(Original Articles)

Functional Outcome in Patient with Osteoporosis Undergoing Teriparatide Treatment: A Prospective Observational Study

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Background : Osteoporosis increases in the risk of fragility fracture which decreases in the quality of life with the limitation of daily living of patients. Once-daily administration of teriparatide (parathyroid hormone) stimulates new bone formation on trabecular and cortical bone surfaces. The anabolic effects of teriparatide are manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. Recently there is no study of functional outcome after teriparatide administration for 24 months. We conduct the study about the functional outcome, the adherence and the cardiovascular adverse event after teriparatide administration for 24 months.

Objective : To study the functional outcome, adherence and cardiovascular adverse event in postmenopausal osteoporosis patients whom undergoing teriparatide treatment.

Material and methods : In this prospective cohort study, we enrolled postmenopausal women with at least hip fracture or two vertebral fracture and bone mineral density T score of less than or equal to -2.50. SF36 scores, serum NT-proBNP level were measured before treatment, 6 months, 12 months, 18 months, and 24 months after treatment. Serum NT-proBNP is a useful cardiovascular biomarker for the diagnosis of heart failure. Increased levels of NT-proBNP in patient treated with teriparatide are associated with cardiovascular adverse event. Adherence is measured by medical procession ratio.

Results : Functional outcome is improved significantly at 12 months (P=0.008). Patients had high adherence for 87 % and the mean of MPR is 0.94. There is no effect of teriparatide on serum NT-proBNP level (P=0.144).

Conclusion : Functional outcome is improved from 12 months after the initiation of teriparatide treatment with high adherence. Teriparatide did not change the concentration of NT-proBNP in plasma after completion of treatment, suggesting that teriparatide does not affect heart function.

Keyword : Teriparatide, Serum NT-proBNP

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ผลการรักษาผู้ป่วยโรคกระดูกพรุนด้วยยา Teriparatide: การศึกษาแบบวางแผนล่วงหน้า

วิร บุญศิริคำชัย พบ., ธนัตต์ วัลลีนุกูล พบ.
กองออร์โธปิดิกส์ รพ.ภูมิพลอดุลยเดช พอ.

ความเป็นมา : ภาวะกระดูกพรุนเป็นภาวะกระดูกหัก ซึ่งมีผลต่อคุณภาพชีวิตและจำกัดการดำเนินชีวิตประจำวัน การรักษาด้วยยา Teriparatide (พาราธัยรอยด์ฮอร์โมน)วันละครั้ง สามรถกระตุ้นการสร้างกระดูกแบบ trabecular และ cortical surface และยังมีผลต่อการสร้างมวลกระดูก เพิ่มผลเลือดในการสร้างมวลกระดูก เพิ่มความแข็งแรงของกระดูก ปัจจุบันยังไม่มี ผลการศึกษาที่แน่ชัดจากการให้ยา Teriparatide ต่อเนื่อง 24 เดือน การศึกษานี้จึงเป็นการศึกษาผลของการรักษาด้วยยา Teriparatide ต่อเนื่องเป็นเวลา 24 เดือน

วัตถุประสงค์ : เพื่อศึกษาผลของการรักษาด้วยยา Teriparatide ในผู้ป่วยหญิงหมดประจำเดือนที่เป็นโรคกระดูกพรุน และความสามารถในการติดตามการรักษา และผลต่อระบบหัวใจและหลอดเลือด

วัสดุและวิธีการ : การศึกษาแบบสังเกตไปข้างหน้า ในสตรีหมดประจำเดือนที่ได้รับการวินิฉัยว่าเป็นโรคกระดูกพรุน ที่มีประวัติ กระดูกเชิงกรานหัก หรือกระดูกสันหลังหัก 2 ครั้ง และค่ามวลกระดูก T-score น้อยกว่าหรือเท่ากับ -2.5 วัดผลโดยใช้ SF36 score, ระดับ NT-proBNP ซึ่งเป็นตัวชี้วัดที่ดีในการวินิจฉัยโรคทางระบบหัวใจและหลอดเลือด ที่เวลา 6 เดือน 12 เดือน 18 เดือน และ 24 เดือน และติดตามความต่อเนื่องของการรักษาด้วย medical procession ratio (MPR)

