Childhood constipation: new insights in testing, treatment and cost

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Tegaserod use in Children: a Single Center Experience

Chapter 7

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ABSTRACT

Background
Tegaserod is increasingly prescribed by pediatric gastroenterologists although there are few published data concerning its use in children.

Aim
To describe the experience of using tegaserod in children.

Methods
Patients treated with tegaserod from 2004 to 2006 were included in this study. Defecation and fecal incontinence frequency, and global assessment of relief of symptoms were assessed.

Results
Seventy-two children (44 girls) ranging from 1.1 to 18.3 years constitute the subject of this report. The median age was 10 years and the median follow-up after initiation of tegaserod was 11.3 months (range, 2.3 - 45.2 months). Indications to prescribe tegaserod were constipation (58%) and a variety of other conditions including functional dyspepsia or IBS (42%). Defecation frequency increased after tegaserod use (1 vs. 7/wk, p<0.001) and presence of fecal incontinence decreased (47% vs. 23%, p<0.001) in the constipation group. Parents rated relief of constipation as moderate or significant in 71% of children in the constipation group. In the group with other indications to start tegaserod, moderate or significant relief for abdominal pain and bloating was noted in 64% and 68% of the patients, respectively. The dose of tegaserod prescribed was 0.22 (range, 0.05-0.87) mg/kg/day. Adverse events were observed in 32% of the patients. The most common side effects were self-limiting diarrhea (20%) and abdominal pain (8%). Only one patient discontinued tegaserod because of side effects; this patient experienced pain at his cecostomy site.

Conclusion
Tegaserod seems to relieve a variety of functional gastrointestinal symptoms in children. Further randomized, controlled studies are needed to support the specific pediatric target of prescribing tegaserod.
INTRODUCTION

Constipation is a common reason for parents and their children to seek medical advice. It accounts for 3-5% of visits to pediatricians and 10-25% of referrals to pediatric gastroenterologists. Systemic review of the literature shows a prevalence of constipation ranging from 0.7% to 29.6% both in Western and non-Western countries. Only a small minority of children have an organic etiology for constipation which directs specific therapy. Treatment of childhood constipation is largely based on clinical experience rather than on evidence based controlled clinical trials. Stool softeners and cathartics in combination with behavioral modifications represent the most used treatment programs to facilitate painless and frequent defecation. However, long-term management is needed in most children and approximately 30% of children beyond puberty continue to struggle with symptoms of constipation, such as infrequent painful stools with fecal incontinence.

Advances in our understanding of the gastrointestinal nervous system have led to the development of new classes of pharmaceutical agents. The central role of serotonin in modulating motility, visceral perception, and intraluminal secretion in the gastrointestinal tract makes the serotonergic system an important therapeutic target. Tegaserod (5-hydroxytryptamine; 5-HT) is a selective serotonin receptor agonist that acts at 5-HT4 receptors in the gut wall. It increases stool frequency, improves stool consistency, stimulates the peristaltic reflex and intestinal secretions and inhibits visceral sensitivity. It also has prokinetic properties in the upper and lower gastrointestinal tract in both male and female. To our knowledge, so far there has only been one study published in adolescents with constipation predominant irritable bowel syndrome and one abstract reporting the experience on the use of tegaserod in four children with severe chronic constipation. The purpose of this study is to report our 2.5-year experience related to the use of tegaserod in children.

MATERIALS AND METHODS

Patient population

This was a retrospective, open-label study. Eligible patients were children evaluated in the Division of Pediatric Gastroenterology at Columbus Children’s Hospital who had been taking tegaserod between January 2004 and June 2006. Some of the patients who were using tegaserod in Jan 2004 had started taking it as early May 2002. They were identified using the pharmacy inpatient and outpatient records and by polling all Division members and their nurses. Pediatric Rome criteria were not used.
due to the retrospective nature of our study. Instead, diagnoses were established by reviewing the patients’ charts and their gastroenterologist’s primary diagnosis.

Clinical outcome
Pre-treatment data were obtained by chart review. Indication to start tegaserod, defecation pattern, number of medications, dose changes and co-morbidities were noted.
Outcome measures were obtained by interviewing parents of the study patients by phone to determine (1) post treatment symptoms of constipation, bloating/distention and/or abdominal pain/discomfort, (2) defecation pattern, (3) medication side effects, (4) tegaserod dose, and (5) discontinuation of tegaserod and reason. Efficacy was assessed by asking the parents if they felt that taking tegaserod had led to symptom relief of constipation, abdominal pain and bloating. Possible answers were: significant, moderate, mild or no relief. The questions were asked by an interviewer who had not had previous contact with the patient. 
This study was approved by the Institutional Review Board of Columbus Children’s Hospital.

Statistical analysis of the data was conducted using the statistical software package SPSS (version 14.0; Inc, Chicago, IL). The results are expressed as median or as a percentage. For comparison between groups, the Mann-Whitney U nonparametric test was used for quantitative variables, and the chi square test was used for categorical variables. A p-value < 0.05 was considered significant.

