SAFETY AND EFFICACY OF TEGASEROD THERAPY IN PATIENTS WITH IRRITABLE BOWEL SYNDROME OR CHRONIC CONSTIPATION

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ABSTRACT

Background
Tegaserod, a 5-HT4 agonist, is effective for treating irritable bowel syndrome and chronic constipation. However, sales of this drug were recently suspended due to concerns about a higher rate of cardiovascular events in patients receiving tegaserod over placebo in clinical trials. Our aim was to review patients in our practice prescribed tegaserod to determine if any of them had suffered a cardiovascular event or other significant adverse effects while on this therapy. Additionally, we attempted to determine the efficacy of tegaserod in clinical practice.

Methods
Patients with irritable bowel syndrome or chronic constipation in our practice prescribed tegaserod were identified through a search of billing codes and charts reviews. These patients were contacted and questioned about symptoms of cardiovascular events or other adverse events while on tegaserod. The efficacy of this drug was determined by a symptom scale during and after stopping tegaserod.

Results
Sufficient data for analysis was retrieved for 51 of 67 patients prescribed tegaserod. Of these, 37 patients (72.5%) experience no adverse events and 14 patients (27.4%) experienced at least one adverse event, including 6 patients (11.8%) with major adverse events (2 patients (3.9%) with atypical chest pain; 4 patients (7.8%) with syncope; and 2 patients (3.9%) who died. One patient died from advanced pancreatic cancer. The other, who had multiple cardiovascular risk factors as well as a previous myocardial infarction, suffered a cardiac arrest 2 days postoperatively following a below knee amputation, and had actually been off tegaserod for 7 days after hospital admission. Patients graded the severity of both abdominal pain and constipation as worse after stopping therapy compared to during therapy ($p<0.0002$ and $p<0.0001$, respectively).

Conclusions
The risk of cardiovascular events during tegaserod therapy may be increased in patients with other risk factors. However, this drug is effective for treating irritable bowel syndrome and chronic constipation, and might be used in a select patient population with severe symptoms but without other risk factors for cardiovascular events.

Key Words: *Tegaserod, irritable bowel syndrome, chronic constipation*

Irritable bowel syndrome (IBS) is characterized by chronic abdominal pain and altered bowel habits, and is the most commonly diagnosed gastrointestinal condition. The prevalence of IBS in population-based studies ranges from 10 to 15 percent.[1-7] IBS affects men and women of all age groups, although young women are most likely to receive this diagnosis.[3] IBS counts for a significant number of primary care visits and is an important cause of worker absenteeism.[8] The etiology of IBS, although not fully understood, involves abnormal perception of visceral activity

as well as psychological factors.[9-11] IBS is subclassified into groups based on the predominant symptoms: constipation-predominant IBS (IBS-C), diarrhea-predominant IBS, and IBS with alternating constipation and diarrhea.[12]

Chronic constipation (unrelated to IBS) affects between two[13,14] and 27 percent[15] of western populations. It is more common in women than men[16] and older compared to younger adults.[17] Lack of physical activity, low income, limited education, prior history of sexual abuse, and depression are all associated with constipation, although the etiology is often multifactorial in an individual patient.[18] There is no single definition of constipation. Most patients define constipation to be one or more symptoms: hard stools, infrequent stools (typically fewer then three per week), the need for excessive straining, a sense of incomplete bowel evacuation, and excessive time spent on the toilet on in unsuccessful defecation.[19-21]

Tegaserod is a 5-HT_4 agonist which acts in the enteric nervous system of the gastrointestinal tract. It stimulates gastrointestinal motility and the peristaltic reflex, providing a rationale for its use in constipation-predominant IBS.[22] In randomized clinical trials it was shown to be beneficial for global relief of symptoms in patients with IBS-C as well as improving bowel habits in patients with chronic constipation.[22-24] Tegaserod was approved for use in the United States for patients with IBS-C and chronic constipation but it was voluntarily withdrawn from the market by Novartis in March 2007 because of concerns about cardiovascular toxicity. An analysis of data collected on over 18000 patients demonstrated adverse cardiovascular events in 13 of 11,614 patients treated with tegaserod (a rate of 0.11%) compared with 1 of 7,031 patients treated with placebo (a rate of 0.01%).[25] In July 2007, the Food and Drug administration (FDA) approved the reintroduction of tegaserod under a restricted access program for women under 55 years of age without cardiovascular disease who have severe IBS or chronic constipation symptoms.[26] The goal of this study was to review patients in our practice prescribed tegaserod to determine if any of them had suffered a cardiovascular event or other significant adverse effects while on this therapy. Additionally, we attempted to determine the perceived efficacy of tegaserod in our clinical practice.

