Bisphosphonates are effective for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP). Their mechanism of action in this secondary osteoporosis is similar to the mechanism in postmenopausal osteoporosis. Patients with GIOP treated with bisphosphonates have a higher bone mineral density than placebo-treated patients (4% and 2% at the lumbar spine and femur, respectively). In addition, there is a trend for a reduction in vertebral fracture incidence in postmenopausal women. In parallel with general bone health measures, bisphosphonate therapy must be considered both in patients initiating and in those on chronic glucocorticoid therapy.

Introduction
There are several studies in the literature regarding the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP) with different bone-sparing agents, but the best evidence of efficacy have been provided by bisphosphonates. Bisphosphonates are widely used as anti-resorptive drugs for the treatment of metabolic bone diseases. They are non-hydrolyzable analogs of pyrophosphate characterized by two C-P bonds (Fig. 1). From the basic P-C-P structure, a great number of variations are allowed by changing the side chains $R_1$ and $R_2$. The anti-resorptive potency of the drug is dependent upon the side chain, and the activity of the different bisphosphonates on bone resorption varies markedly.

At the tissue level, bisphosphonates decrease bone turnover, decreasing the birth of new remodeling units, while allowing normal filling in the remodeling space. This results in a decrease in bone remodeling, and an increase in bone mineral density. These two mechanisms can explain the effect of the drugs on bone strength: a decrease in the thinning of trabeculae, a decrease in the probability of perforation of the thinner trabeculae, and improvement of both the primary and secondary mineralization of bone. Bisphosphonates decrease both the function of mature osteoclasts, and the recruitment and differentiation of osteoclast precursors.

Various mechanisms of action have been described, including changes in the ruffled border, shortening of the osteoclast lifespan by apoptosis, etc. They also may act through the secretion by osteoblasts of an inhibitor of osteoclast-mediated resorption (1-4). The molecular mechanism of action probably differs among the compounds depending upon their struc-
Bisphosphonates in glucocorticoid-induced osteoporosis / C. Roux & M. Dougados

ture. Clodronate can be metabolized to a cytotoxic, non-hydrolyzable analog of ATP by macrophages, and probably osteoclasts (5). In contrast, the nitrogen-containing bisphosphonates (pamidronate, alendronate, risedronate, ibandronate) are not metabolized; it is likely that they act by preventing protein prenylation in osteoclasts, and that their molecular targets are enzymes of the mevalonate pathway or prenyl-protein transferases (6).

Bisphosphonates have shown efficacy in postmenopausal osteoporosis: they decrease the risk of vertebral and peripheral fractures in osteoporotic postmenopausal women (7-10). Surrogate markers of their efficacy are the decrease in biochemical markers of bone remodeling and the increase in bone mineral density (BMD).

In contrast with postmenopausal osteoporosis, the main pathophysiological mechanism in GIOP is a decrease in both the number and the activity of osteoclasts, with a reduced trabecular wall thickness and bone mineralizing surface (11, 12). Glucocorticoids may promote osteoclast apoptosis (12). Changes in bone microarchitecture are different: in GIOP a thinning of the trabeculae is primarily observed, perforated only for a large decrease in trabecular volume (13). The effects of glucocorticoid on osteoclast activity are less clear; an increase in bone resorption has been proposed. Using bone histomorphometry, contradictory results have been obtained on resorption parameters, perhaps because of the effect of the underlying disease. However, the mechanism of action of the bisphosphonates is similar in GIOP and postmenopausal osteoporosis. In a histomorphometric analysis of transiliac biopsies performed in a large study of patients receiving high doses of glucocorticoids (11), it has been shown that the amino-bisphosphonate alendronate has no effect on bone resorption parameters (osteoclasts and eroded surfaces), in contrast with a decrease in biochemical markers of bone resorption (14), indicating a decrease in osteoclast function rather than in osteoclast number. Alendronate markedly decreases the rate of bone turnover, with a large decrease in the activation frequency; the magnitude of this effect is similar to that reported in postmenopausal osteoporosis treatment. This mechanism is the rationale for the use of an anti-osteoclastic drug in GIOP.

Prospective studies have been conducted on both the prevention and treatment of GIOP, with four bisphosphonates: etidronate, alendronate, pamidronate and risedronate.

