In Response to Body Letter to the Editor Regarding “Safety of Intravenous and Oral Bisphosphonates and Compliance with Dosing Regimens”

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The burden of suffering associated with metastatic bone disease is so high that we want to be sure that information on effective therapies is reported in the most complete and balanced way. According to Dr. Body, the gastrointestinal (GI) safety profile of oral ibandronate (50 mg) based on the pooled analysis of two randomized placebo-controlled trials [1] was misrepresented. Of course this was not our purpose; however, if the authors chose not to report the overall incidence of treatment-related GI adverse events, which is an important measure of tolerability for an oral bisphosphonate, one is left with assumptions. Certainly, the reported incidence of treatment-related abdominal pain, nausea, and esophagitis was two to three times higher in the ibandronate group compared with placebo. Thus, based on the reported incidence of these common upper GI adverse events, the general statement that “patients treated with oral ibandronate were twice as likely to experience treatment-related GI adverse events as those receiving placebo” is consistent with the reported data. This statement is also consistent with the reported incidence of GI adverse events in the dose-finding study [2]. Moreover, the reporting of safety data from patients with osteoporosis who received lower doses of oral ibandronate is certainly appropriate in this context. There is no reason to think that these patients would be different from patients with advanced cancer in terms of their risk of developing treatment-related GI adverse events.

With regard to reasons for discontinuation, the statement that “10% of patients receiving ibandronate withdrew from the study because of adverse events” is accurate. There was no intention to imply that these were strictly GI adverse events, although it is certainly possible that a reader might misinterpret this statement.

Dr. Body expressed concern that the potential compliance issues with oral ibandronate were overstated and that the oral dosing regimen was incorrectly described. With respect to the statement on page 32 about the size of the tablets, it is clearly stated that “this is particularly problematic for clodronate.” No specific statement about the size of the ibandronate tablets was made. Second, the requirement, per product labeling, for patients to fast and remain upright for at least 30 minutes following ingestion of oral bisphosphonates is correctly stated on page 32. The reference to a ≥1 hour fast to maintain efficacy was made on page 34 based on a study showing reduced efficacy in patients with osteoporosis who ate within 30 minutes of taking oral ibandronate versus 1 hour [3]. This statement appears to have been taken out of context. It is, however, clear that outside of clinical trials, compliance with long-term oral treatments is an issue and can be particularly poor in less educated and less motivated patients [4].

Finally, we completely agree with Dr. Body’s final sentence that “it is vital that we assess the available literature thoroughly and use good clinical judgment to manage our patients in their best interest.” It is precisely on this premise that we have taken into consideration the thousands of patients in clinical trials and the tens of thousands treated in clinical practice to conclude that intravenous bisphosphonates are the standard of care for the management of metastatic bone disease.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
Dr. Conte has served as a consultant for Novartis.
REFERENCES


