ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (7): 581-588
0114-5916/07/0007-0581/$44.95/0

An Observational Study of Cholecystectomy in Patients Receiving Tegaserod

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Abstract

Background: Registrational studies of patients treated with tegaserod for irritable bowel syndrome (IBS) suggest an increased risk for cholecystectomy versus treatment with placebo.

Objective: To study cholecystectomy rates in association with tegaserod within a large administrative medical claims database.

Methods: Patients were drawn from a large population within the US with commercial medical insurance. The primary analysis consisted of a comparison of the observed incidence rate for cholecystectomy claims among a large cohort of new-to-therapy tegaserod users with an incidence rate published for tegaserod-naive patients classified with IBS within the same insured population.

Results: An inception cohort of 7475 individuals with up to 103 weeks of claims history following initiation of therapy with tegaserod was identified. After a follow-up of 3 months (and thus similar to the longest registrational trials), the observed cholecystectomy incidence rate was 340 per 10 000 person-years (95% CI 258, 442). The rate of cholecystectomy was highest in the earliest months of observation following initiation of tegaserod. The observed cholecystecomy incidence rate is 2.9 times higher than an IBS-specific rate of 119 per 10 000 person-years as published for patients so classified within the same insured population.

Conclusion: Based on a large, inception cohort, we report a strong temporal association between the initiation of tegaserod therapy and an increased rate for cholecystectomy. The effect size at 3 months was similar to the relative risk for cholecystectomy reported in registrational studies comparing tegaserod with placebo. As misclassification of initial diagnosis for patients presenting with biliary colic-like symptoms may occur, precise measurements of tegaserod-related relative risk for cholecystectomy from observational studies are problematic and will require prospective studies.

Background

Tegaserod is a serotonin 5-HT_4 receptor partial agonist initially approved by the US FDA for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. [1] Tegaserod was first marketed in the US in August 2002. For this indication, the recommended dosage of tegaserod is 6mg taken twice daily orally before meals for 4–6 weeks.[1] For those women who respond to therapy at 4–6 weeks, an additional 4- to 6-week course can be considered. Per approved labelling, the efficacy of tegaserod for the treatment of IBS with constipation has not been studied beyond 12 weeks.[1]

IBS with constipation and chronic idiopathic constipation (also a US FDA-approved indication for tegaserod) are both lower gastrointestinal dysmotility disorders. *In vivo* studies show that tegaserod enhances basal motor activity and normalises impaired motility throughout the gastrointestinal tract.[1] Since tegaserod enhances smooth muscle mediation for propulsion in gastrointestinal organs, it is conceivable that this agent may stimulate gallbladder contraction in patients with asymptomatic cholelithiasis leading to biliary colic.

It is noteworthy that premarketing studies for constipation-predominant IBS suggested an increased risk for cholecystectomy with exposure to tegaserod versus placebo.[2] The product label notes that 5 of 2965 (0.17%) patients randomised to tegaserod experienced a cholecystectomy versus 1 of 1740 (0.06%) patients randomised to placebo during phase III IBS clinical trials of 12 weeks' duration.[1] These small numbers result in a relative risk for cholecystectomy with tegaserod versus placebo of 2.9 with a wide 95% CI (0.3, 25).

The purpose of this exploratory, non-controlled, pharmacoepidemiological study was to evaluate any association between tegaserod use and cholecystectomy within a large, administrative database of medical claims accessible via the FDA Cooperative Agreement program.[3]

Methods

This study was based on administrative claims data available for approximately 5 million individuals (calendar year 2001) within 11 geographically diverse health plans within the US with commercial health insurance provided by a large national healthcare company. The age distribution of this population is generally consistent with that of the US population through to age 64 years. Such plans are typically developed using Independent Practice Association models consisting of large networks of clinicians reimbursed on a discounted fee-for-service basis. All commercially insured patients with medical and drug benefits were included in the analyses.

