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AUA: A Hit and a Miss for OAB Drugs

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FEEDBACK

WASHINGTON -- Overactive bladder (OAB) symptoms declined significantly within four weeks after the start of treatment with the investigational beta-3 agonist mirabegron, data from a randomized, placebo-controlled trial showed.

The frequency of urinary incontinence and micturition decreased significantly with two different doses of mirabegron. The symptomatic improvement correlated with improvement in patient-reported outcomes, including treatment satisfaction, symptom bother, and quality of life.

Adverse events occurred in similar proportions of placebo- and mirabegron-treated patients, according to presentations here at the American Urological Association meeting.

"The biggest thing physicians need to know about this drug is that it is the first oral medication that is not an antimuscarinic and that has demonstrated appropriate efficacy in treating overactive bladder," said Victor Nitti, MD, of New York University in New York City.

"We observed a nice difference in effects on OAB symptoms compared with placebo, which is always good, but the real bonus is a lack of side effects. That, coupled with the fact that it is not an antimuscarinic, means that for people who don't respond to antimuscarinics or won't take antimuscarinics, we will at least have something else to try before moving on to the next level of treatment."

Another OAB candidate drug did not fare so well. The prostaglandin EP1 receptor antagonist ONO-8359 failed to distinguish itself from placebo and was inferior to tolterodine, as reported at a late-breaking science session at the AUA meeting.

Not yet approved by the FDA, mirabegron is a first-in-class agent developed specifically for treatment of OAB. The agent selectively binds and activates beta-3 adrenoreceptors on bladder detrusor muscle to facilitate filling and storage.

Development of the drug addresses an unmet need for OAB therapies with different mechanisms of action compared with conventional therapies, most notably, antimuscarinic drugs, said Nitti.

Favorable results from phase II studies of mirabegron led to a phase III, randomized, placebo-controlled study involving more than 1,300 patients with OAB. Investigators at 132 sites in the U.S. and Canada randomized the patients to placebo or to 50- or 100-mg of mirabegron.

The trial's coprimary endpoints were the change in the number of daily episodes of urinary incontinence and micturitions from baseline to 12 weeks, as reflected in

Action Points

- Note that these studies were published as abstracts and presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.
- Explain that mirabegron, an investigational beta-3 agonist, significantly improved incontinence episodes, daily micturition frequency, and patient symptom/quality of life perceptions in those with overactive bladder.
- Point out that a prostaglandin EP1 receptor antagonist was not superior to placebo in another trial in patients with overactive bladder.

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patient diaries.

Secondary endpoints included change from baseline in other parameters of incontinence and micturition, as well as patient-reported outcomes.

Women made up three-fourths of the study population, which had a mean age of 60. About 40% of the patients had mixed stress/urgency incontinence with urgency predominance, a third had no incontinence, and the remainder had urgency incontinence.

After 12 weeks of randomized treatment, the number of incontinence episodes per 24 hours had declined in all three treatment groups, but significantly greater reductions occurred in the 50- and 100-mg mirabegron groups: -1.47 and -1.63 episodes, respectively, compared with -1.12 in the placebo group ($P<0.05$).

A similar pattern emerged from analysis of changes in daily micturition frequency, which declined by 1.08, 1.66, and 1.75 episodes in the placebo, 50-mg, and 100-mg mirabegron groups, respectively ($P<0.05$).

Significant between-group differences favoring mirabegron emerged within four weeks for both incontinence and micturition frequency. Voided volume, mean level of urgency, and grade 3-4 urgency episodes all declined significantly more with mirabegron versus placebo ($P<0.05$).

The most common adverse events were hypertension (5.5%), urinary tract infection (3.2%), headache (3.1%), and nasopharyngitis (3.0%). The incidence and severity of adverse events were similar across the three treatment groups.

Patient-reported outcomes all improved significantly in the mirabegron groups compared with placebo, including treatment satisfaction, symptom bother, and OAB-specific health-related quality of life ($P<0.05$).

In contrast to the mirabegron results, findings from a randomized trial of ONO-8359 showed "no significant improvement or observed tendency for improvement in any ONO-8539 treatment groups," Christopher Chapple, MD, of the University of Sheffield in England, said in conclusion.

Chapple reported data from a study involving 435 patients randomized to placebo, tolterodine, or one of three doses of ONO-8539.

Patients were randomized on the basis of findings from a three-day placebo run-in that showed at least eight micturitions per 24-hour period, at least one urgency episode per 24 hours, and at least six urgency episodes during the three-day run-in.

The primary endpoint was the change from baseline to 12 weeks in the number of micturitions per 24 hours. Secondary endpoints included change in urgency episodes per 24 hours, urgency incontinence episodes per 24 hours, and urine volume voided per micturition.

The results showed no significant differences between any dose of ONO-8358 and placebo for any of the outcomes.

"The potential for a clinical role for prostaglandin E2 EP1 receptor antagonism in the management of OAB is minimal in the currently defined OAB patient population," Chapple said during his summary of the results.

The mirabegron study was supported by Astellas Pharma.

Nitti disclosed relationships with Allergan, American Medical Systems, Astellas, Coloplast, Ethicon Women's Health & Urology, Medtronic, Pfizer, Serenity, and Uroplasty.

Investigators in the mirabegron trial included employees of Astellas Pharma.

The ONO-8359 study was supported by Ono Pharmaceutical.

Chapple disclosed relationships with Allergan, Pfizer, Astellas Pharma, Xention, and Ono Pharmaceutical.

Investigators in the trial of ONO-8359 included employees of Ono Pharmaceutical.

Primary source: American Urological Association
Source reference:
Nitti VW, et al "The selective beta-3 adrenoreceptor agonist mirabegron is effective and well tolerated in patients with overactive bladder syndrome" *AUA* 2011; Abstract 1958.

Additional source: American Urological Association
Source reference:
Nitti VW, et al "Mirabegron improves patient-reported outcomes in patients with overactive bladder syndrome -- results from a North American study" *AUA* 2011; Abstract 1959.

Additional source: American Urological Association
Source reference:
Chapple C, et al "A randomized, double-blind, placebo-controlled phase II study to

investigate the efficacy and safety of the EP-1 receptor antagonist ONO-8539 in overactive bladder syndrome" *AUA* 2011; Late-Breaking Science Forum. Presentation No. 7.

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