New agents to treat lower urinary tract and pelvic floor disorders

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Abstract

For patients with overactive bladder and a suboptimal response to antimuscarinic therapy, there are several options to consider including alteration of the antimuscarinic regimen, switching to an agent with an alternate mechanism of action (i.e., mirabegron), posterior tibial nerve stimulation, or botulinum toxin. These options are summarized in this brief review.

For the pharmacologic management of overactive bladder (OAB), current practice is to start with an oral antimuscarinic therapy. While many patients will obtain some benefit from this intervention, many others will not respond adequately. Additionally, the likelihood of patients persisting with this type of therapy is very low. There is a clear need to improve treatment strategies in OAB. This review will discuss some of the options that can be explored, including setting appropriate treatment expectations, altering the antimuscarinic regimen, switching to a medication with a complementary mechanism of action (i.e., mirabegron), neurostimulation, and botulinum toxin.

Antimuscarinic therapy: Strengths and weaknesses

Antimuscarinic medications have consistently demonstrated superiority for OAB symptom improvement compared to placebo in randomized clinical trials.[1,2] The effects include significant reductions in urinary frequency, urgency, nocturia and urge incontinence.[1,2] Despite the demonstrable efficacy, however, a large proportion of patients with OAB never receive a trial of antimuscarinic therapy.[3] For those who do receive treatment, persistence rates are very low—as low as 3.9% at one year in one analysis.[4] Persistence with OAB medication has been found to be lower than for oral antidiabetics, statins, angiotensin receptor blockers, bisphosphonates or prostaglandins.[5] Importantly, most of the discontinuations occur within the first two months of treatment.[5] The most common reasons patients give for discontinuing therapy are that they don't like being on any medications, they don't like taking medications for too long, they learned to get by without medication, the drug didn't work as expected, or side effects were a problem.[6]

Setting treatment expectations

It is important to understand what each patient is expecting to get out of therapy for OAB. Patient research has shown that there are a variety of outcomes patients are looking for from their OAB management, many of which are related to pharmacotherapy, including "less build-up of water," enhancing the perception of feeling younger, having less conspicuous pads and remaining dry.[7] Actively talking about treatment goals and how to achieve them is an essential part of OAB management.

Adjusting antimuscarinic therapy

Research has shown that a strategy based on patient-requested dose increases can help more patients achieve symptom improvement, highlighting the need for individualized therapy decisions.[8,9]

Switching from one antimuscarinic to another may also be effective for some patients. Market research has shown that the majority of patients who have discontinued one antimuscarinic therapy are willing to try another agent.[10] In a study of 441 patients with OAB who switched to open-label solifenacin after inadequate response to tolterodine, the investigators noted significant improvements in urgency, other diary-documented symptoms of OAB, health-related quality of life and perceived bother of OAB.[11]

Mirabegron, an oral beta3-adrenoceptor (AR) agonist, is another option for patients who do not respond adequately to antimuscarinic therapy. In the SCORPIO study, 1978 patients aged 18 years or older with symptoms of OAB for at least three months were randomized to receive placebo, mirabegron 50 mg, mirabegron 100 mg, or tolterodine extended release (ER) 4 mg orally once daily for 12 weeks.[12] In both the co-primary efficacy endpoints—change from baseline to final visit in the mean number of incontinence episodes and micturitions per 24 hours—both mirabegron groups demonstrated statistically significant improvements versus placebo (Fig. 1). There were no significant differences between the mirabegron groups and the tolterodine group or between the tolterodine group and placebo in the primary endpoint analyses. The incidence

