

Tegaserod for the treatment of irritable bowel syndrome

Evans BW, Clark WK, Moore DJ, Whorwell, PJ

Date of most recent substantive amendment: 05 November 2003

This review should be cited as: Evans BW, Clark WK, Moore DJ, Whorwell, PJ. Tegaserod for the treatment of irritable bowel syndrome (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

ABSTRACT

Background

IBS is a complex disorder that encompasses a wide profile of symptoms. Current drug treatments for irritable bowel syndrome (IBS) are of limited value. Many target specific symptoms only. Tegaserod, a 5HT₄ partial agonist, represents a novel mechanism of action in the treatment of IBS.

Objectives

The objective of this review was to evaluate the efficacy and tolerability of tegaserod for the treatment of IBS in adults and adolescents aged 12 years and above.

Search Strategy

MEDLINE 1966-November 2002 and EMBASE 1980-November 2002 were searched. The text and key words used included "tegaserod", "HTF 919", "irritable bowel", and "colonic diseases, functional". The Cochrane Central Register of Controlled Trials, the Inflammatory Bowel Disease Review Group Specialized Trials Register, and Science Citation Index were also searched. Proceedings from the British Society of Gastroenterology Annual Meeting, and Digestive Disease Week (1998-2002) were hand searched. The manufacturer of tegaserod was contacted. Relevant articles were retrieved, and their reference lists were also reviewed.

Selection Criteria

Randomised or quasi-randomised controlled trials comparing tegaserod with placebo, no treatment or any other intervention (pharmacological or non-pharmacological) in subjects aged 12 years and above with a diagnosis of IBS, focusing on clinical endpoints were considered for review.

Data collection and analysis

Study inclusion and exclusion, data extraction and quality assessment was undertaken by two reviewers independently. Meta-analysis was performed where study populations, designs, outcomes, and statistical reporting allowed

combination of data in a valid way, using the summary statistic relative risk with 95% CI.

Eight short-term placebo-controlled studies fulfilled our inclusion criteria. These were predominantly conducted in women. Seven studies evaluated the efficacy of tegaserod on global gastrointestinal (GI) symptoms in patients with constipation-predominant IBS (C-IBS). One small study evaluated safety in patients with diarrhoea-predominant IBS.

Main Results

The relative risk (RR) of being a responder in terms of global relief of GI symptoms was significantly higher with tegaserod 12 mg (RR 1.19, 95% CI 1.09, 1.29) and tegaserod 4 mg (RR 1.15, 95% CI 1.02, 1.31) compared with placebo, with a number needed to treat (NNT) of 14 and 20 respectively. When all tegaserod doses were combined and compared with placebo (n=4040), the RR of being a responder was 1.17 (95% CI 1.08, 1.27), with a NNT of 17. Although the pooled results indicate statistically significant benefit with tegaserod, the a priori minimal clinically important differences set in two of the four pooled studies were not reached. Tegaserod did not significantly improve the patients' individual symptoms of abdominal pain and discomfort although bowel habit showed a statistically significant improvement with tegaserod 4 mg and there was a non-significant trend in favour of tegaserod 12 mg. When GI symptoms were assessed separately, those indicative of GI motility such as number of bowel movements and days without bowel movements were generally improved with tegaserod although the proportion of patients experiencing diarrhoea was significantly higher in the tegaserod 12 mg group compared with placebo (RR 2.75, 95% CI 1.90, 3.97), with a number needed to harm (NNH) of 20. Effects of tegaserod on GI symptoms such as bloating, stool consistency, and straining were not consistent across the studies.

Reviewers' conclusions

Tegaserod appears to improve the overall symptomatology of IBS but there are currently few data on its effect on quality of life. In addition, more information is needed about its efficacy in men. It would also be of interest to know whether treatment with tegaserod leads either directly, or indirectly, to changes in visceral sensitivity or psychopathology, which are also considered important in the pathophysiology of this condition.

This review should be cited as:

Evans BW, Clark WK, Moore DJ, Whorwell, PJ Tegaserod for the treatment of irritable bowel syndrome (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

BACKGROUND

Irritable bowel syndrome (IBS) is a chronic, relapsing condition (Talley 2002), characterised by the presence of abdominal pain and disturbed bowel habit.

Symptoms of IBS sometimes overlap with other functional gastrointestinal (GI) disorders such as non-ulcer dyspepsia (Jones 2000). Irritable bowel syndrome may also co-exist with organic GI pathology, but whilst many of the symptoms are similar in nature, some occur more commonly in IBS such as easing of pain after bowel movement, looser stools and/or more frequent bowel movements at onset of pain, abdominal distension, and a feeling of incomplete emptying (Farthing 1998).

Although symptoms of the GI tract predominate in IBS, non-GI symptoms are frequent and support the diagnosis. These symptoms include lethargy, poor sleep, backache, urinary frequency, and dyspareunia (Jones 2000). About 40-60% of patients who seek medical advice have evidence of psychopathology (Farthing 1998).

The pattern of symptoms varies between individuals. Many patients have mild symptoms on an intermittent basis, and do not request or require drug treatment. Others can be incapacitated with persistent symptoms and seek medical advice, expecting a permanent cure (Farthing 1998). Difficulty in confirming the diagnosis may lead to increased worry and doubt. A further burden, especially in women, is the risk of unnecessary surgery such as cholecystectomy or hysterectomy, which may aggravate the existing disorder, and cause post-operative complications such as adhesions, and surgery-related changes to bowel habit (Jones 2000).