The initial primary analysis consisted of a comparison of the observed, cumulative incidence rate for cholecystectomy among a large cohort of new-to-therapy tegaserod users (a tegaserod inception cohort) after 3 months of follow-up with the incidence rate published for patients classified with IBS within the same insured population.[4] This time frame is similar to the 3-month treatment length employed in the phase III registrational trials of tegaserod. A secondary comparison was made to an age- and sex-specific incidence rate of cholecystectomy for the population at large.[5]

It is important to note that such an analysis cannot directly determine whether there is a causal association between tegaserod and gallstone-induced symptoms. Instead, any putative association inferred from these data might reflect any of several potential effects associated with tegaserod, including (i) the pro-motility attributes of tegaserod (with the effect of inducing biliary colic in patients with asymptomatic cholelithiasis); (ii) misdiagnosis of symptomatic gallstones as IBS leading to treatment with tegaserod; and (iii) empiric treatment of tegaserod-resistant abdominal pain unrelated to gallstone disease with a cholecystectomy.

Outpatient pharmacy claims data of commercially insured enrollees within the 11 plans were

1 The study was conducted and the article written prior to the voluntary withdrawal of tegaserod (Zelnorm®) from US and Canadian markets in March 2007 because of concerns regarding its cardiovascular safety profile.

screened from 1 August 2002 to 30 June 2004 for prescriptions for tegaserod. It should be noted that tegaserod (as Zelnorm®)[2] was only FDA approved for the treatment of IBS with constipation during this interval; tegaserod received an additional FDA approval for the treatment of chronic idiopathic constipation in patients aged <65 years in August 2004.

The tegaserod inception cohort was formed by screening administrative records for patients with ≥180 days of continuous enrollment prior to their first tegaserod prescription (index date). Patients with a claim for cancer or HIV within the prior 180-day window through to the end of the follow-up period (31 July 2004) were excluded. Individuals were further excluded if their medical claim indicated a cholecystectomy at any time before the first prescription for tegaserod. So as not to exclude a cholecystectomy that occurred upon initiation of the drug, no minimum follow-up window after initiation of tegaserod therapy was required.

Patients included in the inception cohort were followed from the date of their first prescription claim for tegaserod until they (i) experienced the outcome of interest; (ii) disenrolled from the health plan; or (iii) reached the end of the follow-up period (31 July 2004) without a cholecystectomy event. As a result of a claims lag of approximately 6 months, all claims were screened for the outcome of interest through to February 2005. The inception cohort may have included individuals with a cholecystectomy in the remote past, i.e. prior to the 6-month screening window. Therefore, the observed cholecystectomy rate for this cohort of tegaserod initiators may be an underestimate of the rate expected for a population restricted to an intact gallbladder.

Cholecystectomies were identified based on the appearance of Current Procedure Terminology (CPT) procedure codes 47562–47564 and 47600–47620 or 9th Edition of the International Classification of Diseases (ICD-9) procedure codes 51.21–51.24 from the index date through to the end of the follow-up period (31 July 2004).

Although it was not possible to obtain medical records for a hands-on review of putative cases, cases were validated by a review of medical claims for billable services occurring at the time of the cholecystectomy event. A number of revenue codes indicative of surgery were identified, including operating room services, ambulatory surgical care services, treatment or observation room, anaesthesia, recovery room and all-inclusive. The 'all-inclusive' revenue code indicates that services received by a patient during hospitalisation were bundled rather than billed separately. A putative case was considered a validated case if the patient had at least one of these selected revenue codes.

Medical claims were also screened for the primary treatment diagnoses. A diagnosis was characterised as 'primary' if it was designated as such on any physician or facility claim with the same date of service as the cholecystectomy event.

The primary analysis included comparison of the incidence rate (or incidence density) for cholecystectomy observed for the tegaserod cohort after 3 months of follow-up to a published incidence rate of 119 per 10 000 person-years for patients classified with IBS within this same population, as published by Cole et al.[4] The rate for the comparator group was developed for individuals classified as members of an IBS cohort over the 6-year period from 1 January 1995 to 31 December 2000. This time interval falls immediately prior to the time window for the study reported herein but well after the widespread introduction of laproscopic cholecystectomy in 1991.[4,6]

It should be noted that identical claims data are maintained in the research database utilised for the present study; however, the studies were not identical with respect to specific plans and the precise time frame studied. A secondary comparison to an expected rate of 49 cases per 10 000 person-years observed from female residents of Ontario, Canada, aged 45–64 years, was also utilised.[5] Absolute sex- and age band-specific incidence rates were also calculated.

