MAO inhibitors

(DECEMBER 2010)

TO THE EDITOR: I wish to point out an error in the excellent review of MAO inhibitors published in the December 2010 issue of the *Cleveland Clinic Journal of Medicine*. The authors state, "The only selective MAO inhibitor now available in the United States is selegiline, which inhibits MAO-B at low doses but loses its selectivity at dosages greater than 20 mg/day" (on page 861). In fact, a second selective MAO inhibitor has been available in the United States for several years. Rasagiline, developed by Teva Pharmaceuticals and marketed under the brand name Azilect, is a highly selective MAO-B inhibitor indicated for treating the symptoms of Parkinson disease, either as monotherapy or as adjunct therapy to carbidopa-levodopa. However, rasagiline is not indicated for the treatment of depression. Perhaps the authors meant to say that selegiline is the only selective MAO-B inhibitor indicated for treating depression in the United States.

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IN REPLY: Dr. Keller is correct, and we thank him for the clarification. We meant to say that selegiline is the only selective MAO-B inhibitor indicated for treating depression in the United States.

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Gout and chronic kidney disease

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TO THE EDITOR: Thank you for the thorough review of gout and chronic kidney disease in the December 2010 issue of *Cleveland Clinic Journal of Medicine*.

TABLE 2 displays results from the Febuxostat Versus Allopurinol Controlled Trial (FACT), in which we see that 76% of patients treated with febuxostat 80 mg per day achieved a serum uric acid level of less than 6 mg/dL at week 28. With a dose of febuxostat 240 mg per day, 94% of patients were able to reduce their serum uric acid below 6 mg/dL, the threshold needed to prevent precipitation of uric acid crystals. However, the maximum daily dose recommended in the product information for Uloric (febuxostat) is 80 mg, at which approximately 24% of patients failed to lower their serum uric acid levels to less than 6 mg/dL.

When encountering such patients in clinical practice, would the authors advise pushing the daily dose of febuxostat up to 240 mg, if needed? Alternatively, is there any role for combination therapy with both febuxostat and allopurinol for gout patients with severe resistant hyperuricemia?

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IN REPLY: The clinical dilemma Dr. Keller describes is the inability to lower the serum urate to a consensually accepted target level of less than 6.0 mg/dL in patients with significant gouty arthritis, when using doses of febuxostat (or for that matter allopurinol) recommended by the US Food and Drug Administration (FDA). This problem is not limited to the management of the gouty patient with renal insufficiency, and we will describe our approach.

In patients failing to meet target serum

urate levels, patient adherence to the prescribed dosing should be considered first, since as many as 50% of patients do not adhere to their prescribed hypouricemic medication regimen.[1]

As Dr. Keller notes, staying below the FDA-approved daily dosage (in the absence of renal insufficiency) of febuxostat (80 mg) or allopurinol (800 mg) will result in some patients not achieving adequate urate-lowering to ameliorate their gout. With clinical and laboratory monitoring for intolerance, we have increased the dose of allopurinol to above 800 mg when necessary; we have explained to patients that this was above the normally recommended dosage of the drug. Of those patients who have been truly intolerant to allopurinol whom we have needed to switch to febuxostat, there have been a few who have required greater than 80 mg daily, and we have increased the dosage, again with extra vigilance in monitoring (liver tests in particular) and after discussion with the patient. Thus far, we have been fortunate in not having had significant side effects, but we do not assume that all patients will tolerate more than 80 mg daily.

Since both febuxostat and allopurinol inhibit the same enzyme (xanthine oxidase) as their mechanism of action, we do not anticipate an advantage to using combined drug therapy, as opposed to increasing the dose of one or the other of the medications. There might even be some loss of efficacy due to inhibitor competition at the enzyme's active site. Alternatively, in the patient with normal renal function, there might be an advantage to adding probenecid, a uricosuric drug, to either allopurinol or febuxostat, in order to gain some additional hypouricemic effect.

Finally, it is worth reemphasizing that in clinical trials, although febuxostat 80 mg may have outperformed allopurinol at a dose of 300 mg (or less), in clinical practice it is quite reasonable to significantly increase the dosage of allopurinol to at least 800 mg daily as long as it is tolerated, before switching to the very effective but much more expensive alternative. The goal of therapy is, after all, to safely lower the serum urate level to well below its saturation point. Surveys of prescribing habits indicate that physicians have been very reluctant to increase the dose of allopurinol to above 300 mg daily and, unfortunately, do not adequately monitor the efficacy of the therapy in lowering the serum urate level.

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