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Systematic review: incidence of abdominal/pelvic surgery amongst patients using tegaserod in randomized controlled trials

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SUMMARY

Background: In the USA, tegaserod is contraindicated in patients with a history of bowel obstruction, abdominal adhesions or symptomatic gall-bladder disease due to a non-significant difference in abdominal surgery between tegaserod-using and placebo-using patients in Phase III trials.

Aim: To calculate the incidence of abdominal and pelvic surgery in tegaserod-using and placebo-using patients in randomized controlled trials and to assess the possible association between medication and surgery, using pre-specified criteria in a blind adjudication procedure.

Methods: Primary study selection criteria included: (i) randomized controlled trial; (ii) comparison of tegaserod vs. placebo; and (iii) results reporting the incidence of abdominal and pelvic surgery. A panel of experts in epidemiology and functional bowel disorders reviewed the history of each patient who underwent surgery. Experts were blind with regard to whether patients used tegaserod or placebo. Using pre-specified criteria, experts rated the likelihood of an association between medication use and surgery.

Results: Thirteen randomized controlled trials ($n = 9857$ patients) met the primary study selection criteria. No significant difference in the incidence of abdominal/pelvic surgery was identified between tegaserod-using and placebo-using patients: pelvic surgery, 0.16% vs. 0.19% ($P = 0.80$); abdominal surgery (non-cholecystectomy), 0.15% vs. 0.19% ($P = 0.61$); cholecystectomy, 0.13% vs. 0.03% ($P = 0.17$); total abdominal/pelvic surgery, 0.44% vs. 0.41% ($P = 1.00$). Post-adjudication, there was no significant difference in the incidence of abdominal/pelvic surgery between tegaserod-using and placebo-using patients.

Conclusion: Data from randomized controlled trials demonstrate a similar incidence of abdominal/pelvic surgery in tegaserod-using and placebo-using patients.

INTRODUCTION

Tegaserod is a selective partial agonist of serotonin 5-HT4 receptors.[1] The drug exerts motor stimulatory effects in the gastrointestinal tract, resulting in enhanced propulsion in several gut regions.[2] Tegaserod also affects visceral afferent function, blunting the somatic reflex to colonic distension.[3] Because of these effects on colonic motor and sensory function, tegaserod is indicated for the treatment of irritable bowel syndrome with constipation in women. Multiple, randomized controlled trials have demonstrated that tegaserod is effective for women with this disorder.[4–10] These randomized controlled trials have demonstrated that tegaserod improves global irritable bowel syndrome symptoms and individual symptoms of abdominal discomfort, bloating and constipation. Studies in

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patients with chronic constipation have demonstrated that tegaserod increases stool frequency and improves stool consistency, bloating and tenesmus.[11, 12] Tegaserod has been studied in functional dyspepsia patients in Phase II randomized controlled trials,[13–16] and the efficacy of tegaserod in these patients is currently in Phase III development.

In the USA, the prescribing information for tegaserod notes that, in Phase III randomized controlled trials of irritable bowel syndrome patients with constipation,[4–6, 17] 'an increase in abdominal surgeries was observed on tegaserod (9/2965; 0.3%) vs. placebo (3/1740; 0.2%). The increase was primarily due to a numerical imbalance in cholecystectomies reported in patients treated with tegaserod (5/2965; 0.17%) vs. placebo (1/1740; 0.06%).' Subsequently, the US Food and Drug Administration specified in the prescribing information that tegaserod is contraindicated in patients with 'a history of bowel obstruction, symptomatic gallbladder disease, suspected Sphincter of Oddi dysfunction or abdominal adhesions'.

It is unclear whether this numerical imbalance in abdominal/pelvic surgery represents a clinically important finding. Irritable bowel syndrome patients are more likely to undergo abdominal/pelvic surgery compared with healthy controls:[18] irritable bowel syndrome patients are twice as likely to undergo cholecystectomy, 1.5 times more likely to undergo hysterectomy and four times more likely to undergo appendectomy.[18] Overall, over 60% of irritable bowel syndrome patients will undergo abdominal/pelvic surgery[18] with the potential formation of abdominal adhesions. Therefore, studies on the incidence of bowel obstruction due to abdominal adhesions in tegaserod-using patients may clarify the data forming the foundation for this contraindication.

