IV ibandronic acid an upcoming DIVA on the osteoporosis stage

– David Williamson –

Intravenous ibandronic acid [ibandronate] administered once every 2 or 3 months is at least as effective as daily oral ibandronic acid in terms of improvements in bone mineral density (BMD) in women with postmenopausal osteoporosis, according to 1-year results from the ongoing DIVA study presented at The Endocrine Society's 87th Annual Meeting (ENDO 2005) [*San Diego, California, US; June 2005*]. Both the 2-monthly and 3-monthly IV regimens were as well tolerated as the currently established daily oral ibandronic acid regimen and demonstrated similar safety profiles. In addition, efficacy and tolerability data on once-monthly oral ibandronic acid from the MOBILE study were presented in posters, showing efficacy at least equivalent to that of the daily oral regimen, again with a similar safety and tolerability profile. These alternatives to current oral bisphosphonate regimens may therefore present advantages for some women in terms of treatment tolerance and compliance.

Oral bisphosphonates, while being effective agents for the treatment of postmenopausal osteoporosis, have a number of limitations to their use in some patients. These include issues of gastrointestinal tolerance and oesophageal emptying disturbances, and difficulties with complicated oral dosing instructions. IV administration of bisphosphonates may therefore avoid some of the gastrointestinal effects and stringent dosing requirements associated with oral regimens, as well as offer benefits in terms of compliance with therapy.

Ibandronic acid was first approved in the US and the EU as an oral daily bisphosphonate for the treatment and prevention of postmenopausal osteoporosis. Intermittent dosing regimens have subsequently been developed, including once-monthly oral and intermittent IV regimens. At the ENDO 2005 meeting, 1-year results from the DIVA (Dosing IntraVenous Administration) study, comparing IV with the established oral daily ibandronic acid in postmenopausal women with osteoporosis, were presented by Dr Roberto Civitelli from the Washington University School of Medicine, St Louis, Missouri, US.[1]

DIVA: a non-inferiority study

DIVA is a 2-year multinational, double-blind, double-dummy, phase III study designed to demonstrate the non-inferiority of IV ibandronic acid administered every 2 or 3 months compared with daily oral ibandronic acid, and to determine the optimal IV dosing regimen for postmenopausal osteoporosis. The study includes 1386 postmenopausal women aged 55–80 years (time since menopause of ≥ 5 years) with osteoporosis, as evidenced by lumbar spine (L2–L4) BMD T-scores of < –2.5 and ≥ –5. Osteoporosis risk factors, including age, time since menopause, lumbar spine and total hip T-scores, and incidence of previous fracture, were comparable across all three study groups at baseline.

Women enrolled in the study receive either oral ibandronic acid 2.5mg once daily, IV ibandronic acid 2mg administered every 2 months, or IV ibandronic acid 3mg every 3 months. Study participants also receive daily calcium 500mg and vitamin D 400IU. The primary efficacy endpoint was the change from baseline in BMD at the lumbar spine (L2–L4) at 1 year, while secondary efficacy endpoints included the change in total hip, femoral neck and hip trochanter BMD at 1 year and changes in levels of serum C-terminal cross-linking telopeptide of type 1 collagen (CTX), a marker of bone resorption.

Greater BMD increases with IV regimens

At the end of 1 year, efficacy data were available for 381 women in the daily oral ibandronic acid arm of the study, and for 355 and 368 women in the IV ibandronic acid 2mg every 2 months and 3mg every 3 months study arms, respectively. The efficacy data presented were all per-protocol analyses.

The mean percentage change from baseline in BMD at the lumbar spine was significantly greater in women in both the IV ibandronic acid groups, compared with the daily oral ibandronic acid group. This measure increased by 5.1% and 4.8% in the 2-monthly and 3-monthly IV groups, respectively, compared with an increase of 3.8% in the group receiving oral ibandronic acid, demonstrating superiority of both IV regimens over the daily oral regimen.

Women in both IV treatment groups also had greater increases in BMD of the total hip, femoral neck and hip trochanter than those receiving daily oral ibandronic acid [*see table*].

Effects on BMD at 1 year, according to ibandronic acid regimen

	Ibandronic acid		
	IV 2mg 2-monthly (n = 355)	IV 3mg 3-monthly (n = 368)	Oral 2.5 mg/day (n = 381
Mean change from baseline in BMD at 1 year (%):			
Lumbar spine	5.1*	4.8*	3.8
Total hip	2.6**	2.4**	1.8
Femoral neck	2	2.3**	1.6
Hip trochanter	4.1**	3.8**	3

* $p < 0.001$ vs daily oral regimen
** $p < 0.05$ vs daily oral regimen

The percentage changes from baseline in serum levels of CTX were determined at 2, 4, 6 and 12 months for patients receiving IV ibandronic acid 2mg every 2 months, and at 3, 6 and 12 months in the group receiving IV ibandronic acid 3mg every 3 months; changes were recorded at all of these time points for patients on the daily oral regimen. Similar median decreases were seen in all treatment groups after 6 months (–62.5%, –65.1% and –58.4% for the daily oral, 2-monthly IV and 3-monthly IV groups respectively) and at 1 year (–62.6%, –64.6% and –58.6%, respectively).

