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Emerging Clarity in the Identification and Treatment of Overactive Bladder in Men

Vienna - Antimuscarinic agents are first-line therapy for overactive bladder (OAB) based on results of multiple controlled studies, but the challenge in men has been differentiating OAB from other forms of lower urinary tract symptoms (LUTS). The interplay between bladder and prostate and the substantial potential of having more than one source of LUTS has complicated efforts to identify rational first steps in therapy. However, greater clarity has been produced by a consensus being built around very specifically defined symptoms that allow clinicians to create a logical order of treatment options. Of the vast array of questionnaires and objective tools for measuring urinary function, a hierarchy of diagnostic steps is emerging that increases the likelihood of matching the underlying pathophysiology with the appropriate treatment in the shortest period of time. In some cases, the correct therapy is reached by combining rather than by choosing between agents with different mechanisms of action.

The underlying causes of lower urinary tract symptoms (LUTS), as well as their presentation, are often so heterogeneous that there is a tendency to select a first-line treatment by patient profile and hope for a response. With this approach, older males are generally assumed to have an enlarged prostate and therefore receive an alpha-1 adrenoceptor blocker (AAR), while females of the same age are assumed to have bladder-related overactivity and therefore receive an antimuscarinic agent. Guidelines, including those issued by the EAU, are attempting to introduce a rational plan that provides patients with faster symptom relief.

"It is critical that men with LUTS receive the treatment that is appropriate for the underlying pathophysiology. Unfortunately, this is not always the case. In particular, men with overactive bladder (OAB) often receive drug treatments that target the prostate even though [clinician] adherence to management guidelines will help make treatment choices more appropriate," stated Dr. Piotr Radziszewski, Deputy Chair, Department of Urology, Medical University of Warsaw, Poland. While the guidelines provide algorithms with which to consider the diagnostic tests that will reveal the causes of LUTS, the major criterion for considering OAB is the predominance of storage symptoms.

Differential Diagnosis of Storage and Voiding Symptoms

Some of the most characteristic storage symptoms are urgency, nocturia, increased daytime voiding frequency and urinary incontinence. The key voiding symptoms are slow stream, straining, hesitancy, intermittency and terminal dribble. These are not mutually exclusive, and patients with predominant OAB may still report voiding symptoms. In addition, neither of these symptom sets rules out the potential for urinary tract infection (UTI) or other diagnoses, including malignancy, but it does streamline care when diagnostic studies have made conditions other than OAB and prostate enlargement unlikely.

In LUTS, one potential reason for using an AAR without first confirming that the symptoms primarily affect voiding is the perception that these are better tolerated than antimuscarinic agents.

Evolution in Antimuscarinic Therapy

While extended-release (ER) tolterodine has widely replaced oxybutynin because of the convenience of less frequent dosing and better tolerability, the newer antimuscarinic solifenacin appears to offer comparable safety with better efficacy. "It is very important that we define the most effective and well-tolerated antimuscarinic agent because, although these drugs are our mainstay against OAB, we do not want to introduce new difficulties for our patients when attempting to control their urinary symptoms," remarked Dr. Matthias Oelke, Vice Chair, Department of Urology, Hanover Medical School, Germany. "Fortunately, we have seen some progress toward finding agents with a very good benefit:risk profile."

The clinical evidence now appears to favour solifenacin over ER tolterodine. The key study STAR (Solifenacin OD and Tolterodine ER 4 mg OD as an Active comparator in a Randomised trial) (Chapple et al. *Eur Urol* 2005;48:464-70) has been followed by several trials that have substantiated high rates of symptom relief accompanied by low rates of significant adverse effects. In the prospective, double-blind STAR, 1177 patients were randomized to once-daily solifenacin 5 mg or tolterodine ER 4 mg. After 4 weeks, patients were permitted to request a dose increase for better symptom control. Those in the solifenacin group received 10 mg q.d. while there was a dummy increase in the tolterodine group because higher doses are not licensed.