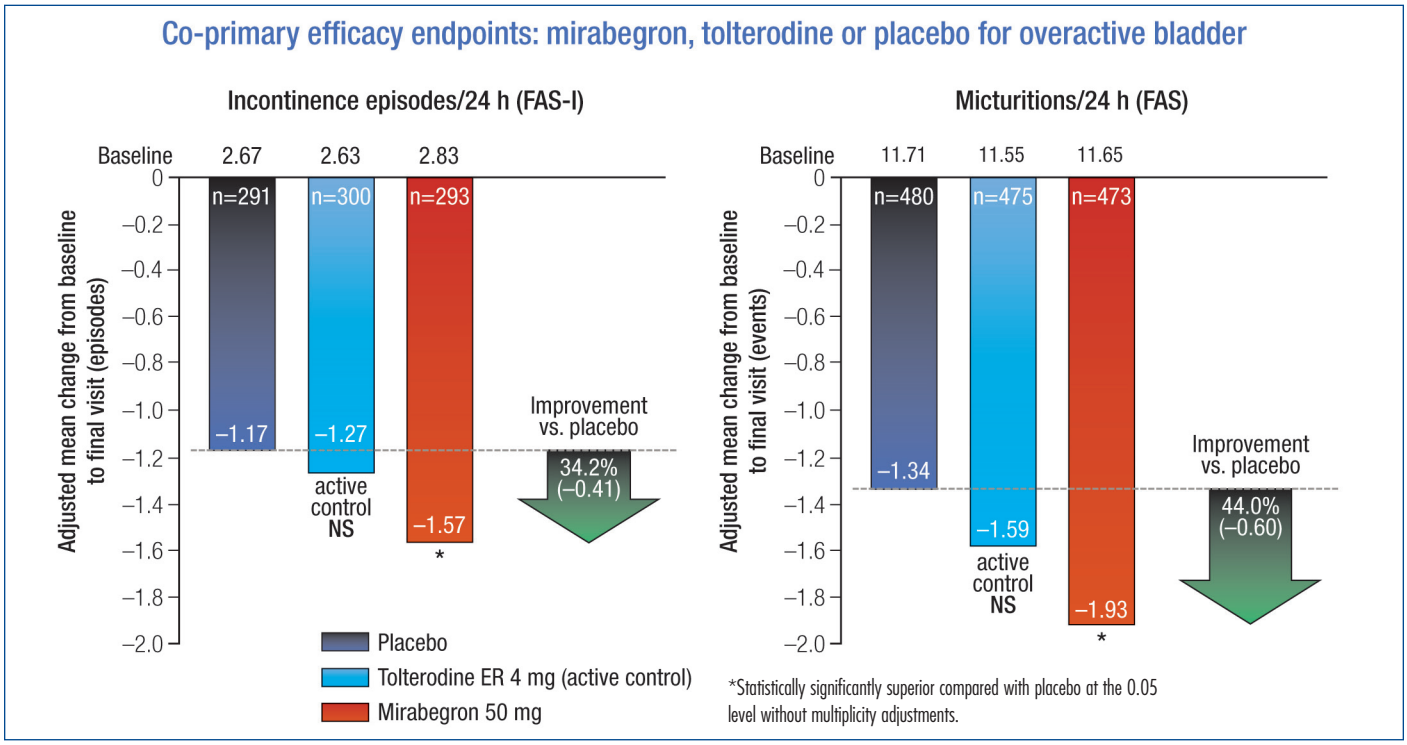

Fig. 1. Co-primary efficacy endpoints: Mirabegron, tolterodine or placebo for overactive bladder.

of treatment-emergent adverse events (TEAEs) was similar across treatment groups.

The efficacy and safety of mirabegron have also been shown in longer-term study. The TAURUS study compared mirabegron 50 mg, mirabegron 100 mg and tolterodine ER 4 mg, each once daily for 12 months.[13] The primary endpoint was TEAEs, with efficacy variables studied as secondary endpoints. With respect to TEAEs, there were no significant differences between treatment groups overall. Dry mouth by 2.8% and 2.3% of the mirabegron 50 mg and 100 mg groups, respectively, and 8.6% of patients in the tolterodine group. Efficacy measures were not significantly different among treatment groups over the one-year period, and efficacy was maintained over that time.

Neurostimulation

If pharmacotherapy fails to provide adequate relief of symptoms, percutaneous tibial nerve stimulation can be considered. In the SUmiT trial, 220 adults with OAB were randomized to 12 weeks of treatment with weekly percutaneous tibial nerve stimulation (PTNS) or sham therapy.[14] In this study, PTNS was associated with significant improvement in bladder symptoms compared to sham; 54.5% of PTNS-treated patients reported moderately or markedly improved responses from baseline, compared to 20.9% of sham subjects.[14]

Botulinum toxin is another option for pharmacotherapy-refractory patients. Clinical trial evidence shows that 200 units of botulinum toxin-A is safe and effective in reducing frequency, urgency and urge incontinence for patients with idiopathic detrusor overactivity with benefits persisting for at least 24 weeks,[15] although the recommended dose is now 100 units for non-neuropathic detrusor overactivity.

Conclusions

There is a need to individualize treatment for patients with OAB to improve short- and long-term adherence. For those who do not initially respond adequately to antimuscarinic medication, dose escalation, switching to another antimuscarinic and switching to a therapy with an alternative mode of action are all options. Should these relatively conservative measures fail, PTNS or botulinum toxin can be considered, as both have demonstrated efficacy in OAB.

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