ผลการศึกษา : ผลการรักษา ผู้ป่วยมีอาการดีขึ้นอย่างมีนัยสำคัญที่ 12 เดือน ($p = 0.008$) ผู้ป่วยติดตามการรักษาได้สูง 87 % โดยมีค่า MPR 0.94 ไม่พบผลข้างเคียงของยา Teriparatide ต่อการเปลี่ยนแปลงของค่า NT-proBNP ในพลาสมาเมื่อจบการ รักษา แสดงว่ายาไม่มีผลต่อระบบหัวใจและหลอดเลือด

สรุป : ผลการรักษาด้วยยา Teriparatide ต่อผู้ป่วยเห็นผลที่ระยะเวลา 12 เดือน โดยมีการติดตามการรักษาที่ดี ยาไม่มีผลต่อค่า NT-proBNP ในพลาสมาหลังสิ้นสุดการรักษา แสดงว่ายาไม่มีผลต่อการทำงานระบบหัวใจ

คำสำคัญ : Teriparatide, serum NT-proBNP

Background

Osteoporosis is a systemic disease, defined as low bone mass and microarchitecture deterioration. Osteoporosis is caused of fragility fracture, especially hip fracture and spinal fracture. It has impacted to lower the quality of life in terms of disability, morbidity and mortality. The incidence in Thailand showed that postmenopausal women over the age of 70 years old have osteoporosis for more than 50 %, but lower in male[1].

Osteoporosis has been defined as a bone mineral density (BMD) of more than 2.5 standard deviations below the average value[2].

Teriparatide, recombinant human PTH[1,3,4] is an anabolic agent indicated in the treatment of osteoporosis. By stimulating osteoblast activity, it causes increased bone formation with resultant improved bone strength and bone mass. These can prevent fracture, reduce back pain, morbidity and mortality[3-6].

The indication for teriparatide treatment according to 2011 Thai Osteoporosis Guideline is The age more than 65 years old with one of these additional;

1. BMD of hip or lumbar spine more than 2.5 S.D. below the average value with ≥ 2 levels of vertebral fracture.

2. BMD of hip or lumbar spine more than 3.5 S.D. below the average value with ≥ 1 level of vertebral fracture

3. Evidence of failed bisphosphonate treatment

a. ≥ 1 level of new vertebral fracture or the collapse of old vertebral fracture after at least 2 years of bisphosphonate treatment

b. BMD of hip decrease ≥ 3 % per year or BMD of lumbar spine decrease ≥ 5 % per year after at least 2 years of bisphosphonate treatment.

There is only limited data that teriparatide treatment for 2 years capable of improving patient functional outcome. Because of the administration of teriparatide is subcutaneous injection daily, it can caused of lower the patient's adherence?

The structure of teriparatide is the parathyroid hormone. The primary hyperparathyroidism (PHPT) is associated with increase occurrence of cardiovascular disease. The N-terminal fragment of the pro-peptide of Brain Natriuretic Peptide (NT-proBNP) has been shown to be elevated in PHPT patients, indicating that continuously high concentration of PTH affect the heart[7-13].

The aims of this paper are to study the functional outcome, the adherence and the cardiovascular adverse event after 2 years of teriparatide treatment.

Material and Methods

Study design and patients

This study is a prospective observational study. We included the postmenopausal osteoporosis women who diagnosed osteoporosis and had indication for teriparatide treatment according to 2011 Thai Osteoporosis Guideline from April 2016 to December 2018 in Bhumibol Adulyadej Hospital. Patients were followed for the 2 years of teriparatide treatment. We excluded from this study if they had any contraindications as describes in teriparatide label. All patients gave written informed consent prior the enrolment and were able to withdraw without consequence at any time. The study was approved by local ethics committees of Bhumibol Adulyadej Hospital.

Data collection

At base line visit, patient demographic characteristics were collected, included age, underlying disease, previous osteoporotic drugs used, history of previous fracture. The patients were attended follow-up every month for received the drugs. The data were collected at approximately 0, 6, 12, 18, 24 months of teriparatide treatment. The patients had not to take other osteoporosis medication during the treatment.

Functional outcome was measured by collecting the SF-36 quality of life score at 0, 6, 12, 18, 24 months of teriparatide treatment. Patients had to do the questionnaire by themselves. The score were presented in mean and standard deviations.

