The efficacy and safety of mirabegron relative to onabotulinumtoxinA in patients with overactive bladder not appropriately managed with an antimuscarinic: A network meta-analysis

Greta Lozano-Ortega1, Katherine Gooch2, David Walker3, Basia Rogula1, Alison Deighton1, Karissa Johnston1, Roger Dmochowski3

1Broadstreet Health Economics & Outcomes Research, Vancouver, BC; 2Medical Affairs, Astellas Pharma Global Development, Inc., Northbrook, IL; 3Urologic Surgery, Vanderbilt University, Nashville, TN

BACKGROUND

- Overactive bladder (OAB) is a relatively common condition, with symptoms affecting up to 35.6% of men and women ≥40 years of age (1).
- In the treatment of OAB, mirabegron and onabotulinumtoxinA have both been found to be efficacious relative to standard-of-care therapies, although they have not been compared head-to-head.
- Limitations to published network meta-analyses (NMAs) comparing mirabegron to onabotulinumtoxinA include the following:
  - No limits imposed regarding prior treatment experience, which has led to heterogeneous evidence informing the comparison of interest.
  - Mirabegron (and antimuscarinic) studies have been typically conducted in a mixed patient population of treatment-naïve and treatment-experienced patients; and
  - OnabotulinumtoxinA studies have been conducted in treatment-experienced patients only (with longer disease history and greater disease severity).

OBJECTIVE

The objective of this study was to estimate the efficacy and safety of mirabegron relative to onabotulinumtoxinA in the management of patients with OAB who have been previously treated with antimuscarinics.

METHODS

Systematic literature review (SLR) & post-hoc analysis
- SLR was conducted using Medline, EMBASE, Cochrane Library, and PubMed, and was guided by the PICOS criteria presented in Table 1. The review focused on treatments and doses approved in the United States for the management of OAB.
- For a study to be included in the SLR, at least 60% of the study participants were required to have previously received pharmacotherapy for the management of their OAB, or have results reported for the subgroup of treatment-experienced patients.
- For mirabegron studies, individual patient data were available, and a post-hoc analysis of the treatment-experienced subgroup was conducted for those studies that failed to meet the minimum inclusion criterion of 80% treatment-experienced patients, and this evidence was considered in the NMA.

Feasibility assessment
- A feasibility assessment was conducted to determine which study endpoints could be included in the NMA based on availability. Criteria included:
  - Evidence of a network that connected mirabegron to onabotulinumtoxinA.
  - Consistency in the evidence base with respect to study patient population; and
  - Consistency in endpoint definitions.

NMA
- Treatments with sufficient evidence for inclusion in the NMA included:
  - Mirabegron (25 and 50 mg/day);
  - OnabotulinumtoxinA (100U);
  - Solifenacin (5 and 10 mg/day);
  - Oxybutynin chloride (10 mg/day);
  - Tolfedine extended release (ER) (4 mg/day); and
  - Placebo (oral, injection, and mix [i.e. oral + injection]).
- The base case network differentiated between placebo injection, placebo oral, and placebo mix to test for differences in placebo response.
- For endpoints where there was no strong evidence noted for different placebo responses, a sensitivity analysis (SA) was conducted, where placebo was pooled into a common placebo, simplifying the network and reducing the number of parameters being estimated.

RESULTS

SLR & post-hoc analyses (Figure 1)
- In total, 19 studies described in 21 publications were included in the NMA; ten studies assessed mirabegron and six studies assessed onabotulinumtoxinA. No study directly compared mirabegron with onabotulinumtoxinA.
- Fifteen eligible publications describing results from 13 studies among treatment-experienced patients were identified in the SLR.
- Six mirabegron studies originally excluded from the SLR were included in the NMA via sensitivity analyses (Figure 1). The proportion of patients who were ≥65 years of age varied between the two treatment groups; ranging from 17.1% to 100.0% in mirabotulinumtoxinA arm studies compared to 42.6% to 53.1% in onabotulinumtoxinA arm studies.
- Type of OAB (i.e., urge urinary incontinence, frequency and mixed) was not reported across onabotulinumtoxinA studies. Across mirabegron studies, urge urinary incontinence was the most common OAB type reported, making up to 53.3% to 61.8% of OAB patients.