The objective of this study was to systematically review randomized controlled trials comparing tegaserod vs. placebo in patients with functional gastrointestinal disorders and to calculate the incidence of abdominal/pelvic surgery. In order to assess the possible association between medication use and surgery, experts in epidemiology and functional gastrointestinal disorders completed a blind adjudication procedure using prespecified criteria. After the elimination of surgical cases that were probably or definitely not related to medication use, post-adjudication incidence rates of abdominal/pelvic surgery were calculated. With these data, the suitability of current contraindications may be more precisely defined.

METHODS

Literature search and study selection criteria

A search of the Medline database from 1995 to 2003 was performed using multiple combinations of the following medical subject heading terms: 'colonic diseases, functional'; 'surgery'; 'complications'; 'clinical trial'; 'tegaserod'. A review of the EMBASE database from 1995 to 2003 was performed by combining the term 'tegaserod' with 'clinical trial'. To access the published literature not yet included in the Medline database, Current Contents/Science Edition was searched between 2002 and 2003 combining the keywords 'tegaserod' with 'clinical trial'. A recursive search of the bibliographies of selected studies was also performed to identify pertinent papers.

The published literature was inadequate for complete data extraction, and so Novartis Pharmaceuticals Corporation provided unpublished study reports. Novartis Pharmaceuticals Corporation also provided documents submitted to the US Food and Drug Administration, including clinical summaries of abdominal or pelvic surgery cases.

The primary selection criteria for inclusion in this systematic review were: (i) randomized controlled trial; (ii) comparison of tegaserod vs. placebo; and (iii) results reporting the incidence of abdominal/pelvic surgery.

Adjudication procedure

All interventions requiring an opening of the peritoneal cavity were considered as abdominal or pelvic surgery, including abdominal wall surgery and all gynaecological and urinary bladder surgery, but excluding tubal ligation and surgery of the prostate. Surgery was only considered if it occurred after the first dose of the study medication, irrespective of whether it was elective or reported as a serious adverse event.

Criteria for assessing the association between medication use and surgery (Table 1) were established prior to the adjudication procedure. Five categories of association were established: definitely related; probably related; possibly related; probably not related; and definitely not related. Guidelines to categorize the association between medication use and surgery were established prior to the adjudication procedure (Table 2). Each surgical case was presented in a blind fashion (i.e. the experts did not know whether tegaserod or placebo had been administered in each case).

Table 1. Criteria for assessing the association between study medication use and surgery

1	Were symptoms prompting surgery present before the patient entered the study?
2	Was the surgical diagnosis present before the patient entered the study?
3	Was the patient on therapy (study medication) long enough for the adverse event to be related to therapy?
4	Was the patient off medication too long for the adverse event to be realistically related to the study medication?
5	Was there a realistic competing cause for the adverse event?
6	Was there objective evidence (e.g. pathology, radiographs) to support the surgical diagnosis?
7	Did the symptoms resolve after surgery?
8	Did the symptoms resolve after the therapy was stopped (positive de-challenge)?
9	Did the symptoms return after therapy was re-instituted (positive re-challenge)?

These criteria are guides to determine whether surgery was 'definitely related', 'probably related', 'possibly related', 'probably not related' or 'definitely not related'. Ultimately, experts utilized their judgement and clinical expertise to assess the data from a case and to decide whether the use of study medication was associated with surgery.

Table 2. Category of association between medication and surgery

Definitely related
Exposure and sequence are correct. Symptoms develop after patient starts medication; surgery performed after patient starts medication; patient on study medication long enough for surgery to be related to study medication; surgery performed during study medication use or shortly after discontinuation of study medication
Positive de-challenge: symptoms resolve with withdrawal of study medication
Positive re-challenge: symptoms return with re-institution of study medication
No obvious competing cause leading to surgery
Objective evidence to support the surgical diagnosis
Probably related
Exposure and sequence are correct
Positive de-challenge
No re-challenge
No obvious competing cause leading to surgery
Objective evidence to support the surgical diagnosis
Possibly related
Exposure and sequence are correct
De-challenge ambiguous or negative
No re-challenge
No obvious competing cause leading to surgery
Objective evidence to support the surgical diagnosis
Probably not related
Exposure and sequence partly correct
Competing cause(s) is more likely cause of surgery
Ambiguous or conflicting evidence to support the surgical diagnosis
De-challenge ambiguous or negative
No re-challenge
Definitely not related
Exposure and sequence are mostly incorrect: symptoms develop before patient starts medication; surgery performed after patient stops medication; surgery scheduled before patient starts medication
Competing cause(s) is more likely cause of surgery
Ambiguous or conflicting evidence to support the surgical diagnosis
De-challenge ambiguous or negative
No re-challenge