The adherence was measured by medication possession ratio (MPR). The total days of drug used, the first date and the last date that patients should be used were collected in each visit. The MPR was measure by the solution

$$MPR = \frac{\text{The total Rx day of supplied}}{\text{Last Rx date - First Rx date}}$$

MPR $\geq$ 0.8	=	high adherence
MPR 0.5 – 0.8	=	moderate adherence
MPR < 0.5	=	low adherence

The serum NT-proBNP levels were collected at 0, 6, 12, 18, 24 months of teriparatide treatment in each patients. The elevation of serum NT-proBNP level more than 357 pmol/l is represent the cardiovascular adverse event in any patient (LVEF $\leq$ 40 %)[8-10]

Statistical analysis

Data were analyzed for study cohort, which included all patients with a baseline visit and each follow-up visit. Descriptive statistics for categorical variables; number, table, percentage, means and standard deviations were used to describe the total study population.

SF-36 changes from baseline were analyzed using a repeated one-way ANOVA measurement. The SF-36 are presented as mean changes from baseline obtained. P-value change from baseline represent the influence of the corresponding factor. Pairwise comparisons between times in the square mean change from baseline to each follow-up visit. The level of significance is set to 5 %. All data were analyzed using SPSS software for window version 18.

Result

31 Postmenopausal osteoporosis women whom age $\geq$ 65 years had received teriparatide treatment. The mean age was 80.74 years old. 15 (48.83 %) patients aged 65-80 years old and 16 patient aged more than 80 years old (51.17 %). In the underlying diseases, 21 (61.74 %) patients had only hypertension, 2 (6.45 %) patients had hypertension and diabetes mellitus, 3 (9.67 %) patients had hypertension and ischemic heart disease, 3 (9.67 %) patients had Dementia and 1 (3.23 %) patient didn't have underlying disease 29. (93.55 %) patients had previous fracture before teriparatide treatment and never used any osteoporotic drugs, 21 (61.74 %) patients had hip fracture, 8 (25.81 %)

patients had spine fracture and 2 (6.45) patients didn't have any previous fracture. Those 2 patients who didn't have fracture had failed bisphosphonate treatment with Zoledronic acid. (Table 1)

Functional outcome

Functional outcome was measured by follow-up the changed of SF-36 quality of life questionnaire scores at 0, 6, 12, 18 and 24 months during teriparatide treatment. 1 of 31 patients had died in 1 year after started teriparatide treatment (from sepsis). In 30 patients who remained in this study, the mean of SF36-scores (from 100) were 67.87 before treatment (0 month), 71.59 at 6 months, 74.19 at 12 months, 76.85 at 18 months and 78.98 at 24 months after started treatment. (Table 2).

Table 1 Demographics Data

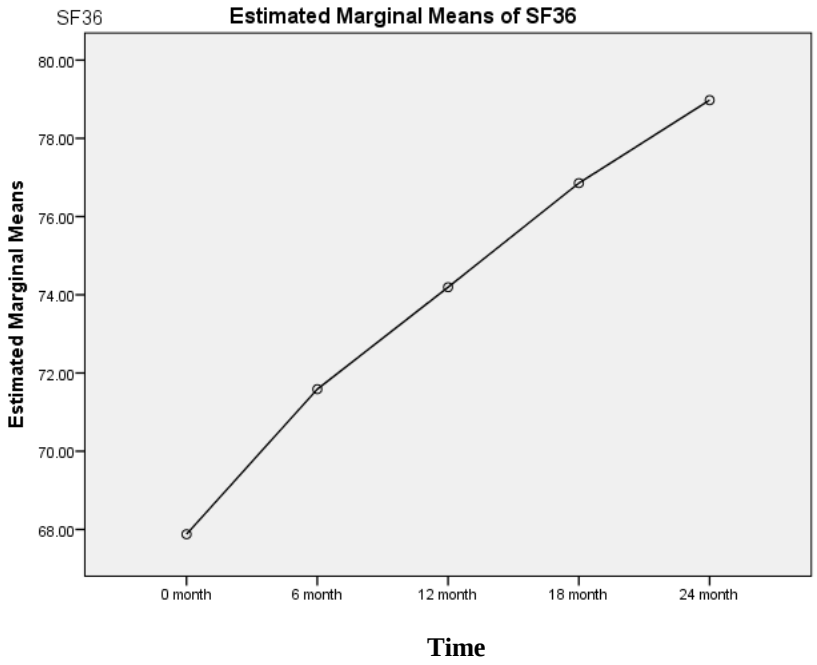
Patient	n	Percentage
Age - 65-80	15	48.83
- ≥80	16	51.61
Mean age	80.74 +/-6.65	
Underlying disease		
- HT	21	67.74
- HT+DM	2	6.45
- HT+IHD	3	9.67
- DM	1	3.23
- Dementia	3	9.67
- None	1	3.23
Previous fracture		
- Hip fracture	21	67.74
- Spine fracture	8	25.81
- None	2	6.45
Previous osteoporotic drugs used		
- Biphosphonate	2	6.45
- Denozumab		
- None	29	93.55

