

Immunogenicity Differs in Abatacept, Infliximab

BY NANCY WALSH
New York Bureau

MONT TREMBLANT, QUE. — Abatacept and infliximab exhibit different characteristics in their propensity to elicit autoantibody seroconversion and in their immunogenicity profiles in patients with rheumatoid arthritis, according to findings from a new analysis of data from a multicenter phase III trial.

As with all immunomodulatory agents, the development of autoimmune disorders and the formation of anti-double-stranded DNA (anti-dsDNA) and antinuclear antibody (ANA) is of concern in patients who are being treated with abatacept or infliximab, said Dr. Jacques Brown of le Centre Hospitalier Universitaire de Quebec.

Recombinant biologic agents also have the potential to elicit immunogenicity, and the associated antibodies might mediate drug clearance or prevent its binding to its pharmacologic target.

Moreover, antibodies against anti-tumor necrosis factor therapy have been associated with decreased efficacy and an increased risk of infusion reactions, according to Dr. Brown.

The current analysis investigated 431 patients with rheumatoid arthritis who had an inadequate response to methotrexate. Patients were randomized to receive either abatacept, 10 mg/kg, on days 1, 15, and 29, and every 4 weeks thereafter; or infliximab, 3 mg/kg on days 1, 15, 43, and 85, and every 56 days thereafter for 6 months; or placebo.

Patients' mean age was 49 years and mean disease duration was 8 years. All had active disease, with a mean Disease Activity Score 28 of 6.8, tender joint counts above 30 and swollen joint counts above 20, and poor physical function on the Health Assessment Questionnaire Disability Index.

At baseline, 87% of the patients who were receiving abatacept were rheumatoid-factor positive, as were 85% of those patients who were randomized to the infliximab group.

At 6 months, 2% of the abatacept group, 5% of the placebo group, and 32% of the infliximab group had become ANA positive, whereas 1%, 4%, and 39% of these groups had seroconverted to positivity for anti-dsDNA antibodies, Dr. Brown reported in a poster session at the annual meeting of the Canadian Rheumatology Association.

By 1 year, 7% of patients in the abatacept group and 48% of the infliximab group had become ANA positive, whereas 2% of the abatacept group and 48% of the infliximab group had become anti-dsDNA positive.

The patients initially randomized to placebo were switched to abatacept at 6 months and were not included in this analysis.

During the 6-month double-blind phase of the trial, none of the abatacept-treated patients developed antibodies against the drug, whereas 62% of the infliximab-treated patients had developed anti-infliximab antibodies.

During the double-blind phase, one patient in each group developed an autoimmune disorder.

One patient on abatacept developed vasculitis, one patient receiving placebo developed leukocytoclastic vasculitis, and one patient on infliximab developed sicca syndrome.

By 1 year, one additional patient who originally was randomized to placebo and later was switched to abatacept developed vasculitis.

Infusion reactions, which most commonly consisted of hypotension, headache, and nausea, were seen in 5%, 10%, and 18% of patients in the abatacept, placebo, and infliximab groups, respectively.

By 1 year these reactions were seen in 7% and 25% of the abatacept and infliximab groups.

The profiles of ANA and anti-dsDNA antibodies were markedly different in the two active treatment groups, although this difference did not translate into an in-

crease in autoimmunity, with very few patients developing autoimmune disorders.

Furthermore, because vasculitis and sicca syndrome are associated with rheumatoid arthritis, it is difficult to determine whether the association is with the disease or with the use of biologic agents, Dr. Brown wrote.

The clinical impact of these differences remains to be elucidated, he added.

The study was sponsored by Bristol-Myers Squibb Co. ■

Focusing on bisphosphonates to build your patients' osteoporosis treatment?

Are they missing something very important?

Bisphosphonates are considered to be one of the most effective medications available. However, patients may be missing something very important if the focus is mainly on their bisphosphonate.



Bisphosphonates can't hold up without calcium and vitamin D^{1†}

For bisphosphonate therapy to be effective, a patient must have adequate intake of calcium. In fact, in the vast majority of bisphosphonate efficacy trials, supplementation with calcium and Vitamin D₃ was a requirement of the methodology.[‡]

Up to 90% of women are estimated to have low calcium intake²

Many doctors assume their patients get enough calcium and Vitamin D in their diets. Yet low calcium intake and vitamin D deficiency, especially in women, is well documented:

- 90% of adult Women aged 20 plus², and
- 73% of adult Men aged 20 plus are estimated to have low calcium intake²

- 85% of postmenopausal women may not get enough calcium³
- > 50% of women treated for Osteoporosis are estimated to be deficient in vitamin D⁴

Even patients taking supplements are still not getting enough calcium. Median Calcium Intake for Females 51+ (1988-1994): < 775 mg/day (from food + supplements)⁵

Patients need a supplement that works with their bisphosphonate therapy

If bisphosphonates are the building blocks of effective Osteoporosis therapy, then calcium with vitamin D is the mortar. Many physicians have found that the calcium / Vitamin D formulation in OS-CAL[®] is an excellent adjunct to their patients' bisphosphonate therapy.