As already mentioned, this study is based on a follow-up of individuals after a first prescription of tegaserod. Interval-specific incident rates by month

2 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Age- and sex-specific distribution and rates of cholecystectomy (n = 100) among a cohort of 7475 initiators of tegaserod therapy

Parameter	Count (%)	Total initiators in cohort	Rate per 1000 initiators
Sex			
Female	91 (91)	6990	13
Male	9 (9)	485	18.6
Age group (y)			
0–19	5 (5)	195	25.6
20–24	4 (4)	388	10.3
25–29	4 (4)	537	7.5
30–34	9 (9)	745	12.1
35–39	12 (12)	895	13.4
40–44	11 (11)	1185	9.3
45–49	27 (27)	1257	21.5
50–54	12 (12)	1024	11.7
55–59	11 (11)	800	13.8
60–64	5 (5)	449	11.1

were also calculated to describe non-cumulative risk over time for this closed cohort. Estimates of non-cumulative, interval-specific incidence were generated by transformation of observed datapoints through a smoothing model (SAS ProcGPLOT, SAS 8.2 for Windows, SAS Institute, Cary, NC, USA).

Results

Across the 11 geographically dispersed health plans, 7671 commercially insured patients were identified for inclusion into the inception cohort. As individuals who are ≥65 years with commercial health insurance may not be representative of all individuals in this age group, the analysed dataset was restricted to 7475 individuals of age <65 years. The median period of claims history following initiation of therapy with tegaserod was 29 weeks (6.5 months) with a range between 1 day and 103 weeks; total person-time under observation was 4758 years. In total, 6990 (93.5%) members of the cohort were identified as female. With respect to anonymity, records did not include specific ages, only 5-year age bands. Thus, the median value for age fell within the age band 45–49 years. The average number of prescriptions identified for this cohort was 2.2 (median 1), consistent with either very infrequent utilisation of the product or early termination of use in some patients. The average number of dispensed pills per prescription was 138 (median 60).

Based on the procedure codes, 103 putative cholecystectomy cases were identified within this cohort following initiation of therapy with tegaserod. Of these, 100 cases were validated using the revenue code criteria as outlined in the methods section; three potential cases had no revenue codes at the time of their cholecystectomy event and were excluded as cases.

More than half of the 100 incident cholecystectomies (n = 57) were observed with the 3-month period following initiation of tegaserod. Twenty-eight of 100 cholecystectomies were characterised

Table II. Summary of cumulative cholecystectomy incidence rates by month after initial prescription of tegaserod in a cohort of 7475 treated individuals

Months following initiation of tegaserod	No. of patients entering interval	No. of incident cases	Cumulative incidence rate (cases/10 000 patient-years)
1	7475	17	282
2	7182	24	351
3	6531	16	340
4	5887	9	309
5	5279	2	267
6	4658	6	254
7	4081	4	242
8	3583	4	234
9	3198	1	221
10	2741	5	223
11	2259	2	218
12	1824	4	221
13	1476	2	220
14	1179	1	218
15	986	0	214
16	804	0	211
17	651	1	211
18	530	0	209
19	407	0	208
20	308	0	207
21	231	1	209
22	148	1	210
23	72	0	210
24	19	0	210
25	0		
Total		**100**	

as inpatient events and 72 were billed as hospital outpatient or ambulatory surgery. Seventy-three cases indicated a primary diagnosis of cholelithiasis.

The age- and sex-specific distribution and (absolute) incidence of cholecystectomy (per 1000 initiators) is shown in table I. Although 91 (91%) of the cases were women, the sex-specific incidence was slightly higher for men (18.6 per 1000 initiators) than women (13 per 1000 initiators). This difference is not statistically significant at the p = 0.05 level. Although the case counts generally increased through age 45–49 years and then decreased, the age-specific incidence appeared to have a bimodal distribution with a peak in the 0- to 19-year-old age group followed by a decrease and a second peak in the 45- to 49-year-old age group. A peak incidence of cholecystectomy in the 45- to 49-year-old age band is consistent with the known age-related peak incidence of cholecystectomy in the general population.[5] However, a separate peak in the age band of 0–19 years is noteworthy given that the age distribution of the population under study is generally representative of the population at large.