A variety of factors lead to presentation in patients with IBS. These vary in nature, e.g. from stress to precipitation by infection. Although the cause of IBS is unknown, the following pathophysiological factors have been implicated (Farthing 1995):

disordered motility (small intestine, colon, oesophagus, and stomach), disordered sensation (visceral hypersensitivity), and central nervous system changes e.g. perception.

The diagnosis of IBS is clinically based, relying on history taking, physical examination, and where necessary, exclusion of other GI pathology. Diagnostic criteria (e.g. Manning, Rome I, and Rome II) have been introduced to aid this process, and are widely used for identifying and recruiting patients into clinical studies of interventions for IBS (Camilleri 2001, Hammer 1999). However, they are probably not used so often in clinical practice.

The aims of treatment in IBS are to improve the quality of life of patients, reduce the number of workdays missed through ill health, and to reduce the frequency of physician visits for both GI and non-GI related reasons (Jones 2000). The mainstays of treatment are explanation and reassurance regarding the nature of the condition, together with appropriate lifestyle adjustments such as dietary interventions, review of current medication, and evaluation of factors that precipitate symptoms. Drug therapy may benefit some patients although current treatments have limited value, with specific benefits being seen in a limited proportion of patients. Drug treatment of IBS can be considered in two categories (Farthing 1998): (i) treatment aimed predominantly at the gut, targeting specific dominant symptoms, using bulking agents, motility agents, and antispasmodics; and (ii) centrally acting agents (e.g. antidepressants). Although also used, the site

of action of antidepressants in IBS is not entirely clear.

Stimulation of colonic motility may be of benefit in IBS patients whose predominant symptoms are constipation-related. Tegaserod is a selective partial 5HT₄ agonist that activates peristalsis in the smooth muscle of the GI tract accelerating gut transit. Tegaserod is an oral preparation that has been licensed for use in over 30 countries world-wide including Australia, Canada, Switzerland, the United States of America, and several Latin American countries. Specific licensed indications vary across the countries; in some, the drug is approved for women only, or specifically for those whose predominant symptom is constipation. In the USA, the recommended dose is 6 mg taken twice daily. In the USA, Canada, and South Africa, the trade name is Zelnorm. In other countries the trade name is Zelmac.

OBJECTIVES

The aim of this systematic review was to evaluate the efficacy and tolerability of tegaserod for the treatment of IBS in adults and adolescents aged 12 years and above.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised or quasi-randomised controlled trials comparing tegaserod with placebo, no treatment or any other intervention (pharmacological or non-pharmacological) were included.

Studies were not excluded on the basis of publication status.

Trials were excluded if they were: studies that only administered one dose of tegaserod e.g. healthy volunteer studies; multi-dose studies that were purely pharmacokinetic; non-randomised studies. Additionally, studies conducted in children under the age of 12 years, and studies reporting only non-clinical outcomes were excluded.

Types of participants

Adults and adolescents (both genders) with a diagnosis of irritable bowel syndrome according to any predefined/specified diagnostic criteria (e.g. Manning, Rome I or Rome II).

Types of intervention

Trials were included if one arm of the trial received tegaserod (HTF 919), which was compared with placebo, no treatment or any other intervention (pharmacological or non-pharmacological).

Types of outcome measures

It has been recommended that the primary outcome measure in clinical trials of interventions in IBS should be some form of global assessment (van Zanten 1999). This recommendation has been adopted by the USA and European drug licensing authorities. Secondary outcomes should include a record of symptoms, and quality of life. In this review the outcomes focused on are as follows.

Main outcome measures:

Effect of treatment on

- 1) quality of life, and
- 2) gastrointestinal symptoms, including abdominal pain, distension (bloating), flatulence, bowel disturbance, constipation, diarrhoea, stool frequency, and stool consistency.

Other outcome measures:

- 3) Patient's compliance with treatment,
- 4) Adverse effects, and
- 5) Withdrawal (rebound) effects following discontinuation of treatment.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Cochrane Inflammatory Bowel Disease Group search strategy

The literature search aimed to locate randomised controlled trials.

Electronic searches of the following databases were conducted:

MEDLINE (ovid 1966 to 2002)

EMBASE (ovid 1980 to 2002)

Science Citation Index

The Cochrane Central Register of Controlled Trials (the former Cochrane Controlled Trials Register)

The Cochrane Inflammatory Bowel Disease Review Group Specialized Trials Register

Databases of ongoing trials: Current Controlled Trials (<http://controlled-trials.com/>);

UK - National research register (<http://www.update-software.com/National/>);

USA - National Institutes of Health

(<http://www.clinicaltrials.gov/>); USA - CenterWatch Clinical Trials Listing Service (<http://www.centerwatch.com/>)

The USA Food and Drug Administration (<http://www.fda.gov>)

Search terms used in MEDLINE included the following list of Index terms and text words, which were adapted for use with other databases:

Index terms (MESH): colonic diseases, functional; serotonin agonist\$

Text words: irritable bowel; irritable bowel syndrome; tegaserod; HTF 919; zelmac; zelnorm; 5HT; 5HT4

An RCT filter was applied to the electronic searches. The searches were

limited to humans. No restrictions were applied with regard to language of publication or participants' age. It was our intention to translate trials reported in foreign languages, but none was identified. Electronic searches were stopped on 1st November 2002. Studies identified after this date and which were considered appropriate were still assessed for eligibility - this occurred with Kellow 2003.

Conference proceedings from (1) the British Society of Gastroenterology Annual Meeting (held in March), and (2) the Digestive Disease Week and the annual meeting of the American Gastroenterological Association (held in May) were searched from 1998 to 2002. Further information on unpublished studies and studies published only as abstracts was sought from the manufacturer Novartis. Reference lists from included trials were scanned to identify additional trials.