RESULTS
Patient population
We identified a total of 89 children who used tegaserod during the study period. Follow-up data of 72 children (81%) were collected; 16 parents could not be reached and one parent refused to participate to our survey. The group with complete follow-up data consisted of 28 boys (39%) and 44 girls (61%) with a median age at initiation of tegaserod of 10 (range, 1.1-18.3) years and a median duration of symptoms before the use of tegaserod of 5.3 (range, 0.1-15.6) years. The median follow up time after initiation of tegaserod use at the time of interview was 11.3 (range, 2.3 - 45.2) months. Indications to start tegaserod were constipation (n=42, 58%) and other reasons (n=30, 42%). Some of the patients who had other main indications to start the medication also had constipation. In order to describe our patient population in more detail, we have arbitrarily divided the patients in those
with only a functional disorder and those with “other conditions” (patients with an underlying organic disease) with the understanding that the latter group might have had functional disorders as well (Figure 1). The study children had tried an average of 2.7 medications before tegaserod was added to their treatment regimen. Nine children had a cecostomy for administration of antegrade enemas and 10 children received feedings through a G- or G/J- tube.

**FIGURE 1. Indications to start tegaserod**

**Clinical outcome**

Table 1 presents baseline characteristics and clinical outcome before and after the start of tegaserod in children with constipation and children with other indications. As expected, the defecation frequency was lower in the constipated group than in the other group (1/wk vs. 7/wk, p=0.02) and increased significantly after tegaserod use (1/wk vs. 7/wk, p<0.001). The number of patients with fecal incontinence decreased significantly during treatment (47% vs. 23%, p<0.001) in the group with constipation. Baseline data on defecation frequency and fecal incontinence were missing in 3 patients in the constipation group and 12 of the group with other indications.

Parents rated global assessment score of relief of constipation after tegaserod use as moderate or significant in 71% of the constipated group and 69% in the other group. Relief of abdominal pain and bloating symptoms after tegaserod were both rated as
moderate or significant in 64% of all cases in the constipated group. In the other group, moderate or significant relief for abdominal pain and bloating symptoms was seen in 64% and 68% of the patients, respectively.

When patients with only functional disorders were compared to patients with other conditions, we found no significant difference in defecation frequency in the children with constipation (1/wk and 3/wk). After tegaserod use, the frequency in both groups increased significantly to 7/wk (p=0.03 vs. p<0.01). The effect of tegaserod on constipation symptoms was moderate or significant in 67% in the patients with
functional symptoms only vs. 77% in the other group. Relief of bloating was found to be moderate or significant in 67% and 69% and relief of abdominal pain was found to be moderate or significant in 69% and 56% in the group with only functional symptoms and the other group, respectively.

Dose
The median dose of tegaserod used was 0.22 mg kg\(^{-1}\) day\(^{-1}\) (range 0.05–0.87 mg kg\(^{-1}\) day\(^{-1}\)). Dose adjustments occurred in 40% of the 55 children who took tegaserod for >6 months (n = 55). The dose was increased in 19 patients because of lack or loss of efficacy and decreased in 3 patients because of diarrhea, abdominal pain, and insurance issues. One child used tegaserod on an as-needed basis and 1 patient used it every other day.

Adverse events
Adverse events were observed in 32% of the study population. They consisted of mild and self-limiting diarrhea (20%), abdominal pain (8%) and headache (4%). Of the children with functional gastrointestinal disorders 38% experienced side effects compared to 23% of the children with other diseases. Overall, 19% of the patients had stopped taking tegaserod at the time of phone interview, six in the constipated group and another eight in the other group (Table 2). Poor therapeutic response was the main reason in 11.1% followed by no longer need for the medication because of symptoms resolution in 4.2% of all cases. Only one patient discontinued using tegaserod because of side effects. This patient experienced pain at the cecostomy site when receiving the medication.

<table>
<thead>
<tr>
<th>TABLE 2. Reasons to discontinue tegaserod</th>
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<tr>
<td>Reason to discontinue tegaserod</td>
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<tr>
<td>Constipated group</td>
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<tr>
<td>n = 4 Poor response</td>
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<tr>
<td>n = 1 Not longer needed</td>
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<tr>
<td>n = 1 Not able to afford it</td>
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<tr>
<td>Other group</td>
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<tr>
<td>n = 4 Poor response</td>
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<tr>
<td>n = 2 Not longer needed</td>
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<tr>
<td>n = 1 Side effect</td>
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<td>n = 1 Non compliant</td>
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DISCUSSION

In this retrospective study describing our 2.5 years of experience with tegaserod in children, no serious side effects were noted. The side effects found were mild and transient in most cases, with none needing medical treatment. Only 1 child stopped using tegaserod because of cramping at the cecostomy site. The global assessment scores for constipation, abdominal pain, and bloating were considered to be moderately or significantly improved in the majority of children. Bowel movement frequency increased significantly and the number of children with fecal incontinence decreased after treatment. No differences were found in the response to the medicine or in side effects between the children with just functional disorders and those with other underlying conditions. These outcomes are in agreement with the data that have been collected in adult studies throughout the last few years. 9-11