Cumulative cholecystectomy incidence rates by month are provided in summary statistics (table II). This table also shows the distribution of individuals within the cohort by length of follow-up (in months). The cumulative rate was highest between the first and second month following the initial tegaserod prescription, peaking at 351 per 10 000 person-years (month 2). Thereafter, the cumulative incidence rate declines, stabilising at 210 per 10 000 person-years (95% CI 171, 254) through 23 months of follow-up. After follow-up of 3 months, the observed cholecystecomy incidence rate was 340 per 10 000 person-years (95% CI 258, 442). This rate is 2.9 times higher than an IBS-specific rate of 119 per 10 000 person-years as published for patients so classified within the same insured population. As an incidence ratio (340/119 = 2.9), it is similar to the point estimate for the relative risk versus placebo previously seen in the registrational studies. An increased risk of a tegaserod-associated cholecystectomy in individuals with asymptomatic cholelithiasis is also suggested by a comparison of the observed cumulative incidence rates to an age- and sex-specific background rate of 49 per 10 000 person-years (incidence ratio = 7 after 3 months and 4.3 after 23 months).

A heightened risk for cholecystectomy was also seen in the non-cumulative, interval-specific incidence rate as modelled in figure 1 and generated by transformation of observed data through a smoothing function for the 18 months following initiation of tegaserod. The rise and subsequent decrease in risk early after the initiation of treatment is consistent with an association between tegaserod and cholecystectomy.

Discussion

The observed cholecystecomy incidence rate after 3 months of therapy within an inception cohort of tegaserod users (340 per 10 000 person-years) was 2.9 times higher than an IBS-specific rate of 119 per 10 000 person-years as published for patients so classified within the same insured population. As an incidence ratio, it is similar to the point estimate for the relative risk versus placebo seen in registrational studies. Although inference from these data is limited, this study provides support for

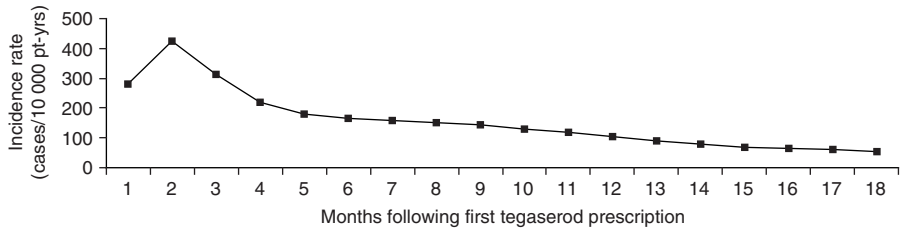

Fig. 1. Trends in the interval-specific incidence rate (based on transformation of observed data through a smoothing model) [as cases/10 000 patient-years] for cholecystectomy through 18 months for a large cohort initiating therapy with tegaserod.

the current labelling suggesting a risk of cholecystectomy in association with tegaserod use.

There are several limitations of our study, most importantly that the analysis is based on a comparison of rates across studies. To this end it is important to note the differences between the tegaserod-recipient inception cohort and the comparison population from which the background rate of cholecystectomy was obtained. As shown in table III, although the two populations had similar age distributions with medium ages falling within the age group of 40–49 years, the tegaserod inception cohort had a higher frequency of females (93.5%) than the frequency of females in the reference population (71.1%). This could lead to an increase in the apparent risk for cholecystectomy within the tegaserod inception cohort since cholecystectomy is more frequent for women than men,[5] although we do not consider the difference sufficiently large enough to explain our results, particularly the strong temporal association between the initiation of tegaserod and the rapid increase in the cholecystectomy rate (figure 1).

As an additional limitation, although the present study attempted to validate putative cases using supporting administrative data, ideally data from primary hospital records would be used to document, through surgical reports, the presence of cholelithiasis, cholecystitis or other pathologic processes of the gallbladder. The presence of cholelithiasis and/or choledocolithiasis in close temporal association with the initiation of therapy with tegaserod would support the hypothesis that the promotility attributes of tegaserod are not limited to the gut but extend to the gallbladder. Medical record confirmation of gallbladder disease or gallstones among many or most of the cases would also help to discount an alternative hypothesis that any increased risk for cholecystectomy from exposure to tegaserod could be attributable to non-gallstone-related abdominal pain refractory to therapy with tegaserod or empirical treatment with cholecystectomy.

