Inadequate responders to osteoporosis treatment: proposal for an operational definition

A. Díez-Pérez · J. González-Macías

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Abstract
Summary The concept of inadequate response to osteoporosis treatment is not clear. In the literature several criteria have been used. We propose an operational definition of an inadequate responder based on the changes observed in bone mineral density and incident fractures while on therapy.

Introduction Fractures may occur in compliant patients even while on active treatment. These cases have been defined as inadequate responders (IR).

Methods We reviewed the basis for this concept and propose an operational definition for IR.

Results Good compliance and adequate calcium and vitamin D supplementation are the first requirement. The second requirement is a treatment period of at least 1 year, since before that time treatment may not have been fully effective. Fractures are the gold standard for measuring efficacy and changes in bone density and turnover markers may be surrogates. We propose classifying patient response as: Inadequate—incident fracture and a decrease in BMD greater than a significant change (Trend Assessment Margin or TAM); Possibly inadequate—incident fracture or a decrease in BMD greater than a significant change (TAM); and Appropriate—no fracture and no decrease in BMD greater than a significant change (TAM). Additional criteria (biochemical markers, bone quality parameters) may be taken into account.

Conclusion A wide consensus on the IR concept is required given its clinical, regulatory, and reimbursement implications.

Keywords BMD · Fracture · Osteoporosis · Treatment · Treatment response

Introduction
Lack of compliance is a major issue in all treatments for chronic diseases, and osteoporosis is no exception. Measured either as medication possession ratios or as persistence, osteoporosis regimens are prone to this phenomenon to such a degree that the percentage of patients under treatment after 1 year varies between 26 and 70% for different studies and dosage regimens [1]. Lack of compliance is linked to an increased risk of fracture when compared with fully or almost fully adherent patients [2, 3]. However, even under the strict conditions of a clinical trial and in patients regarded as compliant (i.e., those correctly taking at least 80% of the doses) fractures may still occur even though they are receiving an active treatment [4–9]. Why, in these patients who are correctly receiving a theoretically protective drug, do these fractures still occur? In other areas of medicine, these cases would be classified as treatment failure. However, in osteoporosis there is a certain reluctance to employ this term, and inadequate response (IR), the more commonly used term, is preferred...
For the sake of convention, the term “inadequate responders” will be used herein to define patients who do not respond as expected. This work aims to provide a basis for this concept, explain what has been reported to date, and, finally, attempt to propose an operational definition of inadequate response to the treatment of osteoporosis. We believe a definition is required, since it determines the critical stage at which the clinician has to consider whether to change a treatment deemed inadequate; furthermore, the definition has reimbursement implications, since in some countries certain drugs are considered second-line and are only covered when a patient’s treatment on what is considered a first-line drug fails to produce the desired results.

Some theoretical premises

1. Satisfactory treatment compliance should be presupposed in any IR analysis. Consequently, treatment compliance must be assessed in cases where the possibility of an IR is considered. Given that an IR implies a possible change in treatment, a drug cannot be judged ineffective if it has not been taken correctly. Tolerance issues and side effects play an important role in this respect, particularly when a clinician has to consider a potential lack of efficacy and, consequently, a change in treatment. Although an accurate assessment of compliance has limitations, self-declared compliance has proved to be reasonably reliable compared with more sophisticated techniques [11–14]. Furthermore, it has the advantage of being more convenient and, at times, has performed better as a predictor of the desired outcome than pill counting or electronic monitoring devices [15].

2. Every treatment needs a certain length of time for the drug to produce the desired effect. Since several post-hoc analyses of some, but not all, pivotal trials observed a reduction in fracture risk after only 6–12 months of treatment [16, 17], 1 year would be a conservative period. On the other hand, increases in bone density explain only a limited part of the antifracture efficacy of the drugs [18]. Therefore, treatment-induced changes in microarchitecture and other elements encompassed in the concept of bone quality (mineralization degree, collagen composition, mineral crystallinity, etc.) have been considered necessary to reduce the increased propensity to fracture. All these changes occur through modifications in the bone remodeling cycle. The duration of one cycle of the bone remodeling unit varies between 3 and 6 months [19]. A certain period of time, therefore, is needed before a therapy can be deemed to have failed.

3. The full activity of a drug can be supported only by the primary analysis of pivotal trials. Therefore, the assessment of IR beyond the study period in the trials is weaker. In practical terms, reasonably reliable information is available on the beneficial effects of most of the standard drugs currently used in osteoporosis for a period of up to 5 years [4–8]. Indeed, some molecules (i.e., anabolics) have been used for much shorter periods [9] and this must be taken into account in their evaluation.