A surgical case does not need to fulfil all the criteria in a specific category in order to be classified in that category. The criteria in each category are guides to determine whether surgery is 'definitely related', 'probably related', 'possibly related', 'probably not related' or 'definitely not related'. Experts utilized their judgement and clinical expertise to assess the data from a case and to decide whether the use of study medication was associated with surgery.

Following the presentation of each surgical case, experts asked questions and discussed the case. After completing a checklist of criteria to assess the association between medication use and surgery, each expert voted by secret ballot on the category of association between study medication use and surgery. If all consultants voted 'probably not related' or 'definitely not related' for a specific case, that case was excluded (i.e. no possible association between study medication use and surgery). The blinding code was not broken until the consultants had completed voting.

It is possible that experts might be biased and state that there is no association between medication use and surgery for every case. Therefore, six additional 'dummy' cases were added to the adjudication procedure. These 'dummy' cases were intentionally constructed to suggest an association between medication use and surgery. Experts were not informed about the presence of the 'dummy' cases. If consultants found no association between medication use and surgery in these 'dummy' cases, this would be suggestive of bias.

Data analysis

Pre-adjudication and post-adjudication incidence rates of abdominal/pelvic surgery in randomized controlled trials were calculated. Post-adjudication incidence rates excluded surgical cases that were eliminated during the adjudication procedure. Sub-group analysis provided pre-adjudication and post-adjudication incidence rates for pelvic surgery, abdominal surgery (non-cholecystectomy) and cholecystectomy. Fisher's exact test (two-sided) was used to determine whether there was a statistically significant difference in the incidence of abdominal/pelvic surgery between tegaserod-using and placebo-using patients.

RESULTS

Characteristics of selected studies

Thirteen separate randomized controlled trials satisfied the study selection criteria.[4–17] These data were collected from irritable bowel syndrome trials,[4–10, 17] chronic constipation trials[11, 12] and functional dyspepsia trials.[13–16] All of these studies were double-blind randomized controlled trials with concealed allocation. As a 2 : 1 randomization schedule was utilized in multiple studies, more study patients received tegaserod ($n = 6197$) than placebo ($n = 3660$). In addition, the proportion of female patients was greater than 80% in all randomized controlled trials.

Pre-adjudication incidence of abdominal/pelvic surgery in randomized controlled trials

Table 3 lists the pre-adjudication incidence of abdominal/pelvic surgery for tegaserod-using vs. placebo-using patients. No statistically significant difference in the incidence of abdominal/pelvic surgery was noted. A numerical imbalance in cholecystectomies between

Table 3. Incidence of abdominal/pelvic surgery during Phase III and post-US marketing randomized controlled trials

	Tegaserod ($n = 6197$)	Placebo ($n = 3660$)	P value
Pelvic	10 (0.16%)	7 (0.19%)	0.80
Abdominal (non-cholecystectomy)	9 (0.15%)	7 (0.19%)	0.61
Cholecystectomy	8 (0.13%)	1 (0.03%)	0.17
Total	27 (0.44%)	15 (0.41%)	1.00

Statistical comparison based on Fisher's exact test (two-sided).

Table 4. Post-adjudication incidence of abdominal/pelvic surgery during Phase III and post-US marketing randomized controlled trials

	Tegaserod ($n = 6197$)	Placebo ($n = 3660$)	P value
Pelvic	3 (0.05%)	1 (0.03%)	1.00
Abdominal (non-cholecystectomy)	4 (0.06%)	1 (0.03%)	0.66
Cholecystectomy	4 (0.06%)	1 (0.03%)	0.66
Total	11 (0.18%)	3 (0.08%)	0.28

Statistical comparison based on Fisher's exact test (two-sided).

tegaserod-using and placebo-using patients was noted: 0.13% vs. 0.03% ($P = 0.17$), respectively. In addition, one case of bowel obstruction secondary to abdominal adhesions occurred in a placebo-using patient. No episodes of bowel obstruction secondary to abdominal adhesions were recorded in tegaserod-using patients.