METHODS OF THE REVIEW

Methods adhered to the guidance laid out in the Cochrane Reviewer's Handbook 4.1.4. Study selection, quality assessment and data extraction were undertaken independently by two reviewers (BWE, WKC). Disagreements were resolved by discussion with referral to a third reviewer if differences could not be resolved (DJM).

Quality assessment considered the four following criteria; selection, performance, attrition, and detection biases (as described in the Cochrane Reviewers' Handbook). Based on these criteria, studies were subdivided into one of three broad categories

- i. Low risk of bias (plausible bias unlikely to seriously alter the results; all quality criteria met)
- ii. Moderate risk of bias (plausible bias that raises some doubt about the results; one or more criteria partly met)
- iii. High risk of bias (plausible bias that seriously weakens confidence in the results; one or more criteria not met)

Data extraction was undertaken using a data extraction form, which collected information on study methods, participants, interventions, outcome measures, and results.

Data synthesis was considered where the study populations, designs, outcomes and statistical reporting allowed combination of data in a valid way. Statistical heterogeneity was explored using the Chi square test with significance set at $p < 0.10$. Provided statistical heterogeneity was not present ($p > 0.10$), the fixed effect model was used for the analyses. If heterogeneity was present, possible sources would be investigated. The summary statistic for dichotomous data was the relative risk (RR), with 95% confidence intervals quoted. The analyses included all randomised participants in the treatment groups to which they had been allocated. Restricted analyses (excluding any unpublished studies, studies published in abstract form, studies enrolling patients using different diagnostic criteria, quasi-randomised studies) were performed where appropriate.

The analyses were conducted using review manager (RevMan) 4.1.4 software.

DESCRIPTION OF STUDIES

A total of eight RCTs, identified from sixteen publications, met our inclusion criteria (Hamling 1998; Lefkowitz 1999a; Lefkowitz 1999b; Muller-Lissner 2001; Fidelholtz 2002; Novick 2002; Kellow 2003; B307). Each of the studies was placebo-controlled. They enrolled a total of 5320 patients. Three studies investigating tegaserod use in patients with IBS were excluded, one non-randomised study, and two RCTs that reported non-clinical outcomes only - refer to the Table of characteristics of excluded studies (Appel-Dingemans 2000; Prather 2000; Tougas 2002).

Four of the eight included studies are reported as fully published papers (Muller-Lissner 2001; Fidelholtz 2002; Novick 2002; Kellow 2003). Data from three other studies are published in abstracts (Hamling 1998; Lefkowitz 1999a; Lefkowitz 1999b), and in information provided in the Briefing Document submitted by the manufacturers to the Federal Drug Administration (FDA) in 2000 (Novartis 2000). No publications were identified for study B307, other than the information provided in the FDA Briefing Document (Novartis 2000). Further information on the trials published only as abstracts and the unpublished study (B307) was sought from the manufacturers (USA contact), but none was received.

Seven studies were conducted in patients with constipation-predominant IBS (C-IBS) (Kellow 2003; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999a; Lefkowitz 1999b; Hamling 1998; B307). The Rome diagnostic criteria were used in these seven studies; Rome I in six studies, Rome II in Kellow 2003. Fidelholtz 2002 enrolled patients with diarrhoea-predominant IBS (D-IBS), based on Rome I diagnostic criteria.

The population studied was predominantly women (refer to table of included studies), with the largest study, Novick 2002, enrolling only women (n=1519). Reported mean age of patients in treatment groups of the included studies ranged from approximately 36 years to 48 years (see Table of included studies). The duration of IBS, reported in six studies, varied between studies and across treatment groups, ranging from means of 7.2 to 16.3 years (Kellow 2003; Fidelholtz 2002; Novick 2002; Lefkowitz 1999b; B307) to medians of 8.2 to 10.0 years (Muller-Lissner 2001). Five studies (four C-IBS and one D-IBS) specified that to qualify for enrolment patients were required to have a 3 month history of symptoms, and fulfill certain symptom criteria (Fidelholtz 2002; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307). In the four C-IBS studies, patients had to fulfill two of three constipation criteria, which were less than 3 bowel movements per day, hard or lumpy stools, or straining at least 25% of the time (Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307). Patients in the Fidelholtz 2002 study were required to have two of three diarrhoea criteria, which were more than 3 bowel movements per day, loose or watery stools, or urgency at least 25% of the time. Refer to the Table of included studies for more information.

Exclusion criteria were only listed in the fully published studies. Patients were generally excluded if they had organic bowel disease; were planning to use drugs that affect GI motility and/or perception; had cathartic colon, or other

conditions known to affect bowel transit (Kellow 2003; Fidelholtz 2002; Novick 2002; Muller-Lissner 2001).

There were some similarities among the studies in terms of study design. Two were phase II dose-finding studies (Lefkowitz 1999a; Hamling 1998), which evaluated daily doses of 1 mg, 4 mg, 12 mg, and 24 mg of tegaserod. Three (Muller-Lissner 2001; Lefkowitz 1999b; B307) were the original phase III studies of the tegaserod clinical trial programme. Of these, Muller-Lissner 2001 and Lefkowitz 1999b were identical in design, evaluating two fixed daily doses of 4 mg and 12 mg. B307 was also similar in design except that the tegaserod 12 mg treatment arm started with a dose of 4 mg, which could be increased to 12 mg according to response (after the first month of double-blind treatment, the dose was increased from 4 mg to 12 mg in 65% of patients). The remaining two studies in C-IBS (Kellow 2003; Novick 2002) evaluated the 12 mg dose of tegaserod only. In the D-IBS population studies by Fidelholtz 2002, 4 mg and 12 mg daily doses of tegaserod were evaluated. Across all trials, all daily doses of tegaserod were taken in two divided doses.

