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

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
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.

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 bisphosphonate, 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 osteocalcin 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. The biological bone markers recognized as dynamic changes of bone help physicians adjust the duration of medicine.

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

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<tr>
<td>Diabetes</td>
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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%.
bisphosphonates. From this study, the biological bone markers manifested the response of bisphosphonates 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 bisphosphonates which makes the bone crack or experience a low energy fracture(6,7). In past times, many papers did not mention this stress fracture(5).

The bisphosphonates are not potent for bone formation or healing. The collagen Type 1 synthesized by osteoblast in form of procollagen 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.

References
การใช้ยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอท

ดร. บุญราภัสณ์ ศิริ ผู้ตรวจ

งานวิจัยการนำยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอทคือการทดลองฉีดยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอทโดยนำยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอทเป็นตัวแบบ ศึกษาในผู้ป่วย 306 ราย เป็นหญิง 282 คนและชาย 24 คนที่มีกลุ่มอาการภูมิแพ้ ซึ่งอย่างง่ายที่สุด ถูกตั้งค่า (0.300 มม.กรัม/มิลลิลิตร) โดยให้รับยา 1 ชั่วโมงต่อ 24 ชั่วโมง ผู้เชี่ยวชาญในเรื่องแบบงาน สถิติและวิทยาการ ไม่รับประทานยาใดๆ หรือมีการหลอกลวงไว้ 1 เดือน พบว่ายาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอทมี 10 เบอร์ ซึ่งไม่ได้ผลหลังใช้ 3 เดือน ทำให้เห็นการรักษาได้ทั้งการประจุลบด้านอีฟโฟซิเอท

ในครั้งนี้การแบ่งการทดลองจะได้รับการรักษาได้ในที่ผ่านมีการทดลองถ้าก่อนไปแล้ว 2 ปี นอกจากนี้การนำยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอท ซึ่งเป็นผลตัวตนแสดงถึงการรักษาได้ทั้งงาน อาจมีการทดลองฉีดยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอทได้ในศึกษาที่มีผล 16.1 เบอร์เข้มที่ใช้ยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอท หรือยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอทได้ในระหว่างที่รักษาได้ นอกจากนี้การนำยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอทได้ใช้ยาแอมโมเนียมร่วมประจุลบด้านอีฟซิเอทที่มีการทดลอง ทำงานได้ที่ผ่านมา พบว่ามีผลที่ผ่านมาก พบว่าน้ำมันที่ผ่านมาเป็นผลการรักษาด้วยยาแอมโมเนียมร่วมประจุลบด้านอีฟโฟซิเอท 38.51 เบอร์เข้ม ผลการตามอย่างการทำตัวเองจะเห็นที่วัดการรักษาคือไม่ได้