Preliminary Report

Monitoring of Risedronate by Biochemical Bone Markers in Clinical Practice

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The study of trend of Risedronate 10 mg/day in menopausal women with a high level of resorptive bone marker(Betacrosslaps,CTx) by the following bone markers:Bone alkaline phosphatase(formation marker)total alkaline phosphatase(TAlP), NMID osteocalcin,undercarboxylated osteocalcin(UcOC)and procollagen type1 carboxyl propeptides(PICP). Risedronate does not suppress bone resorption deeply that enhances the bone recovers quickly after withdrawal. The level of undercarboxylated osteocalcin was increased after one year of treatment; it may be a sign of vitamin K2 deficiency. The bone alkaline phosphatase was decreased at the end of 12 months and Procollagen type 1 carboxyl propeptides(PICP) of twelfth month changed significantly compared to the sixth months of treatment(p= 0.001)

The once week 70 mg/week group also changed of CTx the same as daily dose group.

Keywords: *Resorptive marker, Betacrosslaps,CTx,Bone alkaline phosphatase(B-AlP),Undercarboxylated osteocalcin,UcOC,NMID osteocalcin,Total alkaline phosphatase(T-AlP),Procollagen type 1 carboxyl propeptides(PICP)*

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Risedronate is the third generation of bisphosphonate with its molecule containing amino group and classified as pyridinyl bisphosphonate. Risedronate is recognized as an antiresorptive agent for the treatment of osteoporosis.It is a highly potent antiresorptive agent that binds to hydroxyapatite in bone and inhibits osteoclast-mediated bone resorption[1] Risedronate is approved for the treatment of postmenopausal osteoporosis (PMO) and corticosteroid induced osteoporosis (CIO)[2]. Its action is concentrated on osteoclast apotosis, and many hypothesis proposed it as disturbance of mevalonate-pathway[2],capase stimulator[3]. The characteristic of bisphosphonates decreased bone resorption, high bone resorption is the main cause of bone crack at the same time so bisphosphonate is recognized as an antiresorptive agent.

This kind of bisphosphonate has been available in the Thai market since 2001 so it is a suitable time to review the efficacy and safety in clinical practice.

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The monitoring efficacy is observed by the level of resorptive marker, CTx or Betacrosslaps, Bone alkaline phosphatase (formation marker),Total alkaline phosphatase (TAlP), NMID osteocalcin, and Procollagen type 1 carboxyl and also the level of undercarboxy-lated osteocalcin marker.

Meterial and Method

Monitoring bone markers: NMID osteocalcin, Betacrosslaps (CTx), Bone alkaline phosphatase (B-AlP), Total alkaline phosphatase (T-AlP), Procollagen type1 carboxyl propeptides (PICP) and Undercarboxylated osteocalcin (UcOC).

1. Monitor the level of Betacrosslaps in 29 menopausal women with a high level of CTx (>0.300 ng/ml) All cases took 10 mg per day of Risedronate for one year.

2. Monitor the level of Betacrosslaps in 18 volunteers, menopausal women who took Risedronate 70 mg per week every month for 3 months.

3. Measure the level of vitamin K2 or undercarboxylated osteocalcin after one year.

All volunteers were free of medicine 1 month before the present study and had screened blood for liver function,

renal function, blood sugar were within normal limit. The data was analyzed by SPSS. A p-value of less than 0.05 was considered to be statistically significant

Result

The study of bone resorption marker in the 10mg group showed the betacrosslaps began to decrease significantly (p=0.0001) after one month and kept a constant level at 0.1 ng/ml throughout the year (Fig. 1). The twelfth month of CTx (m=0.139 ng/ml SD=0.054 95%CI=0.118 to 0.16) was lower than the value of CTx at the base line(m=0.802ng/ml SD=0.205 95%CI=0.724 to 0.880) control significantly (p=0.001).

Bone alkaline phosphatase, bone formation marker and undercarboxylated osteocalcin were studied. Bone alkaline phosphatase decreased significantly (p=0.0001) at 6 months and the mean of undercarboxylated osteocalcin (m=0.665ng/ml SD=0.205 95%CI=0.724 to 0.88) started to increase after 1 month and mark high level (mean=1.33 ng/ml) at the end of 12 months p=0.0001 (Table 1).

Preliminary report of the once a week group (70mg/week) of Risedronate. The mean of the base line control of CTx=0.528 SD=0.11 95%CI=0.474 to 0.583 and mean of CTx at the third month was 0.179, SD=0.102, 95%CI=0.128 to 0.23.

The bone resorption marker was decreased significantly (p=0.0001) (Fig. 2).

The liver function and renal function were normal compared to the base line control after the end of the present study of both groups.