Each of the studies was short-term with double-blind treatment periods of 8 to 12 weeks. This was preceded by treatment-free periods of 2 or 4 weeks, and in two studies, was followed by a 4-week withdrawal period (Kellow 2003; Novick 2002).

OUTCOMES

Patients recorded their IBS symptoms daily in paper diaries (details only given in 5 studies; Kellow 2003; Fidelholtz 2002; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b). Assessments were undertaken weekly. In the Novick 2002 study, the assessment was performed using a touch tone telephone system.

Each of the seven studies that enrolled patients with C-IBS evaluated a global outcome (Subjects Global Assessment [SGA]) encompassing GI symptoms (SGA of Relief, or SGA of GI symptoms). The question asked of patients in order to determine the proportion of responders for these endpoints differed among the studies. In the dose-ranging tegaserod studies (Lefkowitz 1999a; Hamling 1998) patients were asked, "Compared to the way you usually felt during the 3 months before you entered the study, are your overall GI symptoms over the past 4 weeks completely, considerably, somewhat relieved, unchanged or worse"? Patients with complete or considerable relief at study endpoint (last 4 weeks of treatment) were called responders.

Novick 2002, Muller-Lissner 2001, Lefkowitz 1999b, and B307 asked patients, "Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week"? Possible answers were: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Patients with complete or considerable relief at least 50% of the time, or with somewhat relief 100% of the time at study endpoint# were called responders (#endpoint was defined as the last 4 available weekly SGA scores, or all weekly SGA scores if fewer than 4 were available).

Kellow 2003 asked, "Over the past week do you consider that you have had satisfactory relief from your IBS symptoms" over the first four weeks of double-blind treatment. Patients answered yes or no. Patients with at least 75% of 'yes' responses were called responders.

Three studies also specified what they considered to be a minimal clinically important difference in the proportion of responders for SGA of Relief between treatments (Kellow 2003; Novick 2002; Muller-Lissner 2001). Refer to the table of included studies.

Other outcomes reported in these studies were patients' assessment of:

abdominal pain and discomfort (6 studies; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999a; Lefkowitz 1999b; Hamling 1998; B307)

bowel habit (4 studies; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307). This endpoint encompassed intensity of abdominal discomfort/pain; intensity of abdominal bloating; number of bowel movements; and average daily stool consistency.

satisfaction with bowel habit (1 study; Novick 2002)

constipation (2 studies; Lefkowitz 1999a; Hamling 1998)

GI symptoms such as bloating, bowel movements (5 studies; Kellow 2003; Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307)

Fidelholtz 2002 focussed on safety and tolerability of tegaserod with respect to effects on GI symptoms (e.g. number of bowel movements, days with loose or watery stools, and stool consistency score).

METHODOLOGICAL QUALITY

Quality assessment of only the fully published studies (Kellow 2003; Novick 2002; Fidelholtz 2002; Muller-Lissner 2001) was performed, as it was difficult to assess the quality of the studies published in abstract form due to the lack of information. Using the Cochrane criteria for selection, performance, detection, and attrition bias, each of the four studies had moderate risk of bias. The four studies were described as randomised. However only Kellow 2003 described the method of randomisation, although the details provided were not sufficient to determine whether the treatment allocation was truly random. It is unclear whether allocation of treatment was concealed in any of the studies.

Performance and detection bias was possible in all four of the studies.

Although three of the studies (Novick 2002; Fidelholtz 2002; Muller-Lissner 2001) stated that tegaserod and placebo tablets were identical in appearance, it is unclear whether personnel providing care and/or assessing outcomes were blind to assigned treatment. In Kellow 2003 it is stated that all personnel were blinded to assigned treatment. Attrition bias is unlikely as each study used intention to treat (ITT) analysis, stated all withdrawals and the reasons for withdrawals, with the exception of Fidelholtz 2002 where only withdrawals due to adverse events were listed.

In all but Fidelholtz 2002 the treatment groups within each study were comparable at baseline. There are concerns regarding the comparability of the treatment groups at baseline in the Fidelholtz 2002 study. The mean number of bowel movements per week, $p < 0.02$ and the mean number of days with 4 or

more bowel movements per week, $p < 0.05$ were significantly higher in the placebo group than either of the tegaserod groups (4 mg and 12 mg). This may introduce considerable bias in view of the small size of the study ($n=86$).

RESULTS

SGA OF RELIEF

Data from four studies that compared tegaserod 12 mg with placebo ($n=3194$) and reported responder rates were combined (Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307). Individually, of the four studies, statistically significant benefit was apparent in two (Muller-Lissner 2001; Lefkowitz 1999b), with a trend for benefit with tegaserod seen in the other two (Novick 2002; B307). The Chi square test indicated no significant heterogeneity between the four studies. Therefore, the fixed-effects model was used in the meta-analysis. The RR for being a responder in terms of SGA of Relief at endpoint with tegaserod 12 mg compared with placebo was 1.19 (95% CI 1.09, 1.29), indicating statistically significant benefit. The risk difference (RD) for this comparison was 0.07 (95% CI 0.03, 0.10), with a number needed to treat (NNT) of 14. When a restricted analysis was performed, combining data from the two fully published studies, the RR was 1.16 (95% CI 1.04, 1.29) indicating statistically significant benefit. The RD for this comparison was 0.06 (95% CI 0.02, 0.10), with a NNT of 17. Kellow 2003, who used a different definition of responder and at a different time point also reported a significantly higher responder rate with tegaserod 12 mg compared with placebo (see Table 1). This result met the Kellow 2003 criteria for a minimal clinically important difference between groups. Complete numerical results were not reported for each treatment group in the publications of Lefkowitz 1999a and Hamling 1998.

