Osteoporos Int (2017) 28:1757–1758
DOI 10.1007/s00198-017-3923-5

LETTER

Significant improvement of bone mineral density and bone turnover markers by denosumab therapy in bisphosphonate-unresponsive patients: response to comments

M. Kamimura[1] · Y. Nakamura[2,3] · S. Ikegami[2] · S. Uchiyama[2] · H. Kato[2] · A. Taguchi[4]

Received: 9 January 2017 / Accepted: 10 January 2017 / Published online: 27 January 2017

Dear Editor,

We thank Drs. Fu and Sheng [1] for their interest in our article [2]. Many studies [3–5] have shown the long-term results of bisphosphonate (BP) therapy. However, such studies were based primarily on the averaged results and did not address BP-unresponsive patients.

The ultimate goal of osteoporotic treatment is the prevention of a fracture [5, 6]. As it is impossible to demonstrate fracture prevention on a case by case basis, the evaluation of osteoporotic treatment can be estimated by surrogate markers. Bone mineral density (BMD) is the most useful marker for long-term evaluation since correlations with fracture risk have been established [5, 6]. In our cases, bone turnover markers clearly decreased by BP therapy. However, there have been several cases where initially increased BMD values decreased over time [2 and unpublished data].

Fu et al. stated that we unreasonably selected patients who were treated with BPs for 2 years and who were deemed to show a poor response to BPs. This claim is erroneous. Most patients had undergone BP therapy for longer than 3 years, and the average BP treatment period was 5 years. We selected non-responders among poor-responders based on five measurements of BMD values over 2 years since the assessment of BMD twice might have caused minus bias. We believe that minus bias may be minimized. Although, it is unknown that five measurements over 2 years are ideal.

We selected non-responders at the lumbar spine and hip and separated them from responders [2]. BMD values greatly increased in those non-responders. However, it remains unknown whether the BMD-increasing effects in non-responders are superior to those in BP responders.

As Fu et al. suggested, atypical femoral fractures (AFF) may increase. However, the frequency of AFF is quite rare, even with the use of BPs or denosumab [5, 7]. Also, there is no definitive evidence that osteonecrosis of the jaws (ONJ) is brought about by antiresorptive drugs [, 8]. We have published that patients with self-reported kyphosis had a significantly higher risk of problematic delayed wound healing after tooth extraction as compared with those without. Therefore, patients with vertebral fracture associated with osteoporosis may be at a greater risk for ONJ [9]. We maintain that the benefits of denosumab treatment are greater than the risks of ONJ or AFF even after BP therapy.

Adler et al. have recently described the ASBMR task force guidelines for BP therapy duration from a risk-benefit perspective [5]. Briefly, patients with major osteoporotic fractures or at high risk of fracture should continue BP therapy orally for up to 10 years [5]. Elsewhere, Taguchi et al. have reported that the frequency of ONJ and fracture increases after the cessation of BPs [10].

In conclusion, although this reply letter to our manuscript provides good suggestions on future studies in denosumab therapy, we believe that our currently published findings remain of value in terms of the benefits of denosumab for BP-unresponsive patients.

✉ Y. Nakamura
yxn14@aol.jp

[1] Center of Osteoporosis and Spinal Disorders, Kamimura Orthopedic Clinic, Kotobuki-Toyooka 595-17, Matsumoto 399-0021, Japan

[2] Department of Orthopaedic Surgery, Shinshu University School of Medicine, Asahi 3-1-1, Matsumoto 390-8621, Japan

[3] Department of Orthopedic Surgery, Showa-Inan General Hospital, Akaho 3230, Komagane 399-4117, Japan

[4] Department of Oral and Maxillofacial Radiology, Matsumoto Dental University, 1780 Gobara Hirooka, Shiojiri 399-0781, Japan

Compliance with ethical standards

Conflicts of interest None.

References

1. Fu S, Sheng Z (2017) Comments on Kamimura et al.: significant improvement of bone mineral density and bone turnover markers by denosumab therapy in bisphosphonate-unresponsive patients. Osteoporos Int. doi:10.1007/s00198-017-3923-5
2. Kamimura M, Nakamura Y, Ikegami S, Uchiyama S, Kato H, Taguchi A (2016) Significant improvement of bone mineral density and bone turnover markers by denosumab therapy in bisphosphonate-unresponsive patients. Osteoporos Int. doi:10.1007/s00198-016-3764-7
3. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, Compston JE, Drake MT, Edwards BJ, Favus MJ, Greenspan SL, McKinney R Jr, Pignolo RJ, Sellmeyer DE (2016) Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 31:1910
4. Adler RA (2016) Bisphosphonates and atypical femoral fractures. Curr Opin Endocrinol Diabetes Obes 23:430–434
5. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA (2004) Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350: 1189–1199
6. Ishtiaq S, Fogelman I, Hampson G (2015) Treatment of postmenopausal osteoporosis: beyond bisphosphonates. J Endocrinol Investig 38:13–29
7. Cummings SR, Cosman F, Lewiecki EM, Schousboe JT, Bauer D, Black D, Brown T, Cheung AM, Cody K, Cooper C, Diez-Perez A, Eastell R, Hadji P, Hosoi T, De Beur SJ, Kagan R, Kiel DP, Reid I, Solomon DH, Randall S (2016) Goal-directed treatment for osteoporosis: a progress report from the ASBMR-NOF working group on goal-directed treatment for osteoporosis. J Bone Miner Res. 19. [Epub ahead of print] Review
8. Khan AA, Morrison A, Hanley DA, Felsenberg D, LK MC, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sándor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J (2015) Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 30:3–23
9. Khan AA, Morrison A, Kendler DL, Rizzoli R, Hanley DA, Felsenberg D, McCauley LK, Oryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Dabagh RA, Davison KS, Sándor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J; (2016) Case-based review of osteonecrosis of the Jaw (ONJ) and application of the international recommendations for management from the International Task Force on ONJ. J Clin Densitom. 2016; S1094–6950 30196–2
10. Taguchi A, Kamimura M, Nakamura Y, Sugino N, Ichinose A, Maezumi H, Fukuzawa T, Ashizawa R, Takahara K, Gushiken S, Mukaiyama K, Ikegami S, Uchiyama S, Kato H (2016) Delayed wound healing after tooth extraction and self-reported kyphosis in Japanese men and women. Sci Rep. 6:36309
11. Taguchi A, Shiraki M, Sugimoto T, Ohta H, Soen S (2016) Japan Osteoporosis Society. Lack of cooperation between physicians and dentists during osteoporosis treatment may increase fractures and osteonecrosis of the jaw. Curr Med Res Opin 32:1261–1268