Post-adjudication incidence of abdominal/pelvic surgery in randomized controlled trials

Table 4 lists the post-adjudication incidence of abdominal/pelvic surgery for tegaserod-using vs. placebo-using patients. Sixteen of 27 (59%) surgical cases in tegaserod-using patients were excluded and 12 of 15 (80%) surgical cases in placebo-using patients were excluded because there was no possible association between medication use and surgery. Post-adjudication, the numerical imbalance in the cholecystectomy rates between tegaserod-using and placebo-using patients decreased to 0.06% vs. 0.03% ($P = 0.66$), respectively.

All six 'dummy' cases inserted into the adjudication procedure were classified as study medication 'probably related' or 'possibly related' to surgery by the experts.

Classification of surgical cases excluded during adjudication

Four cholecystectomy cases were excluded from the tegaserod group. Two of these patients were diagnosed with symptomatic cholelithiasis before entry into the study. The other two patients had long histories of right upper quadrant pain with decreased gall-bladder ejection fractions, but no cholelithiasis. Right upper quadrant pain did not improve in these two patients after elective cholecystectomy.

Five abdominal (non-cholecystectomy) cases were excluded from the tegaserod group: laparotomy to remove a benign pancreatic cyst, Nissen fundoplication for the management of gastro-oesophageal reflux disease, appendectomy (two) and elective colectomy for constipation (this elective surgery was scheduled prior to entry into the study). Six abdominal (non-cholecystectomy) cases were excluded from the placebo group: appendectomy, lysis of adhesions for bowel obstruction, inguinal hernia repair (two), abdominal eventration repair and abdominoplasty.

Seven pelvic surgery cases were excluded from the tegaserod group: bilateral salpingo-oophorectomy for ovarian cysts, oophorectomy for ovarian cyst, cone biopsy as part of gynaecological evaluation, exploratory laparoscopy for pelvic pain (two) and hysterectomy for recurrent uterine bleeding (two). Six pelvic surgery cases were excluded from the placebo group: elective tubal ligation, laparotomy for resection of leiomyoma, laparoscopy for lysis of adhesions from endometriosis, hysterectomy for recurrent uterine bleeding, exploratory laparoscopy for pelvic pain and lysis of adhesions and salpingectomy for tubal pregnancy. The majority of excluded surgeries were elective cases that were scheduled prior to entry into the randomized controlled trials, or were emergent surgical cases that occurred after discontinuation of study medication.

DISCUSSION

Irritable bowel syndrome patients are more likely to undergo abdominal/pelvic surgery compared with healthy controls, and the prevalence of abdominal/pelvic surgery is over 60% in irritable bowel syndrome patients.[18] Although tegaserod is contraindicated in patients with a history of bowel obstruction or abdominal adhesions, there was only one case of bowel obstruction secondary to abdominal adhesions in the randomized controlled trials included in this systematic review, and this patient received placebo. This systematic review confirms that there is no significant increase in the incidence of abdominal or pelvic surgery in tegaserod-using vs. placebo-using patients.

Tegaserod is contraindicated in patients with symptomatic gall-bladder disease partly because of the non-significant numerical imbalance in cholecystectomies reported in tegaserod-using vs. placebo-using patients in Phase III randomized controlled trials. The clinical importance of this numerical imbalance is unclear, as the incidence of abdominal (non-cholecystectomy) surgery and pelvic surgery was higher in placebo-using patients. In order to assess the association between tegaserod use and cholecystectomy, the blind adjudication procedure was completed and four cholecystectomies in tegaserod-using patients were excluded. Two cholecystectomy patients had been diagnosed with symptomatic cholelithiasis prior to study entry, and two cholecystectomy patients had long histories of right upper quadrant pain and decreased gall-bladder ejection fractions, but no evidence of cholelithiasis. These patients showed no improvement in right upper quadrant pain after cholecystectomy. The exclusion of these patients in the post-adjudication incidence of

cholecystectomy reduced the numerical imbalance reported in tegaserod-using vs. placebo-using patients: 0.06% vs. 0.03% ($P = 0.66$), respectively.