NMA (Figure 2)
- Efficacy:
  - OnabotulinumtoxinA was weakly associated with superior efficacy relative to mirabegron (50 mg) reducing the number of micturitions in a 24-hour period (-0.43; credible interval [CI]: -1.22, 0.37). No evidence of differing placebo responses was identified, therefore a SA was conducted where a common placebo was assumed in the network (OR = 0.64; CI: 0.37, 1.08).
  - OnabotulinumtoxinA was weakly associated with better efficacy at reducing the number of incontinence episodes (-0.46; CI: -1.46, 0.53). There was evidence of differing placebo responses across placebo for this endpoint, therefore a SA assuming a common placebo was not conducted.
  - Mirabegron was estimated to be similarly efficacious to onabotulinumtoxinA at reducing nocturia episodes (0.03; CI: 0.00, 0.06). No evidence of differing placebo responses was identified, therefore a SA was conducted where a common placebo was assumed in the network (OR = 0.95; CI: 0.23, 0.35).
- Safety:
  - OnabotulinumtoxinA was associated with greater odds of UTI relative to mirabegron 50 mg (OR = 2.27; CI: 0.87, 5.81). No evidence of differing placebo responses was identified, therefore a SA was conducted where a common placebo was assumed in the network (OR = 3.10; CI: 1.61, 5.88).
  - There was insufficient evidence to establish relative safety for all other outcomes.
- Urinary retention was sufficiently reported across included studies. Between 6 and 16 cases reported urinary retention across onabotulinumtoxinA studies. However, none of these patients treated with mirabegron experienced the outcome, the OR could not be estimated.

Figure 1: Network meta-analysis network structure

Figure 2: Summary of efficacy and safety results for mirabegron 50 mg compared with onabotulinumtoxinA

Efficacy endpoint
- Mean (95% CrI)
  - Total micturitions per 24 hours
    - -0.43 (1.22, 0.37)
  - Total micturitions per 24 hours, SA pooled placebo
    - -0.81 (-1.01, -0.62)
  - Incontinence episodes per 24 hours
    - -0.45 (-1.48, 0.53)
  - Nocturia episodes per 24 hours
    - 0.03 (-0.30, 0.38)
  - Nocturia episodes per 24 hours, SA pooled placebo
    - -0.65 (-2.03, 0.13)

Safety endpoint
- Urinary tract infection
  - OR (95% CrI)
    - 2.27 (0.87, 5.81)
  - Urinary tract infection, SA pooled placebo
    - 3.10 (1.61, 5.88)
  - Treatment-emergent adverse events
    - 1.62 (0.50, 5.43)

LIMITATIONS

- Post-hoc analysis of mirabegron studies on treatment-experienced patients had the potential to affect study randomization.
- Thorough checks were conducted to compare estimates of treatment effect based on the full population study to estimates based on the subset of treatment-experienced patients.
- Overall, estimates aligned with those reported in the original studies, suggesting that no major impacts to randomization effects were present.
- As with all NMAs, this NMA is subject to risk of bias by including evidence from studies with low quality.
- However, the quality of the available evidence was assessed using the framework of the GRADE Working Group, and all identified studies were determined to be of moderate or high quality.

CONCLUSIONS

- In a treatment-experienced OAB population, relative to mirabegron, onabotulinumtoxinA is more efficacious at reducing the number of daily micturitions, with an estimated 54 fewer micturitions per 24 hours.
- OnabotulinumtoxinA is also associated with a three-fold greater odds of UTIs compared to mirabegron.
- Urinary retention was identified as a safety outcome in onabotulinumtoxinA studies; however, due to statistical limitations, relative safety for this endpoint between onabotulinumtoxinA and mirabegron could not be quantified.
- This study contributes to the body of evidence regarding treatment for OAB.
- This is the first study known to focus on a treatment-experienced patient population, to investigate relative safety between onabotulinumtoxinA and mirabegron 50 mg, as well as the first study to address placebo differences.

Table 1: Scope of the literature review

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult individuals diagnosed with OAB (defined as symptomatic overactive bladder, or idiopathic urgency incontinence, or non-neurogenic urge urinary incontinence, or refractory detrusor overactivity, associated with lower urinary tract dysfunction) who have received at least one prior OAB pharmacotherapy intervention:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions/Comparators</td>
<td>Antimuscarinics: o Darifenacin (7.5, 15 mg) o Pioglitazone (4, 8 mg) o Oxybutynin (10 mg) o Oxybutynin chloride (100 mg; syrup: 5 mg; tablet: 5, 10, 15 mg) o Solifenacin (5, 10 mg) o Tolfedine extended release (4 mg/day); and o Placebo (oral, injection, and mix [i.e. oral + injection])</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Mean change from baseline in the number of:</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Number and proportion of patients experiencing:</td>
</tr>
<tr>
<td>Safety</td>
<td>High blood pressure or urgency</td>
</tr>
<tr>
<td>Adverse event-related treatment discontinuations</td>
<td></td>
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<tr>
<td>Treatment-emergent adverse events</td>
<td></td>
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</tbody>
</table>

Study Design Randomized controlled studies


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