For the comparison of tegaserod 4 mg with placebo, data from three studies ($n=1685$) were pooled (Muller-Lissner 2001; Lefkowitz 1999b; B307). Of the three studies, a statistically significant benefit was apparent in one (Muller-Lissner 2001), and a trend in favour of tegaserod in the other two (Lefkowitz 1999b; B307). The pooled data show that the RR of SGA of Relief at endpoint for tegaserod 4 mg compared with placebo was 1.15 (95% CI 1.02, 1.31), indicating statistically significant benefit. The RD for this comparison was 0.05 (95% CI 0.01, 0.10), with a NNT of 20. The same three studies compared 12 mg and 4 mg tegaserod doses ($n=1682$). Pooled data from these were non-significant, RR 1.09 (95% CI 0.97, 1.22).

When all tegaserod doses were combined and compared with placebo ($n=4040$), the RR of being a responder was 1.17 (95% CI 1.08, 1.27), indicating statistically significant benefit (Novick 2002; Muller-Lissner 2001; Lefkowitz 1999b; B307). The RD was 0.06 (95% CI 0.03, 0.09), with a NNT of 17. Although the pooled results indicate statistically significant benefit with tegaserod, the a priori minimal clinically important differences set by Novick 2002 and Muller-Lissner 2001 in their studies were not reached.

ABDOMINAL PAIN AND DISCOMFORT

Three studies reported responder rates, which were combined in a meta-analysis for both 12 mg and 4 mg doses vs placebo (Muller-Lissner 2001;

Lefkowitz 1999b; B307). A responder was a patient who fulfilled the adjustment rules and the following criteria: at least 20 mm and 40% reduction in mean VAS score at endpoint compared to baseline. Individually, the three studies showed disparate results with B307 suggesting no benefit with either tegaserod dose, and Muller-Lissner 2001 and Lefkowitz 1999b showing a trend in favour of tegaserod (both doses). Due to the significant heterogeneity among the studies, the random-effects model was used in the meta-analysis. The RR for being a responder with tegaserod 12 mg compared with placebo (n=1675) was 1.16 (95% CI 0.89, 1.51), and 1.10 (95% CI 0.82, 1.49) for tegaserod 4 mg compared with placebo (n=1685). Both results show a non-significant difference between tegaserod and placebo treatment. When the 12 mg and 4 mg tegaserod doses were compared (n=1682), the results were non-significant, RR 1.05 (95% CI 0.90, 1.23). Pooling all tegaserod doses compared with placebo (n=2521) gave a RR of being a responder of 1.13 (95% CI 0.85, 1.51), which was not statistically significant.

The SGA of abdominal pain and discomfort was also a planned endpoint in the Lefkowitz 1999a and Hamling 1998 studies, but no numerical data were found for the individual tegaserod groups in these studies. Novick 2002 reported mean score differences and not responder rates, which showed significant improvement from baseline with tegaserod 12 mg compared with placebo (-1.01 vs -0.80, $p < 0.003$).

BOWEL HABIT

Three studies reported responder rates, which were combined in a meta-analysis for both 12 mg and 4 mg doses vs placebo (Muller-Lissner 2001; Lefkowitz 1999b; B307). A responder was a patient who fulfilled the adjustment rules and the following criteria: at least 20 mm and 40% reduction in mean VAS score at endpoint compared to baseline. Individually, of the three studies, B307 suggested no benefit with either tegaserod dose, and Muller-Lissner 2001 and Lefkowitz 1999b showed a trend in favour of tegaserod (both doses). No significant heterogeneity was detected. Pooled data from three studies (n=1685) indicate that patients treated with tegaserod 4 mg were significantly more likely than placebo to be responders, RR 1.21 (95% CI 1.02, 1.43). The RD for this comparison was 0.05 (95% CI 0.01, 0.09), with a NNT of 20. The RR for tegaserod 12 mg compared with placebo (n=1675) was non-significant, 1.10 (95% CI 0.93, 1.31). When both tegaserod doses were compared, the result was non-significant, RR 0.91 (95% CI 0.78, 1.07). When all tegaserod doses were pooled and compared with placebo (n=2521), the RR of being a responder was 1.16 (95% CI 1.00, 1.34) indicating statistically significant benefit.

Novick 2002 reported the mean score difference from baseline to endpoint, which was reduced to a significantly greater extent with tegaserod 12 mg compared with placebo (-1.30 vs -0.95, $p < 0.001$).

SATISFACTION WITH BOWEL HABIT

Novick 2002 reported response rates at months one, two and three (see Table 4). A responder was a patient who was 'very satisfied' or 'somewhat satisfied' at 50% of assessments. The response rates at all time points were significantly higher in the tegaserod 12 mg group than with placebo.

CONSTIPATION

This was a planned endpoint in two studies. Hamling 1998 reported responder rates but not for the ITT population, and only for pooled tegaserod groups. A responder was a patient with considerable or complete relief at study endpoint (last 4 weeks of treatment). No numerical data were presented for this endpoint in the publications related to Lefkowitz 1999a.

OTHER GI SYMPTOMS

Muller-Lissner 2001, Lefkowitz 1999b and B307 recorded changes in bloating, abdominal pain/discomfort, bowel movements and stool consistency. The number of days without bowel movements was reduced and the number of bowel movements increased significantly with tegaserod 12 mg compared with placebo. There was a non-significant trend towards reduction in days with significant abdominal pain and discomfort, days with significant bloating, and days with hard or very hard stools in both tegaserod groups compared with placebo. Lefkowitz 1999a reported scores for days with pain, bloating, and bowel movements according to whether they were deemed to be responders, not by treatment group.

