Efficacy of Bisphosphonates Evaluated by Biological Bone Markers

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This research aimed to study the benefits of bone markers on bisphosphonate, alendronate plus (vitamin D3 2800IU) administered once a week as a model especially regarding BetacrossLap, CTx.

The enrolled cases were 306 (female = 282, male = 24) with high CTx (≥0.300 ng/ml). The exclusion criteria were diabetes, abnormal renal or liver profiles, recent fractures and medication 1 month before the study. The duration of observation was 3 months for making decision on treatment. The blood for bone markers were checked at the first and third months.

It was found that 10 percent of alendronate intake showed no response, i.e. neither decrease nor increase in CTx and 16.1 percent of cases showed strong bone suppression, i.e. high anti-resorption which the value of CTx below 0.100 ng/ml after 3 months of the treatment. This bad condition may induce bone crack or stress fracture in the long run. It was also found 83.9 percent of cases presented good responses with the value of CTx at 0.100-0.299 ng/ml after 3 months. These cases can be continuing bisphosphonate until good satisfaction takes place.

The benefits of bone markers help the physicians' decision either to stop or continue the treatment. For the no response group, the bone markers (CTx) will save the cost of treatment. When the anti-resorption is marked (CTx <0.100 ng/ml), the physicians can stop the treatment before unwanted effects occur. The bone markers shorten the time for producing the treatment results and indicting whether the bisphosphonates have been properly used.

The bone markers, formative marker, PINP showed a decrease in bone formation after 3 months; PINP = 38.51%. This is a good lesson to be learned, that bone formation hardly ever occurs especially primary bone formation in cases where bisphosphonates is being taking.

This study manifested the benefits of biological markers with quick response that can help the physicians treat the patients properly, save time and the cost of medication.

Keywords: *Bisphosphonate, Alendronate, Bone markers, CTx, NMID osteocalcin, PINP*

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Bisphosphonates are commonly utilized in medical field especially in orthopedic surgery. A survey of osteoporosis in Thailand[1] showed that the bisphosphonates were the most popularly used.

The main action of bisphosphonate is anti-resorption by inducing apoptosis of osteoclast at the active site. There are many conditions of bone resorption by osteoclast such as osteoporosis, Paget's bone disease, Glucocorticoid inducing osteoporosis, menopausal osteoporosis, senile osteoporosis, etc. At some stages of the above-mentioned conditions, the osteoclasts are inactive; they are called low bone turnover. Physicians should decide before the introduction of these conditions whether to start the therapy with the anti-resorptive agents such as bisphosphonates or with the stimulator for bone formation. Sometimes, it is very hard to make a decision. An over treatment of bisphosphonates may be harmful to the bone[2,3] meanwhile an inadequate treatment will aggravate the bone resorption.

Treatments really need effective tools for therapy adjustment. At present, there are only biochemical bone markers providing accuracy and quick response for physicians to make a decision. New

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bone markers have advanced techniques such as a monoclonal antibody for detection of the remnants of collagen type 1, osteocalcin with release in tiny unit (nanogram) to the circulation during the process of bone remodeling. The values can be compared with the normal ones[4,5].

The bone markers consist of CTx, a resorptive marker, a bone formation marker, PINP and NMID osteocalcin.

The purpose of this study was to use bone markers monitoring the efficacy and result of bisphophonate, alendronate.

Material and Method

All fasting bloods were checked at the central laboratory of Siriraj Hospital with a method of monoclonal antibodies. For BetcrossLap, CTx was checked by Roche Cobas 6000 analyzer. The PINP and NMID oseocalcin were done under the process of ECLIA (Electro-chemiluminescence immunoassay, Roche Diagnostics, Mannheim).

Every case required a blood screening for general health such as diabetes, renal problems, liver malfunctions and history of recent fractures and were excluded (Table 1).

No medicine was to have been taken within one month of joining the project.

Total cases were 306; they had high bone resorption, which was proved by a high resorptive marker, CTx (>0.300 ng/ml).

Every case took alendronate plus (vitamin D2800 IU) once a week for three months.