Table 2 Detail results of the SF-36 test during the teriparatide treatment (mean ± SD)

	0 month	6 month	12 month	18 month	24 month
Physical component scale % change	68.30 +/- 13.78	71.11 +/- 11.45	74.87 +/- 11.88	77.50 +/- 10.55	77.47 +/- 10.85
Mental component scale % change	66.67 +/- 14.67	72.21 +/- 12.03	73.43 +/- 11.15	76.05 +/- 11.33	80.45 +/- 9.50
Total % change	67.87 +/- 14.83	71.58 +/- 11.96	74.19 +/- 11.84	76.85 +/- 11.24	78.98 +/- 10.25

For SF-36 scores, a higher score represents a better quality of life (functional outcome)

Figure 1



SF-36 changes from baseline

p = 0.00001 for Multivariate test

p < 0.05 for pairwise comparison of 0 month versus 12 months

p < 0.001 for pairwise comparison of 0 month versus 18 months & 24 months

p < 0.05 for pairwise comparison of 6 month versus 18 months & 24 months

p < 0.05 for pairwise comparison of 12 months versus 24 months

From the study, the mean of SF-36 scores had rising through time (Table 2). From the analysis using repeated one-way ANOVA measure, it was found that in the Multivariate study, the SF-36 scores change from baseline was significant at all visits, P value = 0.00001 ($P < 0.05$). The Pairwise comparison method showed the change of SF-36 scores at 6 months after treatment compared with before treatment was not statistically significant P = 0.235, the change of SF-36 scores began to significant at 12 months after treatment P = 0.008. And the change of SF-36 scores from 6 months compared to 12 months after treatment was not significant P = 0.375 while the change from 6 months started to significant when compared with 18 month after treatment P = 0.005. The estimate marginal mean was shown in fig.1

Adherence

From 31 patients in the study. Medical Possession Ratio (MPR) of any patient was calculated from the total day of drug used, the first date and the last date that patients should be used and found that 4 (12.9 %) patients had moderate adherence (MPR 0.5-0.8), 27 (87.09) patients had high adherence (MPR > 0.8). The mean of MPR in this study was 0.94. Therefore the patients had high adherence in teriparatide treatment. The distribution of MPR was shown in Table 3.

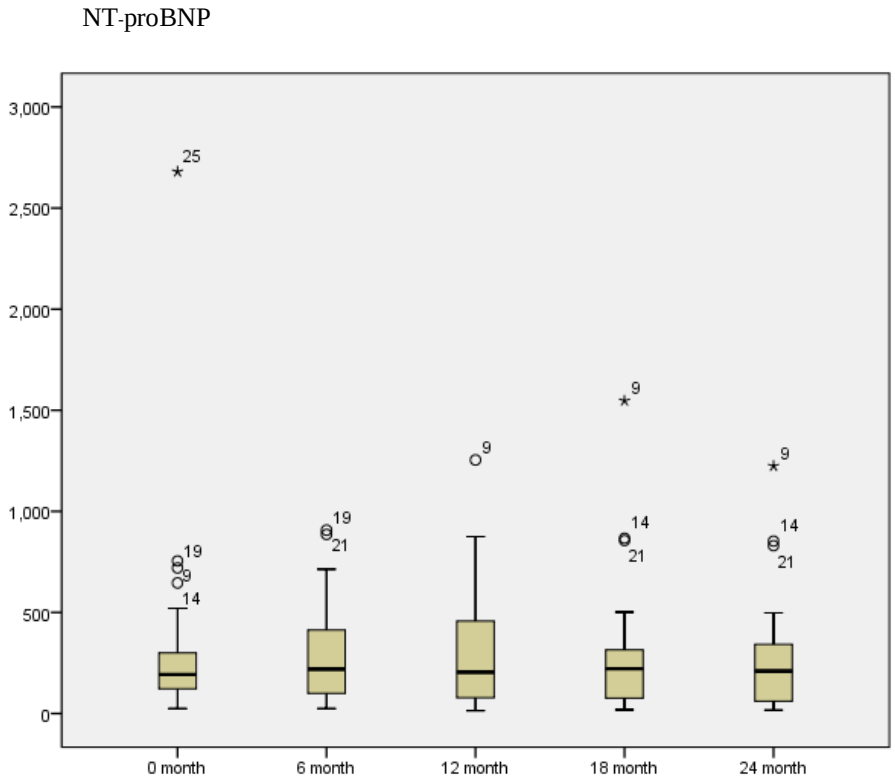
Table 3 Distribution of new teriparatide users by medication possession ratio (MPR) in 24 months