Kellow 2003 and Novick 2002 also reported on some individual GI symptoms. Days with hard or lumpy stools and days with at least moderate abdominal pain and discomfort were significantly fewer with tegaserod 12 mg compared with placebo, with no significant differences identified between groups in bloating, number of bowel movements, stool consistency, urgency, or straining (Kellow 2003). In the Novick 2002 study, the number of bowel movements increased significantly, and bloating, straining, and stool consistency scores fell significantly with tegaserod 12 mg from baseline compared with placebo.

TOLERABILITY

Numerical data for each treatment group (ITT analysis) were only reported for four studies (Kellow 2003; Fidelholtz 2002; Novick 2002; Muller-Lissner 2001). See Tables 5 to 8. Data on events reported in each of the three studies that were conducted in individuals with C-IBS were pooled (Kellow 2003; Novick 2002; Muller-Lissner 2001). A consistent effect on diarrhoea was seen in the three studies. The RR of diarrhoea with tegaserod 12 mg compared with placebo (n=2621) was significantly higher, 2.75 (95% CI 1.90, 3.97). The RD for this comparison was 0.05 (95% CI 0.03, 0.07), with a number needed to harm (NNH) of 20. Of the other pooled adverse events, none of these occurred with a significantly higher frequency with tegaserod 12 mg although there was a trend in that direction; headache RR 1.18 (95% CI 0.97, 1.44); abdominal pain RR 1.11 (95% CI 0.86, 1.43); and nausea RR 1.20 (95% CI 0.88, 1.63).

DISCUSSION

In individuals, predominantly women, with C-IBS tegaserod 12 mg and 4 mg significantly improved patients global assessment of IBS symptomatology compared with placebo. Tegaserod did not significantly improve patients'

abdominal pain and discomfort although bowel habit showed a significant improvement with tegaserod 4 mg and there was a non-significant trend in favour of tegaserod 12 mg compared with placebo. When GI symptoms were assessed separately, those indicative of GI motility such as number of bowel movements and days without bowel movements were generally improved with tegaserod, whereas effects of treatment on symptoms such as bloating and stool consistency and straining were not consistent across the studies.

The effect of publication bias was explored using a restricted analysis of pooled SGA of Relief at endpoint data for tegaserod 12 mg vs placebo. The direction of the evidence was the same when the unpublished study (B307) and the study published as an abstract were excluded from the analysis, although the NNT was higher when the unpublished studies were excluded (NNT 17 vs 14). The comparison of the 4 mg and 12 mg doses of tegaserod did not show a clear distinction between the two doses.

Whilst the meta-analysis has shown a significant treatment effect with both tegaserod doses compared with placebo, such a consistent effect was not seen in the individual studies. In particular, a significant difference between tegaserod 4 mg or 12 mg and placebo groups was not observed in B307, the results of which have not been published other than in the FDA briefing document. It should be noted that in study B307, the patients in the higher dose group started off with a dose of 4 mg, which was increased to 12 mg in 65% patients. In the Lefkowitz 1999b study, only published in abstract form, a significant difference was seen with tegaserod 12 mg compared with placebo, but not with tegaserod 4 mg. Lefkowitz 1999b was the first phase III study to be completed, which prompted a change in the definition of responder because a significant treatment effect was not seen with tegaserod compared with placebo (Novartis 2000). The data listed in this review are the results of the retrospective analysis of results from the Lefkowitz 1999b study that was performed when the revised definition of responder was agreed, which reduced the threshold for response. The definition of responder is described in the outcomes section.

With regard to tolerability in the studies, diarrhoea occurred with a significantly higher incidence in the tegaserod 12 mg group, which is not surprising given the drug's mode of action. The balance of improving symptoms of C-IBS without causing diarrhoea may be difficult to achieve. It was not possible to pool data for the 4 mg dose as the two studies contributing the relevant data enrolled different study populations (diarrhoea-predominant IBS in Fidelholtz 2002, and constipation-predominant IBS in Muller-Lissner 2001). The other documented events (abdominal pain, headache, nausea), represent some of the typical GI and extra-intestinal symptoms of IBS. Because other GI stimulants are known to have cardiac effects, e.g. cisapride (also a 5HT₄ partial agonist), the electrocardiographic effects of tegaserod were investigated in studies Muller-Lissner 2001, Lefkowitz 1999b and B307 (n=2525) and the results have been published (Morganroth 2002). The data from these short-term studies did not identify statistically significant differences between tegaserod 4 mg or 12 mg and placebo groups in the proportion of patients with prolonged QTc intervals, or the overall frequency of electrocardiographic abnormalities.

Individuals enrolled in the studies included in this review fulfilled Rome

diagnostic criteria, which were originally developed in order to allow greater comparability of drug effects between studies of treatments for IBS. Although they are frequently used entry criteria for such clinical studies, in clinical practice, studies evaluating diagnosis of IBS in primary care have found that set diagnostic criteria were rarely used (Thompson 1997) and that many patients given a diagnosis of IBS did not fulfill these criteria (Robinson 2001). Rome criteria have also been criticised for not encompassing some clinical patterns seen by clinicians (Camilleri 2001), such as not taking into account postprandial exacerbation of symptoms; excluding subgroups based on predominant bowel dysfunction; and not encompassing patients in whom functional, painless diarrhoea may be associated with postprandial urgency, borborygmi, and a sense of incomplete rectal evacuation. It is difficult to determine how representative the patients enrolled in the clinical trials are of those who present in the primary care setting with symptoms of IBS.