PATIENTS AND METHODS

Study Design

We sought to determine all patients with IBS-C or chronic constipation prescribed tegaserod in our shared practice of three gastroenterologists. Diagnostic codes 564 (spastic colon, irritable colon, mucous colitis, constipation) and 787 (abdominal pain) in the Ontario Health Insurance Plan were searched from June 2006 to June 2007. Outpatient charts of these patients were reviewed to confirm the diagnosis of IBS-C or chronic constipation as determined by the treating physician. This project was not undertaken as a research protocol, but rather as a quality assurance project to ensure appropriate treatment and follow-up of patients who had potentially suffered a serious adverse event while on tegaserod therapy. All identified patients were contacted by phone and questioned about symptoms of cardiovascular events (cardiogenic syncope, transient ischemic attack (TIA), cerebrovascular accident (CVA), myocardial infarction (MI), angina, and cardiac death) or other adverse events while on tegaserod.

Patients who potentially had suffered a significant event were seen urgently in the clinic for assessment, with appropriate diagnostic workup and management as necessary. The efficacy of tegaserod therapy was determined retrospectively by a symptom scale scored from 0 to 10 during and after stopping tegaserod, with abdominal pain and constipation being scored separately.

Statistical Analysis

The main focus of the survey was to assess the safety of tegaserod therapy in our clinical practice. Descriptive statistics were used to summarize safety data. In addition, we looked at perceived efficacy based upon symptoms following withdrawal of tegaserod. The mean symptom scores and 95% confidence intervals for abdominal pain and constipation were calculated using a paired T test and compared while on tegaserod and after stopping therapy. A two tailed p-value <0.05 was considered statistically significant.

RESULTS

Of 67 patients prescribed tegaserod, 51 were analyzed (figure 1). Eighteen patients had at least one risk factor for cardiovascular disease (tables 1 and 2). Forty-six of 51 (90%) patients had discontinued tegaserod therapy at the time of contact (table 3). Adverse events associated with tegaserod were relatively common; although, severe events were less frequent (table 4).

FIG. 1 Study Population

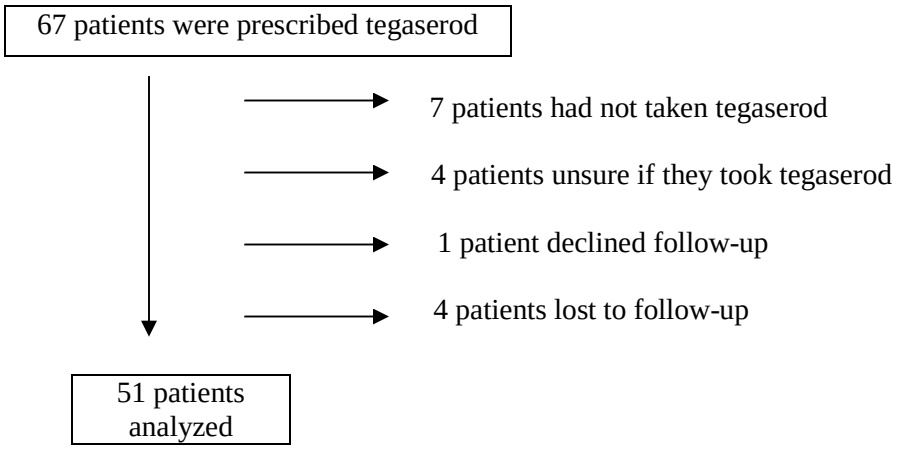

TABLE 1 Demographic Features

Number of patients	51
Sex (M/F)	6/ 45
Mean age, years (range)	47.4 (21-89)
Symptoms being treated	
- Constipation, n (%)	43 (84)
- Abdominal pain, n (%)	41 (80)
Mean duration of tegaserod therapy, weeks (range)*	39.1 (1-240)

* 2 patients were unsure of treatment duration

TABLE 2 Risk Factors for Cardiovascular Disease **(N= 51)**

Age >65 years, n (%)	7 (13.7)
Diabetes mellitus, n (%)	4 (7.8)
Hypertension, n (%)	10 (19.6)
Smoker or ex-smoker, n (%)	21(41)
Dyslipidemia, n (%)	8 (15.7)
Past history of cardiac disease, n (%)	1 (1.9)
Significant family history of cardiac disease, n (%)*	7 (13.7)

* First degree female relative <60 years or male relative <55years

TABLE 3 Reasons for Discontinuing Tegaserod Therapy

Reason, n (%)	**Number of patients (N=49)**
Ineffectiveness	17 (34.7)
Recall from the office	6 (12.2)
Recall from the pharmacy	14 (28.6)
Adverse event	8 (16.3)
Cost	1 (2)

TABLE 4 Adverse Events	**(N=52)**
Adverse events, n (%)	14 (27.4)
Minor adverse events, n (%)	8 (15.7)
-Diarrhea, n (%)	6 (11.8)
-Abdominal pain, n (%)	1 (1.9)
-Allergy, n (%)	1 (1.9)
Major adverse events, n (%)	6 (11.8)
-Syncope, n (%)	4 (7.8)
-Chest pain, n (%)*	2 (3.9)
-Death, n (%)	2 (3.9)

