introducing new formulations of alendronate, which are less willing to cause gastro-oesophageal adverse events. A liquid formulation of alendronate (at the dosage of 70 mg once a week) has been already introduced into the market, with the aim to reduce the prevalence of patients reporting gastro-oesophageal adverse events in real clinical practice. However, the need for dilution with significant volumes of water might limit its widespread use in the general population. Because alendronate is the most used drug in pharmacological treatment of osteoporotic patients all over the world due to its known cost-effectiveness<sup>75-77</sup>, the development of the

newest effervescent formulations of weekly alendronate 70 mg should be favorably considered in the frame of improving antifracture efficacy of current antifracture therapies, in order to reach more acceptable 1-year compliance rates in clinical practice thanks to less frequent dosing and reduced side effects (particularly those affecting the gastro-oesophageal tract). As indicated by our previous studies<sup>39,45,75,76</sup> and suggested by other authors<sup>38,77</sup>, regional administrative databases could be particularly useful in monitoring the compliance to antifracture drugs, but also to other treatments in different therapeutical areas. Moreover, in the view of the World Health Organization (which foster a strong cooperation between patients, physicians and healthcare administrations), these pharmaceutical databases – combined with other demographic, hospital, and primary care datasets available at regional level – may represent the ideal instrument to address the challenge of “real time monitoring” of appropriateness and effectiveness of therapeutic paths available at local level for the treatment of many chronic diseases, with the objective of improving people health and healthcare systems sustainability.

## Conclusions

Alendronate is the most frequently used antifracture therapy among those currently available. The increasing use of the 70 mg weekly dosages and newest formulations of this drug – such as the effervescent drinkable solution – is expected to increase adherence to the antifracture therapy in osteoporotic patients, thus, resulting in better clinical outcomes and possible savings due to lower fractures prevalence and hospitalization rates.

**Table I.** 1-year compliance rate to different dosages of the most used antifracture drugs (percentage of patients still on treatment at 12 months).

Reference	Alendronate 70 mg OAW	Alendronate 70 mg+Vit. D	Residronate 35 mg OAW	Ibandronate 150 mg monthly	Strontium Ranelate daily
Iolascon et al 2013 <sup>38*</sup>	12.6%	15.7%	15.8%	21.6%	5.0%
Piscitelli et al 2011 <sup>39*</sup>	54.3%	50.6%	56.0%	53.2%	24.3%

\*Data from administrative database on the general population of a whole region.

### Conflict of Interest

In the past 5 years, P.P. has received funding for consulting/speaking by Sanofi-Aventis, Novartis, Servier, Ely Lilly, Abiogen and Amgen. In the past 5 years, M.A. has received funding for consulting/speaking by Sanofi-Aventis, Fidia, Ibsa, Servier, Ely Lilly, Abiogen, MSD, Pfizer, Roche, and BMS. The other Authors have not Conflict of Interest.

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