4. Fractures are the main pathologic event in osteoporosis and the cause of patient morbidity and mortality. Moreover, fracture is one of the most potent individual predictors of risk of subsequent fractures [20]. As a result, lack of fractures constitutes the gold standard of efficacy in osteoporosis treatment trials. However, no treatment completely prevents fractures. Therefore, a treatment can be efficacious even in an individual patient suffering a fracture. Consequently, the occurrence of a fracture alone is not a sufficient criterion for a response to treatment to be declared inadequate.

5. Bone mineral density (BMD) changes are commonly considered as a good surrogate for osteoporosis assessment. However, this method is subject to debate for the evaluation of response to bone drugs [16]. Although the magnitude of change varies greatly among drugs, it does not necessarily imply different efficacies. Furthermore, since a decrease in BMD probably has to occur before the possibility of an IR can be considered, the question is what magnitude of change is considered significant given that the natural tendency of the skeleton is to lose bone mass at the age where osteoporosis occurs. The usual recommended parameter is the so-called “least significant change” (LSC) with a 95% confidence interval [21]. However, this parameter has applicability problems in clinical practice, since it requires measurement of the precision error for a given laboratory and region and, even in the best-case scenario, its value is in the order of 3% (LSC=2.8 × precision error). Two less stringent change criteria have been proposed for the convenience of the average practice. One is the Trend Assessment Margin (TAM=1.8 × precision error), which yields a 90% confidence interval for single-sided tests [22]. Another pragmatic solution may be the Smallest Detectable Difference (SDD) [23], which relies on the absolute change. The former has been established at 2% of change and the SDD as a BMD change of at least ±0.05 g/cm² at L1–L4 and ±0.04 g/cm² at the total hip to be considered significant. However, decreases in BMD while on treatment can be observed, although the patients still benefit from a reduction in fracture risk. Exploratory analyses of the pivotal trials of different
8. Propensity to suffering falls is one of the major determinants of osteoporotic fractures and has been extensively demonstrated as an independent predictor of the event [20, 31]. However, the drugs used to treat osteoporosis, with the significant exception of vitamin D [32], do not influence this element. On the contrary, a great propensity to fall can predispose to fracture such that it counteracts the benefit of any treatment, even with a good biological response to a drug. Although falling can introduce an element of uncertainty into the assessment of an IR, it probably obligates the clinician to reassess the entire strategy, placing more emphasis on the prevention of falls before considering that the treatment is not working, since the final goal, fracture avoidance, is jeopardized.

9. Osteoporosis is a common term covering a wide range of conditions and pathophysiologic situations that result in increased bone fragility [20]. Therefore an individual drug cannot be expected to be fully effective in every single patient to whom it is administered. This is probably one of the main reasons for the therapeutic ceiling of all treatments, even in the ideal conditions of pivotal trials. The challenge is to discriminate retrospectively and, even better, predict in advance which patients are most likely to respond inadequately to a particular drug. No pharmaceutical company has explored this issue in depth despite having extensive information on patients from controlled trials who have sustained a fracture while on treatment. We have to accept, however, that the lack of agreement on the definition of IR does not provide the conceptual basis for such an analysis. Moreover, there is no evidence that a patient who responds inadequately to one drug will respond better to a different one. Although there is a need for such data, a prerequisite is again to define IR. Meanwhile, what occurs in real life is that the clinician decides very intuitively who/what is an IR and modifies the treatment accordingly. A consensus on what is an IR and subsequent treatment trials in these patients would offer more homogeneity and rigor to current practice.

In summary, in a patient with good treatment compliance and adequate calcium and vitamin D supplementation, any event suggesting an IR should be observed after the period required for the drug to exert its therapeutic effect. Even in such circumstances, a subgroup of patients should be assumed to have an IR.

Definitions in the literature

Several attempts made in the literature to define IR [10, 33–39] were based on bone mineral density, fractures, or both. Del Puente et al. [33], in a study of postmenopausal women with primary osteoporosis treated with alendronate, defined nonresponders as having an increase in BMD of less than 2% vs baseline. Twenty-eight percent of the treated patients fell into this category. Heckman et al. [34], analyzing a series of men and women treated with cyclic etidronate or daily alendronate, considered nonresponders as those showing a negative change in BMD vs baseline or suffering...
an incident fracture after 1 year of treatment. The incidence in nonresponders was 35%. Sawka et al. [35] in the CANDOO study observed 18% nonresponders to the treatment, defined as an incident clinical fracture either after 2 years of starting treatment or as a loss of 3% or more vs baseline between 13 and 24 months on therapy. Lewiecki [36] defined nonresponders as those who showed a decrease in BMD greater than the least significant change with a 95% confidence interval. The National Institute for Clinical Excellence in the UK [37] proposed that a nonsatisfactory response might be a case of a new fragility fracture, despite fully adherent treatment for a 1-year period and a decrease in BMD to a value below baseline.