The patients had blood checked after the first and third months for bone markers: CTx, NMID osteocalcin and PINP. If the value of CTx did not decrease by 30 percent from the base line after 3 months, they were excluded and moved to a non-response group, of patients who would take other medicine.

Results

Each month, the results of bone markers were recorded as showed in Table 1.

There were three types of responses: Non-response means CTx was not suppressed by bisphosphonate to below the normal limit, High response means the downward of CTx to below or equal to 0.1 ng/ml and Good response means CTx = 0.1-0.299 ng/ml (Fig. 1A).

Discussion

Bisphosphonates are still essential for the treatment of bone resorption at present. They have strong power for anti-resorption of bone, which commonly occurs in menopausal women. If the resorption happens for a long time, the bone texture will diminish and this leads to osteoporosis. In the past, bone density was used to measure and diagnose bone loss. This tool is too late for detection because some amount of bone has already been lost. This study shows an early detection of bone loss by the biological bone markers, i.e. CTx or Beta CrossLap. When bone loss occurs some bone texture will be released into the circulation such as remnants of old collagen, a pro-collagen and a specific bone protein, osteocalcin or bone gla protein (BGP). The brand-new method can detect the released products of bone by antibody-antigen reaction though the process of monoclonal antibody, which is a specific detection of the remnants of collagen or osteocalcin. So, the tiny amount (a nanogram of the particle or one billionth of a gram) of these products can be detected. If the values of these products are higher than normal levels, they are the indicators of bone loss or bone formation[4,5]. The biological bone markers recognized as dynamic changes of bone help physicians adjust the duration of

Table 1. The characteristic cases. The previous medication and recent fracture (within 3 months) were excluded

Total case (n)	306
Age	42.72
Gender	
Female	282
Male	24
CTx above 0.3 ng/ml	0.3 ng/ml+
Renal profile	Normal
Liver profile	Normal
Diabetes	Negative

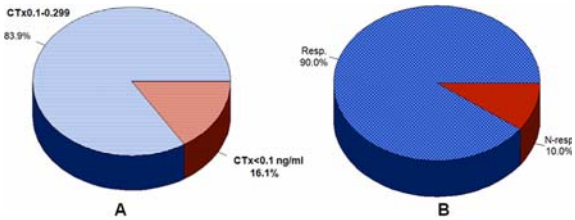

Fig. 1 A) The good response (83%) of alendronate treatment, CTx = 0.1-0.299 ng/ml. High suppressed group was 16.1% with CTx <0.1 ng/ml. B) The successful results of suppress bone turnover (A) was 90% and the non response group (N-resp) was 10%.

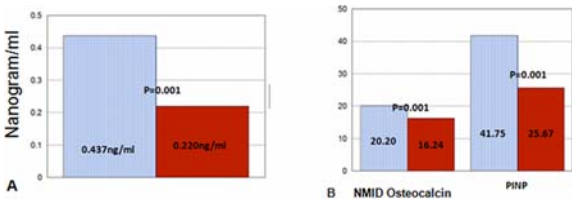

Fig. 2 A) The results of antiresorption by CTx after 3 months, the baseline = 0.437 nanogm/ml (vertical strip) and the 3-month value = 0.220 ng/ml (black column) which was recognized as a good response. B) The results of good response consisted of NMID osteocalcin and PINP between before (vertical striped) and after treatments (black column). All biological bone markers were significant with p = 0.001.

bisphophonates. From this study, the biological bone markers manifested the response of bisphohonates because some cases (10%) showed no response that the value of CTx did not decrease and some cases showed CTx increased. If the bone markers are used, the treatment of bone resorption can be changed in time. This means the cost will be saved and unwanted effect of bisphosphonates can be avoided. The benefits of these markers are capability of detecting the over suppression of bone by bisphophonates which makes the bone crack or experience a low energy fracture[6,7]. In past times, many papers did not mention this stress fracture[8].