A randomized, double-blind, placebo-controlled cross-over study was performed in irritable bowel syndrome patients and healthy volunteers to assess the effect of tegaserod on gall-bladder emptying and common bile duct diameter.[19] Three separate cohorts of patients were examined: (i) 12 healthy volunteers who received tegaserod 6 mg b.d. or placebo; (ii) 18 patients with irritable bowel syndrome with constipation who received tegaserod 6 mg b.d. or placebo; and (iii) 18 patients with irritable bowel syndrome with constipation who received tegaserod 12 mg b.d. or placebo. During a 1-week baseline evaluation, healthy volunteers and irritable bowel syndrome patients underwent real-time ultrasonography. Patients were then randomized to receive either tegaserod or placebo for 2 weeks, followed by real-time ultrasonography. Patients subsequently completed a 1-week washout period, followed by a 2-week treatment period with the other treatment. The second treatment period was also followed by real-time ultrasonography. These studies demonstrated no differences in fasting gall-bladder volume, meal-stimulated gall-bladder emptying, luminal diameter of the common hepatic duct and common bile duct or plasma levels of cholecystokinin in tegaserod-using vs. placebo-using patients.

There is no specific evidence to suggest that patients with symptomatic gall-bladder disease or suspected Sphincter of Oddi dysfunction are more likely to suffer complications with tegaserod use compared with placebo. However, these randomized controlled trials did not specifically identify patients with these pre-existing conditions. Therefore, there is no specific evidence on the safety and tolerability of tegaserod in patients with symptomatic gall-bladder disease or suspected Sphincter of Oddi dysfunction. Given these data, it is unclear whether the contraindication for patients with symptomatic gall-bladder disease or suspected Sphincter of Oddi dysfunction is warranted. Interestingly, another review has reported that tegaserod-using and placebo-using patients show a similar incidence of any type of surgery or serious adverse event.[20]

The adjudication procedure utilized in this study sought to minimize bias through several mechanisms: (i) experts were blind with regard to whether patients used tegaserod or placebo; (ii) the criteria to determine the association between study medication use and surgery were objective and were specified prior to the adjudication procedure; (iii) 'dummy' patients were added to ensure that the experts did not perform a biased adjudication (i.e. automatically state that there was no association between the study medication and surgery); and (iv) even if a single expert stated that there was a possible association between study medication use and surgery, that case was included in the post-adjudication calculation of surgery incidence rates. With this adjudication procedure, only cases of abdominal/pelvic surgery that were not associated with study medication were excluded.

This systematic review and adjudication procedure have some limitations. As women comprised over 80% of the study population in the randomized controlled trials, it is unclear whether the results can be generalized to male patients. The trials did not identify prospectively patients with pre-existing surgical disease or pre-existing symptomatic cholelithiasis, which is a confounding factor in our analysis. In addition, the trials did not specifically identify patients with pre-existing episodes of bowel obstruction, previous abdominal/pelvic surgery or symptomatic abdominal adhesions, and the absence of these data may be a confounding factor in our analysis. Nevertheless, only one episode of symptomatic bowel obstruction due to abdominal adhesions was reported, and this adverse event occurred in a placebo-using patient. These 13 randomized controlled trials recorded data on approximately 10 000 patients. Therefore, this sample size may be too small to identify a significant association between tegaserod use and a rare, but serious, adverse event. Post-marketing surveillance studies will further define the safety profile of tegaserod.

In conclusion, the frequency of abdominal/pelvic surgery is numerically similar in tegaserod-using and placebo-using patients in randomized controlled trials. Furthermore, the frequency of cholecystectomy is also numerically similar in tegaserod-using and placebo-using patients in randomized controlled trials. However, these randomized controlled trials did not specifically identify sub-groups of patients with symptomatic gall-bladder disease or suspected Sphincter of Oddi dysfunction, and so the evidence may be inadequate to support or refute the current contraindication for tegaserod use in these patients. As no tegaserod-using patient in these trials needed surgery for bowel obstruction due to abdominal adhesions, there is no evidence in randomized controlled trials to support the current contraindi-

cation to tegaserod use in patients with a history of bowel obstruction or abdominal adhesions.

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