OS-CAL is proven effective in reducing fracture risk independent of bisphosphonates⁶ and to improve bone density and strength.⁷

And OS-CAL offers unsurpassed absorption. Gastric acidity has been clinically proven to have no impact on absorption (when taken with meals); and, differences in in vitro solubility also have little to no impact on human absorption.⁸⁻¹¹

Only one supplement has been clinically proven to reduce hip fracture risk by 29%^{6*}

In the past, calcium + vitamin D were thought to provide some benefit in terms of fracture risk, but until recently there were no definitive clinical trials to prove this fact.

The NIH Women's Health Initiative changed our thinking by demonstrating that the OS-CAL formulation can have a significant clinical impact on bone fracture risk.

Only OS-CAL is proven to reduce hip fracture risk by 29% (n=21,406 taking

≥80% of study medication).^{6*} And, given the significant impact variability found with different formulations on calcium absorption, these results can't be ascribed to other calcium + vitamin D supplements.¹²

Patient acceptance and compliance are critical to effectiveness

Patients who adhered to study medication reduced their risk of hip fracture by 29%.^{6*}

"Only OS-CAL is proven to reduce hip fracture risk by 29%^{6*}"

This effect was noticed in patients who were taking ≥80% of their medication. OS-CAL was designed with patient acceptance and compliance in mind.

- Patients can take fewer and smaller tablets because they contain approximately 60% more elemental calcium than calcium citrate tablets.

- Package labelling helps compliance between OS-CAL and bisphosphonate medications.
- Dosing is tied to meals, thus providing a simple memory cue.
- Smaller, coated tablets are easier to swallow.
- Tablets taste good, and are available in sugarless and chewable formats.
- There were no significant gastrointestinal side effect differences between OS-CAL and placebo.

*Based on a study conducted by NIH. When taken as directed, OS-CAL formulation of 500 mg calcium + 200 IU vitamin D₃. †Prescribing information for: Fosamax[®] & Fosamax plus D[™] - Merck, Actonel[®] & Actonel[®] with Calcium - Procter & Gamble, Boriva[®] - Roche

1 Guenther C et al. Nothing works without Calcium and Vitamin D. Oasis online abstracts Presentation T393. 2 USDA's Continuing Survey of Food Intakes by Individuals 1994-1996. 3 Women's Health News 85 percent of postmenopausal women do not get enough calcium. Sept 26, 2005. NAs 2004. The American Society for Bone & Mineral Research 27th Annual Meeting. 4 Holick MF et al. Prevalence of Vitamin D inadequacy among postmenopausal north american women receiving osteoporosis therapy. Jnl Clin Endo 90(6):3215-3224 2005. 5 Surgeon General's report on bone health & osteoporosis, Chapter 6, 2004. 6 Jackson RD et al. Calcium plus Vitamin D supplementation and the Risk of Fractures. N Eng J Med V354;7 Feb 16, 2006. 7 Chen Z et al. The Effect of Calcium plus Vitamin D Supplement on Hip Geometric Structures: Results from the Women's Health Initiative CaD Trial. Oasis online abstracts Presentation T1207. 8 Recker RR. Calcium absorption and achlorhydria. N Engl J Med. 1985;313:70-73. 9 Bo-Linn GW, et al. An evaluation of the importance of gastric acid secretion in the absorption of dietary calcium. J Clin Invest. 1984;73:640-657. 10 Heaney RP et al. Absorbability and Cost Effectiveness in Calcium Supplementation. Jnl Am Col Nut V20 Num3, 239-246 2001. 11 Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of calcium as the carbonate and citrate salts, with some observations on method. Osteoporosis Int. 1999;9:19-23. 12 Heaney RP. NAD Claim Submission and approval. Data on file GSK © GlaxoSmithKline 2008



"If bisphosphonates are the building blocks for effective Osteoporosis therapy, then calcium with vitamin D is the mortar."

For your patients on bisphosphonate therapy, don't forget the OS-CAL twice a day every day with meals



OS-CAL
calcium carbonate + vitamin D₃

GlaxoSmithKline
Consumer Healthcare