Discussion

Risedronate has a trend of normalized coupling because its power of antiresorption has not over suppressed bone remodeling, average CTx =0.139 ng/ml at the end of one year when compared to the normal value of CTx=0.312 ng/ml [3] During Risedronate treatment it was found that the level of undercarboxylated osteocalcin increased progressively and at the end of 12 months was 1.33 ng/ml. However, this level was still

Table 1. Change of bone markers after 10mg/day of Risedronate

Markers	CTRL	1M	3M	6M	12M
CTx ng/ml	0.802	0.1	0.15	0.121	0.139
NMID	21.35	13.44		11.11	12.24
T-AlP U/L				51.79	52.03
B-AlP	32.2			12.44	8.55
PICP ng/L				105.76	121.27
UcOC ng/ml	0.573	0.926			1.33

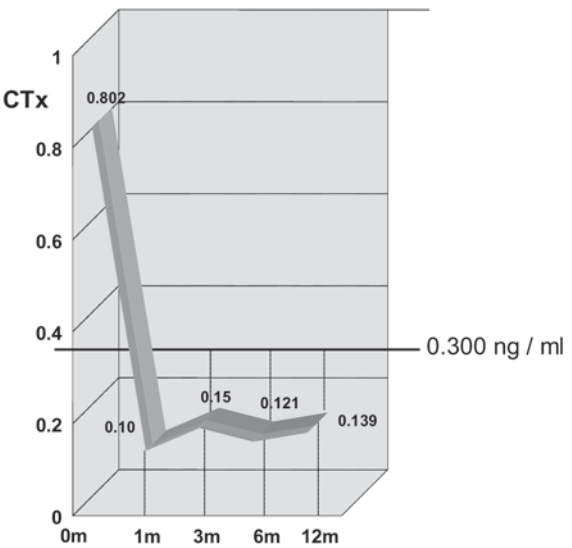

Fig. 1 The level of betacrosslaps (resorptive bone marker) decreased after one month significantly (p=0.0001) in the 10 mg /day-treated group

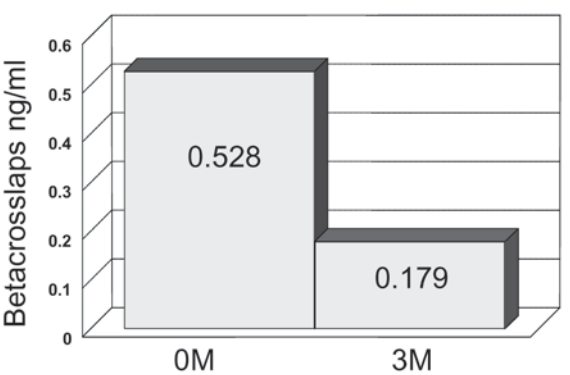

Fig. 2 After 3 months the betacrosslaps decreased below the normal level (p=0.001) in the once a week group of Risedronate

in the normal limit of UcOC and when compared to young adult, females it was 2.62 ng/ml[4] but the long term of Risedronate therapy, and the undercarboxylated osteocalcin which reflected the status of vitamin K2 should be considered carefully as it may lead to vitamin K2 deficiency in long term treatment.

The bone alkaline phosphatase (B-AlP), bone formation marker was decreased after one year of treatment compared to the base line control. The value of CTx and B-AlP did not suppress deep bone remodeling. If the other risks of osteoporosis can be controlled, Risedronate therapy can be stopped and let the natural

process go on, however, repeated therapy with Risedronate does not lead to resistanted[5].

The daily dose has stronger antiresorption than a once daily dose at the end of three months. Both types have good efficacy, in clinical practice, the once a week dose is considered as good compliance.

The present study showed that bone formation markers: Bone alkaline phosphatase, total alkaline phosphatase and Procollagen type 1 carboxyl propeptides (PICP) were decreased after treatment. Decrease of PICP to 222.69 ng/L at the end of 12 months means that the osteoblast still synthesized collagen at a low amount compared to the normal level of PICP[6] in young female adults. Bone alkaline phosphatase of the twelfth month was decreased compared to the sixth month so mineralization did not create well while the total alkaline phosphatase at the twelfth month was the same as the value for young Thai adult females[7] so the mineralization can progressively form under antiresorptive therapy.

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การติดตามการเปลี่ยนแปลงของ ไบโอเค็มมิคัล โบน ม้ารคเคอร์หลังใช้ยาไรสิโดรเนต ลดการสลายตัวของกระดูกในทางคลินิก

ณรงค์ บุณยะรัตเวช

จากการติดตามผลของ ไรสิโดรเนต (Risedronate) ที่ใช้ในผู้ป่วยสตรีวัยหมดประจำเดือนที่มีค่า CTx สูงกว่าปกติพบว่าไบโอเค็มมิคัล โบน ม้ารคเคอร์ ทุกตัวมีค่าลดลงจากค่าปกติแต่ไม่ต่ำเกินไป ซึ่งเมื่อเลิกใช้ยา การฟื้นตัวกระดูกได้เร็ว หลังใช้ยาครบหนึ่งปีพบว่าค่า undercarboxylated osteocalcin สูงกว่าก่อนได้รับยา อาจเป็นเพราะกระดูกต้องการวิตามิน เคสองมากขึ้นในการสร้างหลังจากการละลายตัวสงบลงแล้ว ค่าของ PICP ซึ่งเป็นไบโอเค็มมิคัล โบน ม้ารคเคอร์ ที่แสดงภาวะกระดูกสร้างกลับค่อยเพิ่มกว่า ค่าเดิมก่อนได้รับยา แสดงว่ากระดูกปรับตัวในการสร้าง แม้ว่าการใช้ยานานครบหนึ่งปี โดยสรุปยานี้สามารถห้ามการสลายกระดูก ได้แต่รบกวนการสร้างน้อยมาก