In our study, we used tegaserod doses varying from 0.05 to 0.87 mg kg\(^{-1}\) day\(^{-1}\), with a median dose of 0.22 mg kg\(^{-1}\) day\(^{-1}\), indicating that the effective dose of tegaserod may range widely among patients. At the time of the study, tegaserod was available in tablets of 2 mg or 6 mg and could easily be divided in half, making doses as small as 1 mg possible. No suspensions were available, but stability and compatibility tests of tegaserod from crushed tablets mixed in various beverages and foods showed that tegaserod was stable in and compatible with water and apple juice. 12

The limitations of this study are those inherent to retrospective and open-label studies in which data are collected in a clinical context. Some parents were interviewed months or even years after the start or discontinuation of tegaserod. Most children used multiple medicines, some of which were started at the same time as tegaserod, making it challenging to attribute the improvement solely to tegaserod. However, our data are encouraging considering that we were treating a highly selected group of patients who had tried several other medications before resorting to the use of tegaserod.

Marketing of tegaserod was suspended in March 2007 after retrospective analysis of data from clinical studies showed a statistically significant difference in cardiovascular ischemic events in adult patients taking tegaserod compared with those receiving placebo (incidence of 0.11% vs 0.01%, respectively). The Food and Drug Administration (FDA) has indicated to the manufacturer its willingness to consider limited reintroduction of tegaserod in the future after further investigation.

The risk of development of ischemic colitis or a noxious effect on cardiac parameters were concerns that led to close scrutiny of tegaserod when first introduced to the market in view of the previous experience with alosetron and cisapride. Alosetron, a 5-HT\(_3\) antagonist, used for severe diarrhea-predominant IBS in women was withdrawn the same year it was introduced in 2000, after systematic review of the published data
and cases reported to the FDA indicated that the risk of ischemic colitis associated with alosetron was significantly higher than with placebo. Some of these cases lead to death. Public pressure and the design of a careful postmarketing surveillance strategy led the FDA to re-approve use of alosetron under severe restrictions in 2002. Until now, no convincing mechanism has been proposed to explain the associated relationship between ischemic colitis and alosetron. Rare cases of ischemic colitis possibly associated with tegaserod use were also reported after the initiation of marketing of the medication. However, no valid mechanism for tegaserod-associated ischemic colitis has been ascertained and after careful review it remains questionable whether these cases were directly attributable to tegaserod or due to an interaction with other medical conditions or concomitant medications. There also seems to be an increased risk for colon ischemia in patients with IBS, irrespective of the use of serotonergic agents. There were no known cases of ischemic colitis in patients receiving tegaserod within the tegaserod trial program that includes more than 14,000 treated adults. The FDA did however update the precautions section of the approved labeling of tegaserod to alert for tegaserod-associated ischemic colitis. We did not encounter any case of rectal bleeding or colitis in our study.

Changes in cardiac parameters represent another subject of interest after approval and subsequent restricted licensing of cisapride, a nonselective 5-HT4 receptor agonist, which was withdrawn from general use because of its propensity to prolong the QT-interval. This effect is thought not to be related to the 5-HT4 receptors but to be associated with blockage of the potassium channel. Tegaserod is not structurally related to cisapride and both in vitro studies and analysis of electrocardiographic data from 2,516 patients with IBS and 36 healthy adults showed that tegaserod did not influence electrocardiographic parameters.

The recently found increased cardiovascular ischemic events led to the withdrawal of all marketing activities of tegaserod. These events occurred primarily in adults patients who had pre-existing cardiovascular disease and/or cardiovascular risk factors. The proposed mechanism is that the moderate affinity tegaserod for the 5-HT1 receptor might cause constriction of the coronary arteries resulting in cardiovascular ischemic events, an effect that could be more pronounced in atherosclerotic vessels. Pre-clinical studies, however, showed a low potency and very low contractile activity of tegaserod at 5-HT1D receptors and even an antagonist activity at 5-HT1B receptors. It can be argued that even the slightest risk of such serious adverse events does not outweigh the benefit for disorders that are not lethal. One should not underestimate the considerable morbidity that accompanies childhood gastrointestinal motility problems and defecatory disorders, conditions which cause physical and emotional distress and are associated with significant decrease in quality of life. Most children described in this report had tried several other available therapies and found
substantial benefit from use of tegaserod. In many cases, using tegaserod was the last treatment attempt before resorting to placement of a colostomy, a cecostomy, or tube feedings.

In summary, in this study we found that tegaserod contributed to the relief of a variety of functional gastrointestinal symptoms, such as constipation, abdominal pain and bloating in children with a heterogenous group of severe gastrointestinal symptoms. Tegaserod may represent an adjuvant or an alternative option to treat various gastrointestinal symptoms in a selective group of children who continue to be symptomatic despite use of more traditional medical and behavioral interventions.
REFERENCE LIST