MPR	Patient (n=31)	Patient (%)	Mean
< 0.5	0	0	
0.5-0.8	4	12.9	
> 0.8	27	87.09	0.94

Cardiovascular adverse event

The result of serum NT-proBNP following in 31 patients showed the mean of serum NT-proBNP was 321.73 pmol/l (95 %CI : 140.05 - 503.41) at before treatment, 280.20 pmol/l (95 %CI : 188.14 - 372.2) at 6 months, 300.70 pmol/l (95 %CI : 189.94 - 411.45) at 12 months, 300.60 pmol/l (95 %CI : 181.08 - 420.11) at 18 months, 274.73 pmol/l (95 %CI : 171.02 - 378.44) at 24 months after started teriparatide treatment. The distribution of lower and upper of 95 % Confidence interval was overlapped in every times follow-up as showed in Table 4. The Multivariate study showed that the change of serum NT-proBNP level was not statistical significant P = 0.144. The relation of serum NT-proBNP level to times was shown in fig 2.

Figure 2



Relation of serum NT-proBNP level to times

Serum NT-proBNP level wasn't changed from baseline

P = 0.1444 (P > 0.05) for the multivariate test

From the 31 patients, 6 patients had serum NT-proBNP more than 357 pmol/l and had to exclude from the cardiovascular adverse event study because it couldn't be realized if the rising of serum NT-proBNP came from the effect of teriparatide treatment. The serum NT-proBNP was elevated to more than 357 pmol/l in 5 of 25 patients at 6 months after started teripartide treatment, and another 1 was elevated to more than 357 pmol/l at 12 months after started teriparatide treatment. None of the rest was elevated through times. Therefore 6 (24 %) patients had cardiovascular adverse event during teriparatide treatment and 19 (76 %) patients had no cardiovascular adverse event.

From the change of serum NT-proBNP was not statistical significant, therefore the teriparatide treatment was not effect the heart.

Bone mineral density (BMD) was follow-up yearly. It was found that the mean of lumbar spine BMD was -4.4 at before teriparatide treatment, -3.9 at 12 months and -3.3 at 24 months after teriparatide treatment. The mean of hip BMD was -4.1 at before teriparatide treatment, -3.8 at 12 months and -3.6 at 24 months after teriparatide treatment. Therefore the BMD was rising through times during teriparatide treatment.

Discussion

The result showed that SF-36 scores was rising through time. Therefore the teriparatide treatment gradually improved functional outcome with statistical significant at 12-18 months after started teriparatide treatment and maintained until at least the end of treatment.

Patients had high adherence to teriparatide treatment. The mean of medical possession ratio was 0.94 and 87.09 % of patient was high adherence (MPR > 0.8)[15].

There were not cardiovascular adverse event after teriparatide treatment. After 24 months, only 6 (24 %) patients had cardiovascular adverse event and one of these had rising of serum NT-proBNP while sepsis before the end of her life.

In addition, the teriparatide treatment increased bone mineral density. In average, the lumbar spine BMD was increase 1.1 and the hip BMD was increase 0.5 during treatment.

Conclusion

In the medical treatment of osteoporosis. Teriparatide is an anabolic agent. Besides the improvement of bone mineral density, teriparatide treatment also improved functional outcome and quality of life. The improvement was started to see at 1 year after started the teriparatide treatment.

The administration of teriparatide was subcutaneous injection once a day. Therefore it needed to get cooperation from the patients but the adherence from the patients was still high. Teriparatide was a recombinant parathyroid hormone. Although the primary hyperparathyroidism increased cardiovascular disease, the long term of teriparatide treatment (24 months) still did not effected the heart.

The study discovered more of the advantages and the limitations of the teriparatide which is an only drug in anabolic agent group in treating osteoporosis. The knowledge can be used while chosen the appropriate drugs for treating the osteoporosis patients.