IBS is a complex disorder that encompasses a wide profile of symptoms. Tegaserod appears to improve the overall symptomatology of IBS but there are currently few data on its effect on quality of life. In addition, more information is needed about its efficacy in men. It would also be of interest to know whether treatment with tegaserod leads either directly, or indirectly, to changes in visceral sensitivity or psychopathology, which are also considered important in the pathophysiology of this condition.

REVIEWER'S CONCLUSIONS

Implications for practice

For women with constipation-predominant IBS, tegaserod offers modest improvement of their global GI symptoms, but may not address symptoms of abdominal pain and discomfort. The treatment may be an option for short-term relief of symptoms. In practice the division between constipation-predominant and diarrhoea-predominant IBS may not be clear-cut in some patients. It is not yet apparent whether there is a sub-group of women with C-IBS who may gain most benefit from tegaserod treatment.

Implications for research

Ongoing research aims to investigate the existence of a rebound effect on withdrawal of tegaserod, and the effects of withdrawal on symptomatic control. Longer-term studies would help determine the duration of benefit with tegaserod treatment, and its safety with prolonged use. Information on the effects of tegaserod treatment on quality of life of patients, and on medical consultation rates, as well as comparative studies of tegaserod with established IBS treatments would be valuable in defining its place in therapy.

ACKNOWLEDGEMENTS

Interim funding for the IBD Review Group has been provided by the Canadian Institutes of Health Research (Institutes of Infection and Immunity & Nutrition, Metabolism and Diabetes). Miss Ila Stewart has provided support for the IBD

Review Group through the Olive Stewart Fund.

We would like to thank corresponding authors of papers for responding promptly to enquiries related to their publications. We would also like to acknowledge the support of the editorial base of the Cochrane Inflammatory Bowel Disease Review Group who have provided support and encouragement with the development of this review.

POTENTIAL CONFLICT OF INTEREST

Dr Whorwell's unit has previously and is currently in receipt of financial support from Novartis including funding for a randomised controlled trial of tegaserod therapy.

REFERENCES

References to studies included in this review

B307 {published data only}

*Novartis Pharmaceuticals Corporation East Hanover, New Jersey. [Zelmac (tegaserod) Advisory Committee Briefing Document]. <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627b1a.pdf>. 2000 (accessed 18/11/2002):1-93..

Fidelholtz 2002 {published data only}

*Fidelholtz J, Smith W, Rawls J, Shi Y, Zack A, Ruegg P, Lefkowitz M. Safety and tolerability of tegaserod in patients with irritable bowel syndrome and diarrhea symptoms. *Am J Gastroenterol* 2002;97:1176-1181.

Rawls J, Lefkowitz M, Shi Y, Zack A, Dunger-Baldauf C, Ruegg PC. [Tegaserod is well tolerated in diarrhea-predominant irritable bowel syndrome]. *Gut*. ;47 (Suppl 3)2000:A217.

Hamling 1998 {published data only}

*Hamling J, Bang CJ, Tarpila S, Stewart W, Rueegg PC. [Titration regimen indicates partial 5-HT4 agonist HTF 919 improves symptoms of constipation predominant irritable bowel syndrome (C-IBS)]. *Digestion*. ;59 (Suppl 3)1998:735 (abstract B5324).

Novartis Pharmaceuticals Corporation East Hanover, New Jersey. [Zelmac (tegaserod) Advisory Committee Briefing Document]. <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627b1a.pdf>. 2000 (accessed 18/11/2002):1-93..

Kellow 2003 {published data only}

*Kellow J, Lee OY, Chang FY, Thongsawat S, Mazlam MZ, Yuen H, Gwee KA, Bak YT, Jones J, Wagner A. [An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel

syndrome]. *Gut* 2003;52:671-676.

Kellow JE, Lee O, Thongsawat S, Zawawi M, Yuen H, Gwee K, Jones J, Wagner A. Tegaserod is an effective therapy for non-diarrhea irritable bowel syndrome in an Asian-Pacific population. *Gut*. ;51 (Suppl 2)2002:A11 (abstract 035).

Lefkowitz 1999a {published data only}

*Lefkowitz MP, Ruegg P, Shi Y, Dunger-Baldauf C. [Relief of overall GI symptoms and abdominal pain and discomfort as outcome measures in a clinical trial of irritable bowel syndrome with HTF 919]. *Gastroenterology*. ;1161999:A1027 (abstract G4462).

Novartis Pharmaceuticals Corporation East Hanover, New Jersey. [Zelmac (tegaserod) Advisory Committee Briefing Document]. <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627b1a.pdf> 2000 (accessed 18/11/2002):1-93.

Whorwell P, Muller-Lissner S, Langaker KJ, Wald A, Pruitt R, Ruegg P. [Short and long-term safety and tolerability of tegaserod in patients with IBS]. *Gut*. ;45 (Suppl 5)1999:A260 (abstract P0966).

Lefkowitz 1999b {published data only}

Krumholz S, Tanghe J, Schmitt C, Heggland J, Shi Y, Ruegg PC. [The 5HT4 partial agonist, tegaserod, improves abdominal bloating and altered stool consistency in irritable bowel syndrome (IBS)]. *Gut*. ;45 (Suppl 5)1999:A260 (abs P0965).

Lefkowitz M, Shi Y, Heggland J, Dunger-Baldauf C, Ruegg PC. Tegaserod rapidly improves abdominal pain, bloating and bowel function in patients with C-IBS. *Gut*. ;47 (Suppl 3)2000:A217 (abstract P833).

