Original Article

Study Subjects and Ordinary Patients

R. Dowd, R. R. Recker and R. P. Heaney
Creighton University, Osteoporosis Research Center, Omaha, Nebraska, USA

Abstract. Clinical trials of treatment agents impose strict and often necessary inclusion and exclusion criteria, while patients presenting to physicians for treatment frequently exhibit complicating features that would have excluded them from entry into study. To quantify the degree of discordance between ordinary patients and study subjects, a retrospective chart review was carried out of all new patients with osteoporosis seen in an academic medical center within a consecutive 40-month period, meeting clinical treatment criteria. Each patient chart was reviewed for the inclusion and exclusion criteria of four large, multicenter study protocols. There were 120 consecutive female patients seeking health care, with bone density T-scores below −2.0 and/or with one or more low-trauma fractures. The four trials would have accepted 4, 5, 25 and 8 of our 120 patients. The trial with the most liberal inclusion criteria would have taken only 21% of the total. Principal reasons for ineligibility were comorbidity, prior treatment with bone-active agents, and current therapy with glucocorticoids, anticoagulants and anticonvulsants. Some of these exclusions inevitably reflect the patient mix of a referral center; nevertheless, comorbidity and its therapy are common in the age range in which osteoporosis is prevalent and would, therefore, be expected to be present in patients in general medical practice as well. Thus a large fraction, perhaps the majority, of patients with diagnoses of osteoporosis who are candidates for treatment by their physicians, are not eligible for entry into typical treatment trials. The results of such trials may, therefore, have uncertain applicability to types of patients excluded, both for safety and for efficacy.

Keywords: Comorbidity; Controlled trial; Osteoporosis; Randomized; Selection bias

Introduction

The clinical trial – randomized, double-masked and placebo-controlled – is recognized as the standard means of establishing efficacy of treatment agents [1]. The reason is that it is the only secure method of attributing causality in observed associations between treatments and beneficial outcomes. In order to eliminate factors that might confound or obscure such treatment effects, clinical trials commonly employ extensive sets of inclusion and exclusion criteria. Experienced clinicians have long recognized that many of the patients they see in routine clinical practice, and for whom they must make therapeutic decisions, would not be eligible for inclusion in the study groups of such trials. This exclusion inevitably raises questions about the applicability of trial results to ordinary patients.

We set out to assess the magnitude of the mismatch between study subjects and ordinary patients by determining both the extent to which patients with osteoporosis presenting to us for medical care would have been eligible for any one of four clinical trials currently being conducted in our unit, and then assessing the principal reasons responsible for the exclusion of those who would not have been eligible.

Materials and Methods

Patient Referral Sources

For this study, we did a chart review of all new patients seen in our Osteoporosis Clinic from March 1995
Table 1. Principal inclusion criteria for four multicenter clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55–75</td>
<td>55–80</td>
<td>50–80</td>
<td>50–80</td>
</tr>
<tr>
<td>BMD (T-score)</td>
<td>–2 to –5, any vertebra</td>
<td>–2 to –5, any vertebra</td>
<td>≤–2.5, total spine or femoral neck</td>
<td>≤–2.5, total spine or femoral neck</td>
</tr>
<tr>
<td>Fractures</td>
<td>1–4, vertebral; &lt;3 lumbar</td>
<td>1–4, vertebral; &lt;3 lumbar</td>
<td>0</td>
<td>1 vertebral</td>
</tr>
</tbody>
</table>

through June 1998. Two hundred and thirty-six charts were reviewed. One hundred and twenty of these patients were women who met the criteria for a diagnosis of osteoporosis (see below) and who had all the necessary measurements to enable us to apply the criteria employed in determining eligibility for entry into clinical trials, i.e., hip and spine densitometry scans and lateral spine radiographs. Many of our patients are self-referral women with a family history of osteoporosis, desirous of preventing the pain and disability they have seen in close relatives. Additionally, there were a few physician referrals, principally from gynecologists or from primary care physicians who have patients either unable to tolerate or apparently not responding to traditional treatments. In addition, we see certain unusual cases: young individuals with low-trauma fractures, those with chronic illnesses, transplant patients, and men with osteoporosis.

Patient Treatment Eligibility

For the purposes of this analysis, new patients presenting to our Osteoporosis Clinic were considered eligible for one of the approved osteoporosis treatment regimens if they had bone mineral density (BMD) T-score values at the hip or spine below –2.0 and/or one or more low-trauma fractures, and no other medical condition responsible for their bone status. Only female patients who had valid measurements for all the bone and clinical variables required to make decisions concerning study inclusion or exclusion were included in this analysis. The records of 20 men meeting these same criteria and seen during the same time interval were not included.

Clinical Trials

Of the several randomized, double-masked, placebo-controlled drug trials currently being conducted in our unit, we selected four with differing inclusion and exclusion criteria. They are typical of the multicenter trials in which this unit has participated over the past 20 years. For this analysis, the four trials are labeled A, B, C and D, and their principal inclusion criteria are listed in Table 1. Additionally, the protocols excluded individuals with a variety of other diagnoses, as well as those currently receiving bone-active agents or estrogen, as well as anticoagulants, anticonvulsants, corticosteroids and immunosuppressants. Typical disease exclusions included prior cancer at any site other than skin, diabetes mellitus, rheumatoid arthritis, convulsive disorders and gastrointestinal disturbances (ranging from reflux esophagitis to regional ileitis). Treated hypothyroidism was also an exclusion criterion if there had been a change in thyroid replacement therapy in the previous 6 months.

Most protocols excluded patients with histories of estrogen use within 6–12 months, and use at any time of bisphosphonates, fluoride or calcitonin. Patients disqualified because they were receiving estrogen or anti-osteoporosis therapies, who were otherwise eligible for entry into study, were nevertheless counted as eligible in this analysis, since they were otherwise typical of the patients entering these four trials. Thus our analysis to some extent overstates the actual inculdability of our patients in the four multicenter trials for which we did the analysis.

Results

The results of our analysis are given in Table 2, which shows that, of the 120 new patients who would have been eligible for preventive or therapeutic treatment of their osteoporosis, only between 3.3% and 20.8% would have been eligible for entry into the various studies. Table 3 shows the principal reasons, the most common of which were comorbidity and treatment with various medications. In most instances more than one exclusion factor applied. In the cases in Table 3 in which estrogen or osteoporosis therapeutic agents were listed as an exclusion factor, the patients would all have been excluded because of comorbidity, regardless of whatever therapy they may have been receiving.

Table 2. Eligibility of patients for medical treatment of for study (n = 120)

<table>
<thead>
<tr>
<th>Medical treatment</th>
<th>Study entry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>100%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>