* 2 patients had both chest pain and syncope

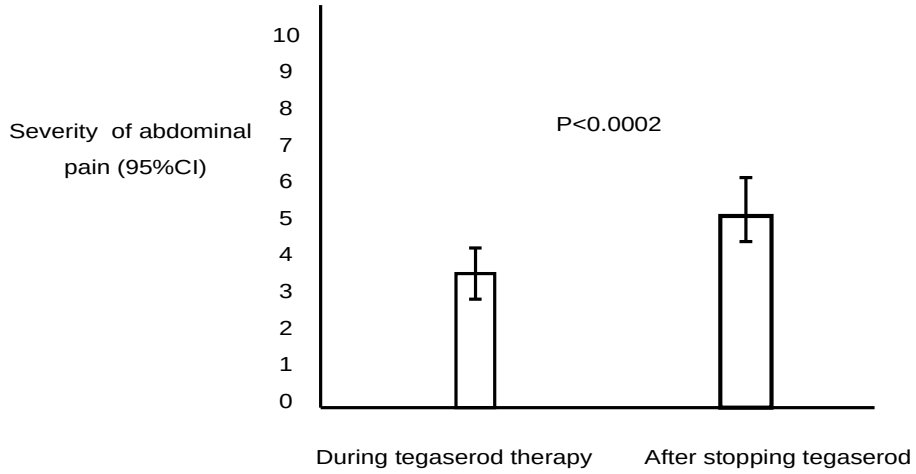

Figure 2 : Severity of abdominal pain during and after stopping tegaserod therapy

Six patients (11.8%) were found to have had at least one major adverse event during tegaserod therapy, including 2 deaths (3.9%). One death was due to advanced pancreatic cancer. The other patient, who had a history of coronary artery disease, diabetes mellitus, hypertension, smoking, and end stage renal failure on dialysis, died suddenly 2 days post-op below knee amputation. The tegaserod had been held for 8 days pre-operatively. Neither death was attributed directly

to tegaserod, as the half-life of this drug is only 11 hours. Four patients (7.8%) developed syncope, 3 of them after starting tegaserod therapy. Of these patients, 2 (3.9%) had chest pain as well. Investigations into the chest pain and syncope were reviewed and did not identify any cardiovascular pathology, although one patient was lost to follow-up. Symptoms related to IBS-C or chronic constipation were worse after stopping tegaserod therapy compared to during treatment (figures 2 and 3). The mean abdominal pain score increased from 3.5 to 5.2 ($p<0.0002$) while the mean constipation score increased from 3.7 to 6.3 ($p<0.0001$) after discontinuation of tegaserod.

DISCUSSION

In our practice, we found tegaserod to be safe and effective in the treatment of IBS-C and chronic constipation. Patients' symptoms were better controlled on tegaserod therapy than after discontinuation, consistent with what has been reported in the literature. A Cochrane review found tegaserod to be effective for achieving global relief of symptoms in patients with IBS-C and for achieving complete spontaneous bowel movements in patients with IBS-C.[24]

In our study 6 of 51 patients (12%) had a major adverse event, including 2 who died. However, neither death was directly attributed to tegaserod therapy. The other patients who could be assessed were investigated and no pathology was identified.

Several studies have assessed the safety of tegaserod therapy in patients with IBS-C and chronic constipation.[24,27-32] A Similar rate of adverse events (headache, diarrhea and ischemic colitis) were reported from phase 3 clinical trials and post-marketing studies.[33] The cardiac safety of tegaserod was demonstrated by the analysis of over 10000 electrocardiograms taken from tegaserod users in clinical trials.[34] In randomized clinical trials, tegaserod therapy did not demonstrate significant prolongation of the QT interval or cardiac arrhythmias.[29] A data base of 2603 patients on therapy matched to 15618 untreated patients were followed for an average of 2.5 years. Cardiovascular event rates were low and similar in both groups.[30] However, this medication was voluntarily withdrawn from the market by Novartis because of concerns about cardiovascular toxicity. An analysis of data collected on over 18000 patients demonstrated adverse cardiovascular events in 13 of 11,614 patients (0.11%) treated with tegaserod compared with 1 of 7,031 patients (0.01%) placebo-treated patients.[25] However, more recently, the Food and Drug administration (FDA) allowed the reintroduction of tegaserod for women less55years of age without cardiovascular disease for the treatment of severe IBS-C or chronic constipation symptoms.[26]

There are several limitations to our study. It was performed as a quality assurance project rather than a formal research protocol. As such, it was retrospective and had a small sample size. The diagnosis of IBS-C or chronic constipation was as per the treating gastroenterologist rather than based on formal criteria. We used an unvalidated retrospective scoring system to determine the effectiveness of tegaserod for symptom relief.

In conclusion, a number of potentially serious adverse events were identified, but none were clearly linked to the use of tegaserod. Following withdrawal of the medication patient symptoms for IBS or chronic constipation deteriorated. Given that IBS-C and chronic constipation can be quite disabling for patients suffering from these disorders, we agree with the FDA that tegaserod should be available to a select patient population with severe symptoms but without other risk factors for cardiovascular events.

Acknowledgements

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