Etidronate

Prospective studies have been conducted with etidronate, using cyclical intermittent use, 400mg/d for 14 days, following by calcium supplementation for 76 days, and repeated every 3 months for either 1 or 2 years. Both controlled open studies and placebo-controlled studies (15-25) suggest that intermittent cyclic etidronate is able to reverse the loss of bone mineral density in patients with GIOP. BMD increases at both the spine (5% -7%) and total hip (2.5% - 6.8%), compared to controls. Three prospective placebo controlled studies of one year duration have been conducted in patients initiating high dose glucocorticoid treatment for various medical conditions, including polymyalgia rheumatica, rheumatoid arthritis and vasculitis (22-24). Glucocorticoid treatment was started within 3 months prior to study entry, at a mean daily dose equal to or greater than 7.5 mg/day. In the European study (24), there was a statistically significant difference between etidronate and placebo groups at the lumbar spine (+0.3% versus -2.8%). At the femoral neck, the bone loss was decreased by a half, although the difference was not statistically different (effect of treatment: 1.3%). In the Canadian study (23), the same result was observed at the spine (+0.6% versus -3.2%) and a significant difference was observed at the great trochanter (+1.5% versus -2.7%). The changes in the femoral neck were not different between the groups. In these studies there was no difference in the incidence of adverse events (including problems involving the gastrointestinal tract) between the placebo and treated groups. Because these studies were conducted using the same protocol, data were pooled, allowing analysis between subgroups (25). Similar treatment effects were seen in the diseases subgroups. The benefit of the treatment at the lumbar spine was 2.9%, 3.3% and 4.4% for men, premenopausal and postmenopausal women respectively. At the femoral neck and great trochanter differences between the placebo and etidronate groups were observed for postmenopausal women only. In the pooled prevention studies, 7 and 14 patients in the etidronate and placebo groups experienced a total of 8 and 34 vertebral fractures, respectively. Five patients had 5 non-vertebral fractures in the treated group, whereas 8 patients had 12 non-vertebral fractures in the placebo group (25).

In recent studies of etidronate for the treatment of GIOP (20, 21), there was a significant difference between the etidronate and placebo groups at the lumbar spine of 4.1% and 5.4% after 1 and 2 years, respectively (25). In these patients on long-term steroid therapy, who were also receiving calcium, lumbar spine BMD was unchanged during follow-up.

Alendronate

Alendronate is a potent amino-bisphophonate which has a positive effect on BMD in patients receiving glucocorticoids (26) and in patients with Cushing’s disease (27).

A large prospective study by Saag et al. (14) was performed on patients taking a median dose of 10 mg of prednisone daily at baseline. In this one-year study, 477 men and women were randomized to receive either alendronate 5 mg/d or alendronate 10 mg/d or placebo. All of the patients received 800 to 1000 mg of elemental calcium and 250 to 500 IU vitamin D daily. Patients with different diseases were comprised in the cohort, including 30% with rheumatoid arthritis and 20% with polymyalgia rheumatica. BMD increased at the spine (2.1% and 2.9% in the alendronate 5 and 10 mg groups) at the trochanter (1.1% and 2.7%), at the femoral neck (1.2% and 1.0%) and at the total body (0.4% and 0.7%). In women, BMD changes in the 10 mg alendronate treated group were dependent on the hormonal status: +2.0% in premenopausal women, +1.5% in postmenopausal women on hormonal replacement, and +4.0% in postmenopausal women without estrogen therapy, respectively. It is noteworthy that the
change in spine BMD in the placebo group was related to the duration of glucocorticoid therapy: -1% in the 34% of patients treated for less than 4 months, -0.6% for those treated for 4 to 12 months, and +0.2% in patients treated for more than 12 months. In contrast, nei-
ther the duration of glucocorticoid ther-

apy nor the underlying disease influ-
enced the response to alendronate. Urinary excretion of N-telopeptides of type I collagen (a marker of bone resorp-
tion) decreased by 60% and serum bone-
specific alkaline phosphatase concentra-
tions decreased by 27% in the alendro-
nate group (14). New vertebral fractures
during the study were uncommon: 2.3% of the patients in the 2 alendronate treat-
moment groups (pooled) versus 3.7% in the placebo group. A trend for a treatment
effect was observed in post-menopausal
women. The treatment with alendronate
was safe. However, abdominal pain was
more frequent in patients receiving alen-
dronate 10 mg/d than in the other two
groups. There was no increase in side
effects involving the esophagus in the
alendronate groups, compared to the pla-

Pamidronate

Pamidronate is another potent amino-
bisphosphonate, that is widely used for
the treatment of malignant hypercalce-
emia and Paget’s disease. Pamidronate 150 mg/d was proposed in 1988 for the treatment of GIOP, and a
benefit on vertebral mineral density over
two years, as measured by quantitative
computed tomography, was seen (28, 29). However, the effects of oral pami-
dronate on the upper gastrointestinal tract
preclude its long-term use, and intrave-
nous administration has been studied
(30).