More recently, Jakob et al. [38], in the OSSO study, retrospectively defined nonresponders as patients with a fragility fracture despite treatment for at least 12 months before the event. Sixteen percent of the eligible cases belonged to this group. Adami et al. [10], in the ICARO study, defined nonresponders as patients receiving antiresorptives for at least 6 months who suffered a new fragility fracture. This was the case in 25% of patients, which included noncompliant patients, the most frequent reason for nonresponse. In the EUROFORS trial, Obermayer-Pietsch [39] defined inadequate response as a new fragility fracture after 12 months of treatment, a T-score below −3 or a decrease in BMD of more than 3.5% at any location after 24 months of treatment. These different proposals are summarized in Table 1. It appears that, in the more recent definitions, fractures have gained ground in comparison with BMD, probably for the reasons already discussed.

### Basis for a definition

In accordance with what has been stated previously, therapeutic response can be evaluated in patients with idiopathic osteoporosis and good treatment adherence, and who are receiving calcium and vitamin D supplements. The evaluation time should be at least 12 months on therapy, as this time limit is considered to be a conservative estimate of efficacy.

Fracture is the predominant outcome. BMD, however, is also widely accepted as a response marker and some degree of positive response should be expected after treatment. Nevertheless, we know that, even in treated patients with decreases in BMD, the risk of fracture is lower than in placebo-treated cases with a similar degree of BMD change [40]. In any event, within a group of treated patients, the greater the response in terms of BMD, the lower the risk of fracture [41].

Any definition, to be clinically useful, has to be convenient and based on data compiled from everyday practice. This necessarily implies simplification and, therefore, some of the elements discussed above cannot be used in a definition for the sake of their clinical applicability.

Bearing all these considerations in mind, we propose the following definitions:

1. Inadequate response—incident fracture and a decrease in BMD greater than 2%, defined as a significant change according to the concept of the Trend Assessment Margin (TAM).
2. Possible inadequate response—incident fracture or a decrease in BMD greater than 2% (TAM).
3. Adequate response—no fracture and no decrease in BMD greater than 2% (TAM).

All these outcomes are based on patients with good compliance who have been under treatment for a minimum of 1 year.

### Limitations of the proposed definition

Not all antiresorptives, even within the same group, induce the same degree of BMD change [42]. On the other hand, anabolic agents and strontium ranelate induce far greater effects on BMD than antiresorptives [8, 9]. Specifically, strontium induces artifactual increases in BMD and this should be taken into account when a patient is receiving this drug. However, since the changes induced by PTH and strontium are greater, and given the convenience of a common rule, the proposed threshold can be accepted as a conventional compromise for all treatments. In this respect, the dominant role of an incident fracture should always be borne in mind in the definition of poor response.

The definition of what constitutes a fracture is still under debate when vertebrae are considered [43]. However, as the proposed definition is intended to be clinically useful, it obviously has to be taken into account whenever the clinician diagnoses a fracture.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>BMD decline</th>
<th>Incident fracture</th>
<th>Minimum treatment (months)</th>
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<tr>
<td>[33]</td>
<td>2000</td>
<td>Yes</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>[34]</td>
<td>2002</td>
<td>Yes</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>[35]</td>
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<td>Yes</td>
<td>Yes</td>
<td>&lt;24</td>
</tr>
<tr>
<td>[36]</td>
<td>2003</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>[37]</td>
<td>2004</td>
<td>Yes</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>[38]</td>
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<td>–</td>
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<tr>
<td>[39]</td>
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</table>
Some considerations for the future

This proposed definition needs to be debated and gain consensus in order to be operational. Pertinent bodies might include this debate as a priority both for the practicing clinician and the field of osteoporosis in general.

A good opportunity to further validate and analyze this theoretical proposal may derive from an analysis of the treatment arm in the main trials on the various drugs used to treat osteoporosis. A sensitivity and specificity analysis of these data might offer the ultimate support for this proposed definition. In the long term, a good definition of the most suitable drug for a given patient would represent the best consolidation of the various treatment options and lay the groundwork for the development of productive cooperation among academia, pharmaceutical companies, and regulatory authorities.

The prediction of an appropriate response in the individual patient may come in the future from the still largely unexplored field of pharmacogenomics. Some data are already available [44–48], but there is still a long way to go before this approach is ready for clinical use. Nonetheless, some substantial progress can be made if a consensus can be reached on the definition of the concepts of adequate and inadequate responses.

Finally, the development of more precise tools to determine the risk of fracture and its reduction under treatment may be of great help in deciding when a treatment is eliciting an adequate response. Structure analysis [49, 50], finite element analysis [51], and virtual bone biopsy [52], among other techniques for direct assessment of bone strength, offer a future perspective for deciding when to switch treatment because the patient presents an IR.

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Conflicts of interest None.

References