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TITLE PAGE

Title: Relative Efficacy of Tegaserod in a Systematic Review and Network Meta-analysis of Licensed Therapies for Irritable Bowel Syndrome with Constipation.

Short Title: Efficacy of Tegaserod in a Network Meta-analysis of Treatments for IBS-C.

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Abbreviations:

AE	adverse events
FDA	Food and Drug Administration
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
RCT	randomized controlled trial
RR	relative risk

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INTRODUCTION

Irritable bowel syndrome is a chronic functional bowel disorder affecting 1 in 10 people, and associated with poor psychological health, reduced quality of life, and increased health care expenditure. [1] The etiology is complex and incompletely understood. [2] Approximately one-third of patients have IBS with constipation (IBS-C), [1] for which there are licensed therapies available in the USA. We summarized comparative efficacy of these in a recent network meta-analysis of randomized controlled trials (RCTs). [3] Tegaserod, a 5-hydroxytryptamine-4 receptor agonist, approved by the Food and Drug Administration (FDA) for IBS-C, was withdrawn in 2007 following a small excess number of cerebrovascular and cardiovascular ischemic events in patients taking the drug. [4] However, since our network meta-analysis, it has been re-introduced in the USA. It is therefore important to understand its efficacy relative to other available licensed therapies for IBS-C.

METHODS

The methodology is as in our previous network meta-analysis, [3] updated with three 12-week phase III RCTs (trials 301, 351, and 358) of tegaserod, [5-7] containing 2472 female patients with IBS-C. Data from these trials provided evidence to the FDA Gastrointestinal Drugs Advisory Committee, [8] leading to the decision to reintroduce the drug. Briefly, we performed a network meta-analysis using the frequentist model, with the statistical package "netmeta" (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 3.4.2), to explore indirect treatment comparisons of efficacy and safety of each medication.

We used a relative risk (RR) of failure to achieve the FDA-recommended endpoint for efficacy in patients with IBS-C (≥30% improvement in abdominal pain and an increase of ≥1 complete spontaneous bowel movement/week from baseline for ≥50% of weeks). We ranked treatments according to their P-score, which is a value between 0 and 1, based on the point estimates and standard errors of the network estimates. P-scores measure the extent of certainty that one treatment is better than another, averaged over all competing treatments.

The 12-week trials of linaclotide, plecanatide, and tenapanor adhered to the FDA-recommended endpoint for patients with IBS-C. The RCTs of lubiprostone applied these criteria retrospectively to a subset of patients in two phase III studies. For tegaserod, *post hoc* analyses using a similar endpoint (≥30% improvement in abdominal pain/discomfort, with an increase of ≥1 bowel movement/week from baseline for ≥50% of weeks) were presented to the FDA in 2018. [8] We also extracted overall numbers of adverse events (AEs), AEs leading to study withdrawal, and individual AEs.

RESULTS

There were 14 trials providing data for failure to achieve the endpoint of interest. [3, 5-7] There were 9113 patients randomized; 4992 received active treatment. When data were pooled there was low statistical heterogeneity (I^2 = 35.5%). All treatments were significantly more effective than placebo, but linaclotide 290mcg o.d. was ranked most effective (P-score 0.89), in three RCTs (RR 0.81; 95% CI 0.76-0.86) (Figure 1). This means that the probability of linaclotide

being the most effective when all treatments, including placebo, were compared with each other was 89%. Tegaserod 6mg b.i.d. was ranked third (RR 0.85; 95% CI 0.80-0.91, P-score 0.59). Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages (Supplementary Table 1).

Linaclotide 290mcg o.d., linaclotide 500mcg o.d., and plecanatide 3mg o.d. were associated with a significant increase in overall AEs, compared with placebo. Tegaserod 6mg b.i.d., linaclotide 290mcg o.d., plecanatide 6mg o.d., and plecanatide 3mg o.d. were associated with significantly higher trial dropouts due to AEs, compared with placebo, with plecanatide 3mg o.d. the worst (P-score 0.08). There were no significant differences between any active therapy and placebo for abdominal pain or headache. Diarrhea was more likely with all treatments, except lubiprostone 8mcg b.i.d, but was less likely with tegaserod 6mg b.i.d. than tenapanor 50mg b.i.d. or linaclotide 250mcg o.d., 290mcg o.d., or 500mcg o.d. Finally, only lubiprostone 8mcg b.i.d was significantly associated with nausea.

DISCUSSION

Including data from three RCTs of tegaserod in this network meta-analysis did not change the original rankings of linaclotide 290mcg o.d. or tenapanor 50mg b.i.d., which remained first and second for efficacy. Although all drugs were superior to placebo, none were superior to each other. We may have overestimated efficacy of tegaserod, as the endpoint to define treatment response was not as rigorous as in the other RCTs. Tegaserod appeared as safe as other drugs for IBS-C, in terms of

adverse events collected in these trials. However, it has been reintroduced only for use in women under 65 years with no prior history of cardiovascular disease, and with only one risk factor for future cardiovascular disease.

FIGURE LEGENDS

Figure 1. Forest Plot of the Indirect Evidence for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

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