Addressing a question regarding the fracture efficacy of the IV regimens, Dr Civitelli commented that the study was not powered for this, but the incidence of

IV ibandronic acid an upcoming DIVA – *continued*

fractures seen at the end of 1 year was approximately the same across the three study arms.

IV regimen well tolerated

IV ibandronic acid therapy was reported to be well tolerated overall, with a similar safety profile to that of the daily oral regimen. The safety and tolerability data included 1382 patients. A similar percentage of patients in all three groups (76–81%) experienced an adverse event, and serious adverse events were reported in 8%, 8.9% and 7.5% of patients in the daily oral (n = 465), 2-monthly IV (448) and 3-monthly IV (469) groups respectively. The overall incidence of renal adverse events was low and similar in all three treatment groups (2–3% of patients). There was a higher incidence of influenza-like illness (onset within 3 days and duration of ≤ 7 days) in the IV treatment groups (3.6–3.8%) than in the oral treatment group (0.6%), but these symptoms generally occurred only following the initial administration and resolved without symptomatic treatment.

Dr Civitelli concluded that overall both IV ibandronic acid regimens were at least as effective and well tolerated as daily oral ibandronic acid, and in terms of the BMD gains in the lumbar spine, the IV regimens were superior to the daily oral regimen.

MOBILE assesses monthly oral regimens

Data from year 1 of the 2-year MOBILE (Monthly Oral iBandronate In LadiEs) study were also presented at the meeting, and showed that monthly oral dosing is at least equivalent in efficacy to daily oral dosing, with a similar safety and tolerability profile.[2,3] This randomised, double-blind, phase III non-inferiority study involving 1602 postmenopausal women compared the efficacy and safety of monthly oral ibandronic acid with the established oral regimen of ibandronic acid 2.5mg once daily. Three different monthly regimens are included in this study: two single doses of oral ibandronic acid 50mg each on consecutive days; a single dose of ibandronic acid 100mg; or a single dose of ibandronic acid 150mg. Women in all treatment groups received daily calcium 500mg and vitamin D 400 IU.

All three monthly regimens were found to be non-inferior to the daily regimen in terms of the increases in BMD at the lumbar spine; this increased by 4.3% in the 2 x 50mg study arm, 4.1% in the 100mg arm and 4.9% in the 150mg arm, compared with an increase of 3.9% in the 2.5mg daily arm. Moreover, the 150mg monthly regimen was superior to the daily regimen for this endpoint (p = 0.002). Increases in total hip, femoral neck and hip trochanter BMD were similar for all the treatment groups. Women in all treatment groups also had similar reductions from baseline in serum CTX levels, although a significantly greater proportion of patients in the 150mg monthly treatment group than in the daily treatment group had reductions of 50% and 70%.

The monthly and daily ibandronic acid regimens showed similar safety and tolerability profiles, with a comparable overall incidence of adverse events and treatment-related adverse events across the four study groups. The incidences of upper gastrointestinal adverse events were similar in all the treatment groups (18% for the 2.5mg once daily group, compared with 15.9% for 2 x 50mg, 21.7% for 100mg and 16.9% for 150mg monthly groups).

1. Civitelli R, et al. Efficacy of intermittent intravenous ibandronate injection therapeutically equivalent to daily oral ibandronate in postmenopausal osteoporosis. 87th Annual Meeting of the Endocrine Society : 135 (plus oral presentation) abstr. OR41-2, 4 Jun 2005.
2. Bolognese MA, et al. Efficacy of monthly and daily oral ibandronate is at least equivalent in postmenopausal women with osteoporosis. 87th Annual Meeting of the Endocrine Society : 457, 4 Jun 2005.
3. Drezner M, et al. Once-monthly dosing of oral ibandronate is as well tolerated as once-daily dosing in postmenopausal osteoporosis. 87th Annual Meeting of the Endocrine Society : 454-455, 4 Jun 2005.

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» **Editorial comment:** Regulatory filings seeking the approval of IV ibandronic acid [Roche, GlaxoSmithKline, Chugai Pharmaceutical] for the treatment of postmenopausal osteoporosis have been placed in the EU and the US. Once-monthly oral ibandronic acid has been approved and launched in the US, and has received a positive opinion recommending marketing authorization in the EU for the treatment of osteoporosis in postmenopausal women.