*Lefkowitz M, Shi Y, Schmitt C, Krumholtz S, Tanghe J. [The 5HT4 partial agonist, tegaserod, improves abdominal discomfort/pain and normalizes altered bowel function in irritable bowel syndrome (IBS)]. *Am J Gastroenterol*. ;941999:2676 (abstract 396).

Novartis Pharmaceuticals Corporation East Hanover, New Jersey. [Zelmac (tegaserod) Advisory Committee Briefing Document]. <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627b1a.pdf> 2000 (accessed 18/11/2002):1-93.

Schmitt C, Krumholz S, Tanghe J, Heggland J, Shi Y, Lefkowitz M. [Tegaserod, a partial 5HT4 agonist improves abdominal discomfort/pain and altered bowel function in irritable bowel syndrome]. *Gut*. ;45 (Suppl 5)1999:A258 (abstract P0960).

Muller-Lissner 2001 {published data only}

Mueller-Lissner S, Fumagalli I, Bardhan KD, Pace F, Nault B, Pecher EC, Rueegg PC, Lefkowitz MP. [Tegaserod, a 5HT4 receptor partial agonist, relieves key symptoms of irritable bowel syndrome (IBS)]. *Gastroenterology* 2000;116 (Suppl 2):A175 (abs 1000).

*Muller-Lissner SA, Fumagalli I, Bardhan KD, Pace F, Pecher E, Nault B, Ruegg P. Tegaserod, a 5-HT₄ receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001;15:1655-1666.

Novartis Pharmaceuticals Corporation East Hanover, New Jersey. [Zelmac (tegaserod) Advisory Committee Briefing Document]. <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627b1a.pdf> 2000 (accessed 18/11/2002):1-93.

Novick 2002 {published data only}

Lefkowitz M, Ligozio G, Glebas K, Hegglund JE. [Tegaserod provides relief of symptoms in female patients with irritable bowel syndrome (IBS) suffering from abdominal pain and discomfort, bloating and constipation]. *Gastroenterology*. ;120 (Suppl 1)2001:A22 (abstract 104).

*Novick J, Miner P, Krause R, Glebas K, Bliesath H, Ligozio G, Ruegg P, Lefkowitz M. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2002;16:1877-1888.

References to studies excluded from this review

Appel-Dingemans

*Appel-Dingemans S, Rawls J, Hegglund J, Campestrini J, Sechaud R. [Similar pharmacokinetics of tegaserod (HTF 919) in patients with constipation- and diarrhoea-predominant irritable bowel syndrome]. *Gastroenterology*. ;1182000:Abstract 5340.

Prather 2000

*Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. [Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome]. *Gastroenterology* 2000;118:463-468.

Tougas 2002

*Tougas G, Snape WJ, Otten MH, Earnest DL, Langaker KE, Pruitt RE et al. [Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome]. *Aliment Pharmacol Ther* 2002;16:1701-1708.

References to studies awaiting assessment

Lin 2003

Lin S, Zhou L, Xinguang L, Ke M, Wang H, Cheng L, et al. [Tegaserod provides rapid, effective relief of abdominal pain/discomfort, bloating and constipation in Chinese patients with irritable bowel syndrome with constipation (IBS-C)]. *Digestive Disease Week*. 2003:Abs S1017.

Munoz 2003

Munoz VC. [Relapse of symptoms following withdrawal of tegaserod treatment in irritable bowel syndrome with constipation (IBS-

C)]. Digestive Disease Week. 2003:Abs T1804.

Nyhlín 2003

Nyhlín H, Bang C, Elsborg L, Silvennoinen J, Holme I, Berge M, et al. [Tegaserod is an effective and safe therapy for irritable bowel syndrome in a Nordic population]. Digestive Disease Week. 2003:Abs M1645.

Additional references

Camilleri 2001

Camilleri M. Management of the irritable bowel syndrome. Gastroenterology 2001;120:652-658.

Farthing 1995

Farthing MJ. Irritable bowel, irritable body, or irritable brain?. BMJ 1995;310:171-175.

Farthing 1998

Farthing MJ. New drugs in the management of the irritable bowel syndrome. Drugs 1998;56:11-21.

Hammer 1999

Hammer J, Talley NJ. Diagnostic criteria for the irritable bowel syndrome. Am J Med 1999;107:5S-11S.

Jones 2000

Jones J, Boorman J, Cann P, Forbes A, Gomborone J, Heaton K, et al. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. Gut 2000;47 (Suppl 2):1-19.

Morganroth 2002

Morganroth J, Ruegg PC, Dunger-Baldauf C, Appel-Dingemanse S, Bliesath H, Lefkowitz M. Tegaserod, a 5-hydroxytryptamine type 4 receptor partial agonist, is devoid of electrocardiographic effects. Am J Gastroenterol 2002;97:2321-2327.

Novartis 2000

Novartis Pharmaceuticals Corporation East Hanover, New Jersey. [Zelmac (tegaserod) Advisory Committee Briefing Document]. <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627b1a.pdf>. 2000 (accessed 18/11/2002):1-93..

Robinson 2001

Robinson A, Lee V, Thompson DG. Irritable bowel syndrome diagnosed in primary care: how many patients fulfil Rome II criteria?. Gut. ;48 (Suppl 1)2001:A45 (abstract 164).

Talley 2002

Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease. Lancet 2002;360:555-564.

Thompson 1997

Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel

syndrome: the view from general practice. *European Journal of Gastroenterology & Hepatology* 1997;9:689-692.

van Zanten 1999

van Zanten SJO, Talley NJ, Bytzer P, Klein KB, Whorwell PJ, Zinsmeister AR. Design of treatment trials for functional gastrointestinal disorders. *Gut* 1999;Suppl II:II69-II77.

* *Indicates the major publication for the study*