References

1. Domenico M, Enzo R, Salvatore L, Carmelo L, Grazia M, Rosaria S, Maurizio R, Sara M, Valentina F, Giuseppe T, Biagio C, Michele C. Changes of the quality-of-life under the treatment of severe senile osteoporosis with teriparatide. Archives of Gerontology and Geriatrics 2009;49:35-8.
2. Ljunggren O, Barrett A, Stoykov I, Langdahl BL, Lems WF , Walsh JB, Pammer AF, Gerald Rajzbaum, Jakob F, Karras, Marin F. Effective osteoporosis treatment with teriparatide is associated with enhanced quality of life in postmenopausal women with osteoporosis: the European Forsteo Observational Study. BMC Musculoskeletal Disorder 2013;14:251.
3. McNeilly T, Mcnally C, Finch M, Beringer T. Recombinant PTH: A Study of the Outcome of Teriparatide Therapy for 138 patients with Osteroporsis. Ulster Med J 2013;82(2):89-93.
4. Iolascon G, Gimigliano F, Malavolta N, Tarantino U, Fornari R, Greco E, Di Pietro G, Gimigliano R, Lenzi A, Resmini G, Migliaccio S. Effectiveness of teriparatide treatment on back pain-related functional limitations in individuals affected by severe osteoporosis: a prospective pilot study. Clinical Cases in Mineral and Bone Metabolism 2012;9(3):161-5.
5. Udombhomprabha A, Boonhong J, Tejapongvorachai T. Health-Related Quality of Life of the Thai Hip Fracture Patients after the one year of Post-Hospital Discharge. Srinagarind Med J 2012;27(2).
6. Sally W. Wade, Jeffrey R. Curtis, Jingbo Yu, Jeffrey White, Bradley S. Stolshek, Claire Merinar, Akhila Balasubramanian, Joel D. Kallich, John L. Adams, Hema N. Viswanathan. Medication adherence and fracture risk among patients on bisphosphonate therapy in a large United States health plan. Bone 2012;50:870-5.
7. Tanaka I, Sato M, Sugihara T, Faries DE, Nojiri S, Graham-Clarke P, Flynn JA, Burge RT. Adherence and Persistence with Once-Daily Teriparatide in Japan: A retrospective, Prescription Database, Cohort Study. Journal of Osteoporosis 2013;654218:8.
8. Bonafede M.M., Shi N., Bower AG, Barron RL, A. Grauer, Chandler DB. Teriparatide treatment patterns in osteoporosis and subsequent fracture events: a US claims analysis. Osteoporos Int 2015;26:1203-12.
9. Ellegaard M, Schwarz P, Hansen CR, Faber J, Vestergaard H. Short-term teriparatide treatment does not affect NT-proBNP, a maker of cardiac disease. Scandinavian Journal of Clinical and Laboratory Investigation 2012;7:518-22.
10. Bay M, Kirk V, Parner J, Hassager C, Nielsen H, Krogsgaard K, Trawinski J, Boesgaard S, Aldershvile J. NT-proBNP: a new diagnostic screening tool to differentiate between patients with normal and reduced left ventricular systolic function. Heart 2003;89:150-4.
11. Rajzbaum G, Grados F, Evan D, Liu-Leage S, Petto H, Augendre-Ferrante B. Treatment persistence and changes in fracture risk, back pain, and quality of life amongst patients treated with teriparatide in routine clinical care in France: Results from the European Forsteo Observational study. Joint Bone Spine 2014;81:69-75.

12. Tsan-Wen Huang, Po-Yao Chuang, Shih-Jie Lin, Po-Yao Chuang, Hsin-Nung Shih, Mel S.Lee, Robert Wen-Wei Hsu and Wun-Jer Shen. Effects of teriparatide on cementless bipolar hemiarthroplasty in patients with osteoporotic femoral neck fractures. BMC Musculoskeletal Disorders 201617:300.
13. Songpatanasilp T, Mumtaz M, Chhabra,H Maria Yu, Sorsaburu S. Back pain in patients with severe osteoporosis on teriparatide or antiresorptives: a prospective observational study in multiethnic population. Singapore Med J 2014;55(9):493-501.
14. Bente L. Langdahl, Ljunggren O, Benhamou CL, Marin F, Kapetanos G, Kocjan T, et al. Fracture Rate, Quality of Life and Back Pain in Patients with Osteoporosis Treated with Teriparatide:24-Month Results from the Extended Forsteo Observational Study (ExFOS). Calcif Tissue Int 2016;99:259-71.
15. วีระชัย โควสุวรรณ, ณรงค์ บุณยะรัตเวช, เสก อักษรานุเคราะห์ และ มูลนิธิโรคกระดูกพรุนแห่งประเทศไทย. 2011. แนวทางปฏิบัติบริการดูแลรักษาโรคกระดูกพรุน พ.ศ. 2553.