In a randomised open trial, 32 patients
with inflammatory rheumatic diseases who required first-time corticosteroid
therapy received either calcium alone or
calcium and pamidronate (90 mg at the
first injection, followed by 30 mg every 3 months) (31). A positive change was
measured at the spine (+3.6%) and the
hip (+2.2%) in contrast with a decrease in the calcium group (-5.3% at both sites).
No acute phase reaction was observed,
although this may be obliterated by glu-
cocorticoid treatment.

Optimal compliance and convenience is
ensured by the intravenous administra-
tion of bisphosphonate. This type of treat-
moment certainly deserves further study.

Risedronate

Risedronate is a new pyridinyl bisphos-
phonate, which has been studied in 224
men and women who were initiating
long-term corticosteroid treatment (32).
Patients received either placebo or 2.5
or 5 mg/d of risedronate. After 12 months,
there was no change in BMD compared
to baseline at the spine in the 2 treated
groups, but a 2.8% decrease in the pla-

A randomized trial of treatment of GIOP
by daily risedronate was conducted by
Reid et al. (33). Patients were receiving
high dose oral corticosteroid for more
than 6 months, and all of them received
calcium 1 g and vitamin D 400 IU daily
during the trial. Risedronate 5 mg in-
creased BMD at 12 months, by 2.9%,
1.8% and 2.4% at the lumbar spine, the
femoral neck and the trochanter, while
no change was observed in the placebo
group (p < 0.001, p = 0.004 and p = 0.01,
respectively). Nine out of 60 (15%) pa-
tients in the placebo group and 3 out of
60 (5%) patients in each treatment group
experienced incident vertebral fractures
by month 12, indicating a trend for a re-
duction in fracture risk (significance was
reached when the risedronate-treated
groups were combined). Treatment with
risedronate was not associated with ad-
verse gastrointestinal events.

Recently, this bisphosphonate was stud-
ied in a placebo-controlled trial on 120
women with rheumatoid arthritis requir-
ing long-term glucocorticoid therapy.
The administration over 2 years of 2.5
mg risedronate daily prevented bone loss
at the lumbar spine and femoral trochan-
ter, while significant bone loss was ob-
served in the placebo patients. There was
no difference between the 2 groups at the
femoral neck, although bone density
was maintained by the treatment at this
site. Interestingly, most of the patients
received NSAIDs and risedronate had a
similar upper gastrointestinal profile to
that observed in the placebo group (34).

Conclusion

When analyzing the different treatments
proposed for GIOP, bisphosphonates cer-
tainly have the best effectiveness score.
According to a meta-analysis, the mean
difference in BMD between bisphospho-
nate-treated patients and controls in GIOP
is 4.0% at the lumbar spine, and 2.1% at
the femoral neck (34).

Bone loss is more prominent during the
first months of medium to high-dose glu-
cocorticoid therapy, with a slower rate
of bone loss thereafter. The extent of
change in bone density is mainly related
to the duration of the treatment. In pa-

ents on chronic glucocorticoid treat-
moment, bisphosphonates increase BMD;
they stop bone loss in patients initiating
glucocorticoid treatment.

None of the studies were able to assess
the anti-fracture effect of bisphospho-
nates. There are no data on peripheral
fractures. On the other hand, a trend has
been seen for a reduction in vertebral
fracture risk, especially in post-menopa-
sual women.

In parallel with general preventive mea-
sures for bone health, including calcium
and vitamin D supplementation, and hor-
mone replacement therapy in hypogona-
dic subjects, bisphosphonates should be
considered, both in patients with GIOP
and in patients initiating high-dose, long-
term, glucocorticoid treatment.

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S-51

Bisphosphonates in glucocorticoid-induced osteoporosis / C. Roux & M. Dougados
Bisphosphonates in glucocorticoid-induced osteoporosis / C. Roux & M. Dougados