

## LETTERS TO THE EDITOR

### PLACEBO CONTROLLED STUDY RANDOMIZING LEUPROLIDE ACETATE

To The Editor:

In a recent issue of the *Digestive Diseases and Sciences*, Mathias et al reported the results of a placebo-controlled study randomizing leuprolide acetate against a placebo control in 29 patients, and this was followed up by a one-year open-label study of all patients using a dose range protocol for leuprolide acetate. In an editorial, Dr. Wood addressed the theoretical basis for the proposed effect of this drug. However, given the implications of the two studies, both of which are being reported as positive, I would like to address certain methodologic concerns.

In effect, as a placebo-controlled study, the results of the three-month study must be considered negative in that there were no significant differences at the end of treatment between active drug and placebo. However, the authors decided to emphasize that there were significant effects in the change between baseline and the end of treatment in the leuprolide group relative to placebo. My concern here is that the groups do not appear to be comparable in that the baseline total symptom score for leuprolide is almost 25% greater than the placebo group. This might mean that the significant effect of the leuprolide group may be an artifact of patient selection rather than a result of the drug itself.

There are additional concerns. First, the subjects were reported to have moderate to severe illness. Therefore it is unclear why they selected study subjects based on a score greater than 15 out of a maximum of 60. It would be helpful to know the distribution of scores for the patients with mild to moderate illness. The authors also report a shortened transit time in the leuprolide-treated patients compared to placebo-treated subject, but the results were not significant ( $P < 0.107$ ). While it is reported that bowel habits changed toward normal, the symptoms were not evaluated, and therefore could not be reported. Finally, it is noted that half of the leuprolide-treated patients (7/14) had significant adverse affects.

The second study followed both groups in an open trial and the subjects took daily injections for 9 (the original placebo group) or 12 (the active treatment group) months. They report highly significant results in both groups based on  $P$  values. My concern is that it appears that the baseline results, particularly for the

original placebo control, are somewhat different from that reported in the placebo-controlled study. For example, for the symptom pain in the original placebo group went from a baseline of 7 to a treatment score of 6. However, in the open study the baseline score was reported as 8. This is true for most of the other symptom scores. I would assume that the symptom score should at least be similar to the baseline with both papers. However, even if a different baseline was established, the data show that after the first three months of treatment, the baseline for the second study was even higher than originally. Again, this might artifactually lead to greater levels of significance given higher baseline scores. Finally, as an uncontrolled trial, this study can only be considered preliminary.

After reviewing both papers and the editorial, I've come to the conclusion that there may still be a reason to consider a role of leuprolide in selected patients with functional bowel disorder. However, I believe that physicians should be conservative in prescribing this drug for several reasons: (1) Given the methodological limitations of these studies, the efficacy of this drug must still remain in question, and additional studies are needed to support the conclusions. (2) Side effects are common. (3) The burden to the patient (daily injections) and the consequences of treatment (ie, amenorrhea and its long-term effects) are considerable. (4) The comorbid affects of psychologic disturbance as it affects illness behavior must also be considered. Some patients may have difficulty responding to any type of treatment.

I am hopeful that the study can be repeated, possibly with a larger sample size, since I believe there may be subgroups who may respond. However, the study should be done using a more rigorous design and possibly with concurrent physiologic assessment to determine whether the effects of treatment have the expected physiologic consequences. In the meanwhile, I hope that physicians would exercise caution in prescribing experimental drugs in this most difficult to treat subgroup of patients with functional bowel disorder.

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