Table III. Sex and age distribution of the tegaserod inception cohort and irritable bowel syndrome (IBS) [IBS reference population as described by Cole et al.[4]]

Parameter	Tegaserod inception cohort (n = 7475)	Reference IBS population (n = 108 936)
Sex (female/male) [%]	93.5/6.5	71.1/28.9
Age group (y) [no. (%)]		
0–29	1120 (15.0)	18 715 (17.2)
30–39	1640 (21.9)	27 010 (24.8)
40–49	2442 (32.7)	30 851 (28.3)
50–65+	2273 (30.4)	32 360 (29.7)

Study of the association between a cholecystectomy and tegaserod provides some unique methodological considerations. First, although phase III clinical trials of tegaserod for IBS consisted of daily dosing for 12 weeks, IBS symptomatology typically waxes and wanes. As has been reported, up to 30% of patients with an IBS diagnosis will have symptoms that resolve over the course of a year[7] or evolve into symptoms of a related or overlapping functional motility disorder.[8] This may contribute to the high placebo response rate observed in clinical trials.[9] Indeed, since stress has been reported[10] to predict both the use of healthcare and the persistence of symptoms among patients with IBS, identification of stressors, including potential dietary stressors, has been advanced in the clinical management of IBS symptomatology.[11] Importantly, we speculate that, except for the weeks to months following the initial prescription, many patients with IBS in receipt of a prescription for tegaserod will take the drug as needed. Therefore, prescription records indicating timing of the receipt of a prescription for tegaserod may not reflect actual patterns of drug usage by individuals. The observed cumulative incidence rate was elevated early in the course of follow-up for these individuals and declined thereafter. Since drug exposure was generally limited (median number of prescriptions = one; medial number of dispensed pills = 60), it is likely that usage was probably highest following the initial prescription. The elevated cumulative cholecystectomy incidence rate early in the course of observation coupled with a likelihood of increased tegaserod exposure during the early observation period provide additional evidence of a pharmacological drug effect.

Second, it is problematic to construct a suitable control group for that segment of the tegaserod recipient population treated for IBS based solely on administrative records.[12] The study published by Cole et al.[4] used the broad ICD-9 code 564.1 ('irritable colon') as the primary code for assignment to the IBS cohort despite the fact that the IBS classification component of their study confirmed an IBS diagnosis compatible with Rome II criteria in only 39% of records (from a sample of 89 records recovered). There has been considerable effort to enrich the specificity of the broad ICD-9 code 564.1 ('irritable colon') for a robust diagnosis of IBS. Specifically, Sands et al.[13] have recently described their work in the development of sophisticated algorithms to identify validated IBS populations within administrative records. Nonetheless, because of the recurrent/remittent nature of IBS and a durable response rate in placebo arms of 20–50% in some trials,[14,15] Mertz[9] has argued that confirmatory studies relevant to the population with a robust diagnosis of IBS should be randomised, blinded and placebo controlled. As noted by Cole et al.,[4] the 'risk' associated with membership in an IBS cohort assigned via administrative records may relate in part to misclassification of diagnosis. This point has also been advanced by two of the authors with reference to the determination of background rates of ischaemic colitis in patients given a diagnosis of IBS.[12] Furthermore, speculation that patients with a robust diagnosis of IBS are 'at increased risk' for abdominopelvic and gallbladder surgery is contradicted by the rubric that an IBS diagnosis is realised only after a search for identifiable pathology. The non-causal term 'risk-marker' has been used in order to leave open the possibility that such an association may be a non-causal artifact of administrative data.[16]

Conclusion

Within a large inception cohort we have demonstrated that there was an increased rate of cholecystectomy in individuals following an initial prescription for tegaserod compared with a similar cohort classified with IBS. In addition, the rate observed for this cohort was highest during the earliest period of observation consistent with tegaserod-induced symptoms early after the initiation of treatment and when drug exposure in the recipient population is likely to have been highest. Definitive studies to elucidate causation and/or quantification of the relative risk for cholecystectomy in association with tegaserod should include prospective designs but need not be restricted to randomised controlled studies. Given the frequency of cholecystectomy in the human population, it is possible to consider a prospective case-control study of this association in countries with enough tegaserod utilisation for study power.

Acknowledgements

The authors wish to acknowledge the contributions of Parivash Nourjah Ph.D. in the development of a smoothing model for observed data.

Contract grant sponsor: US FDA (contract grant numbers: FD-U-002067-02 and FD-U-002067-03).

The authors have no conflicts of interest that are directly relevant to the content of this study. All authors have taken due care to ensure the integrity of the work. The views expressed are those of the authors and do not necessarily represent those of, nor imply endorsement from, the FDA or the US Government.

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