At the end of 12 weeks, solifenacin was associated with greater efficacy on a broad array of measures, including fewer episodes of urgency, urgency incontinence, incontinence of any kind, less pad use and increasing volume per micturition.

A dose increase was requested by 48% of solifenacinated patients vs. 51% of those treated with tolterodine. While only 15% of this study population was male, the efficacy results were similar across both genders. As observed in other trials with antimuscarinic agents, the most common adverse events were dry mouth, constipation and blurred vision, but the severity and rates of adverse events were low and similar in the 2 groups. Unlike experience with oxybutynin, for which rates of moderate to severe side effects can exceed 20%, even the incidence of mild dry mouth, the most common side effect, did not exceed 18% with either agent. When safety data were pooled for solifenacinated, so that data included the slightly higher adverse event rates on the higher dose, severe dry mouth was reported in 1.7% and 1.5% of the solifenacinated and tolterodine groups, respectively. Severe constipation occurred in <0.5% of both groups. There were no reports of severe blurred vision in either group.

"Due to the availability of relatively well-tolerated, once-daily antimuscarinic agents, there is a greater opportunity to provide a very large increase in quality of life in patients with OAB," Dr. Oelke maintained. He indicated that this further emphasizes the importance of using antimuscarinic agents as first-line therapy whenever the symptom profile supports a diagnosis of OAB over other causes of LUTS.

SUNRISE Findings

A subsequent multicentre, double-blind trial demonstrated a similar efficacy and safety profile when solifenacinated was compared to placebo. In the 16-week SUNRISE (Solifenacinated in the treatment of UrgeNey symptoms of OAB in a RISing dose, randomized, placebo-controlled, double-blind, Efficacy trial), 863 patients with OAB symptoms for at least 3 months were randomized to receive solifenacinated 5 mg or placebo (Cardozo et al. *BJU Int* 2008;102:1120-7). Again, patients were permitted to ask for a dose increase at the end of 8 weeks if dissatisfied with symptom control. Those in the active-treatment group received 10 mg and placebo patients received a dummy dose increase. On the primary outcome of change from baseline in the number of episodes of severe urgency/24 hours, there was a highly significant advantage

for mean reduction (-2.6 vs. -1.8; $P<0.001$). Moreover, the difference between treatments on this outcome had reached statistical significance within 3 days. At 8 weeks, 46.5% of actively-treated patients vs. 65.8% of placebo patients requested a dose increase.

Most important in regard to encouraging first-line use of an antimuscarinic agent in patients with OAB symptoms, the therapy was well tolerated. When the 2 arms were compared for adverse events of any degree of severity, dry mouth (15.8% vs. 2.7%; $P<0.001$) and constipation (6.9% vs. 2.2%; $P=0.012$) were significantly more common, but almost all of these events were mild in both groups. Blurred vision did not differ significantly (0.8% vs. 0.9%), and there was no significant difference in the discontinuation rate for adverse events (3.6% vs. 2.7%). Again, adverse-event comparison data were pooled from both solifenacinated doses. Fewer events were observed on the lower 5-mg dose.

"One of the advantages of having a once-daily, well-tolerated therapy is that you increase the likelihood of compliance and therefore increase the likelihood of a satisfactory outcome," Dr. Oelke observed. He suggested that a well-tolerated therapy could be particularly critical in the older patients most susceptible to OAB because of concomitant medical issues.

Summary

In patients with LUTS, clinicians should administer an adequate array of examinations to rule out acute problems like UTI and chronic problems such as prostate enlargement. A reasonable battery of tests includes urine analysis, digital rectal examination, prostate-specific antigen levels and a urinary frequency chart. In patients without another explanation for LUTS and a predominance of storage symptoms, the first-line therapy is an antimuscarinic agent in both men and women. In men who remain symptomatic, adding rather than substituting an AAR is appropriate because of the frequency of co-existing pathology. For the same reason, the addition of an antimuscarinic may be appropriate in patients started on an AAR. Once-daily, well-tolerated antimuscarinic agents can facilitate this approach. □

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