The bisphosphonates are not potent for bone formation or healing. The collagen Type 1 synthesized by osteoblast in form of pro-collagen will leak to the circulation into two forms (2 ends of the pro-collagen molecule). The one end called amino-terminal propeptide, PINP and the others is carboxy-terminal propeptide, PICP. These markers are formative indicators of bone, but the marker of bone formation, PINP, is widely used and is available in Thailand.

This study showed the alendronate decreased bone formation (Fig. 2B) about 38.5 percent at the third month of treatment. The bisphosphonates disturb the osteoclastic activities leading to apoptosis. Thus, the osteoblast cannot work normally when osteoclasts are interfered with by the action of bisphosphonates and the function of osteoblasts will be disturbed indirectly. This phenomenon is the "coupling effect". Bone formation rarely occurs through bisphosphonates use especially the primary bone formation.

Potential conflicts of interest

None.

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การใช้โบนมาร์เกอร์ช่วยประเมินผลยาบิสฟอสฟอเนต

ณรงค์ บุณยะรัตเวช, นิตยา สุวรรณเวก

งานวิจัยการนำเอาโบนมาร์เกอร์มาช่วยประเมินผลการรักษาภาวะกระดูกละลายโดยนำยาอาเลนโดเนตเป็นต้นแบบ ศึกษาในผู้ป่วย 306 ราย เป็นหญิง 282 คนและชาย 24 คนที่ตรวจพบกระดูกละลายมีค่า ซีทีเอกซ์ สูงเกินค่าปกติ (0.300 นาโนกรัมต่อมิลลิลิตร) โดยได้รับยาก่อนอาหาร 1 ชั่วโมงสัปดาห์ละครั้ง ผู้เข้าร่วมวิจัยไม่มีโรคเบาหวาน สภาพไตและตับปกติ ไม่รับประทานยาใดๆ หรือมีกระดูกหักก่อนหน้า 1 เดือน พบว่าโบนมาร์เกอร์ชนิดวัดการสลายกระดูกหรือซีทีเอกซ์ ช่วยบอกผลของยาว่าตอบสนองหรือไม่ มี 10 เปอร์เซ็นต์ไม่ได้ผลหลังใช้ 3 เดือน ทำให้เปลี่ยนการรักษาได้ทันเป็นการประหยัดค่ายารักษา ไม่ต้องรอการวัดมวลกระดูกซึ่งกว่าจะรู้ว่าได้ผลหรือไม่ ในทางปฏิบัติต้องกินยาไปแล้ว 2 ปี นอกจากนี้การใช้ซีทีเอกซ์ช่วยดูผลการใช้ยาว่ากดการสลายตัวกระดูกมากเกินไปหรือไม่เพราะการกดนานๆ เพื่อให้กระดูกไม่สลายตัวจะมีผลเสียคือกระดูกจะร้าวและหักง่าย ในการศึกษาครั้งนี้พบว่าค่าซีทีเอกซ์เท่ากับหรือต่ำกว่า 0.100 นาโนกรัมต่อมิลลิลิตร ซึ่งเป็นค่าตัดสินแสดงถึงกระดูกไม่ทำงาน ยานี้มักกดการสลายกระดูกมากถ้าปล่อยนานไปกระดูกจะร้าวได้ ในการศึกษานี้มีผล 16.1 เปอรเซ็นต์หลังใช้ยาสามเดือน นอกจากนี้โบนมาร์เกอร์ซีทีเอกซ์ยังช่วยบอกการทำงานของเซลล์ออสติโอคลาสอย่างดีว่าทำงานระดับใด นอกจากนี้โบนมาร์เกอร์แสดงให้ทราบว่ายาบิสฟอสฟอเนตไม่ใช่ยาทำให้กระดูกสร้างหรือเพิ่มเนื้อ พบว่ามาร์เกอร์ พีวันเอ็นพี เป็นมาร์เกอร์บ่งบอกการสร้างกระดูกกลับลดลงถึง 38.51 เปอรเซ็นต์เมื่อได้รับยาสามเดือนผ่านไป ดังนั้นการใช้โบนมาร์เกอร์ช่วยแพทย์ในการตัดสินใจว่าจะเดินหน้าการรักษาต่อไปหรือไม่