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Zelnorm®: What is the evidence of benefit for IBS?

By Stephanie Lovell, Pharm. D. Candidate, Dean Haxby, Pharm. D. and Kathy L. Ketchum R.Ph., M.P.A:H.A. (All at OSU College of Pharmacy)

Tegaserod (Zelnorm®) was recently approved by the FDA for short-term (less than 12 weeks) symptomatic treatment of females with constipation-predominant irritable bowel syndrome (IBS)[1]

IBS is a common disorder affecting an estimated 15% of the US population.[2] The pathophysiology is not fully understood. It is characterized by disordered intestinal motility and an altered perception of gastrointestinal tract sensations without detectable biochemical or structural changes.[3]

Most patients will not require drug therapy and no single drug has been shown to be beneficial for the IBS symptom complex.[4] The American Gastroenterological Association[5] currently recommends that medication should be directed at the predominant symptoms (Table 1). For diarrhea, loperamide or diphenoxylate, should be considered. Several small studies have shown antispasmodics effective for IBS associated pain.[6] Tricyclic antidepressants (TCAs) have been recommended for pain symptoms, though the evidence is inconclusive and they may aggravate constipation.[7] No comparative studies have been performed with SSRI antidepressants in patients with IBS. Dietary fiber (25g/day) is recommended for patients with constipation-predominant IBS[6] and, most but not all, studies report a significant improvement with bulk laxatives. Gas and pain can be limiting side effects of the bulk laxatives. If an alternate laxative is needed, osmotic laxatives like sorbitol or lactulose are preferred over stimulant laxatives.[5] While laxatives may alleviate the constipation; they have not demonstrated they control the pain component of IBS.[8]

Table 1 – Current Constipation-Predominant IBS Treatment Options[5-10]

Class	Generic Name	Symptom	Dose	Cost/Mth^
Bulking Agents	psyllium (generic)	Constipation	10gm TID	$10
Osmotic Laxatives	lactulose (generic)	Constipation	40gm/60ml QD	$39
Antispasmodics	dicyclomine (generic)	Pain	40mg QID	$28
Tricyclic Antidepressants	amitriptyline (generic)	Pain	75mg QHS	$2
5-HT$_4$ Partial Agonist	tegaserod (Zelnorm)	Constipation, Pain	6mg BID	$132

^ AWP-13% or MAC from OMAP First DataBank Drug File on September 6, 2002

Several neurotransmitters, including 5-HT, are reported to be involved with the regulation of motility and pain in the gastrointestinal (GI) tract. 5-HT$_4$ receptors are thought to have a role in pain perception and motility. Partial agonists of 5-HT$_4$ receptors, like tegaserod, may therefore be able to reduce abdominal pain and normalize GI function. It has been shown *in animals* to normalize impaired motility of the GI tract, as well as to moderate visceral sensitivity during colorectal distention.[11]

Clinical Efficacy

Three, 12-week prospective, double-blind and randomized trials were conducted and submitted to the FDA for the application and approval of tegaserod.[11,12,13] While the studies involved large numbers of patients, the interpretation of the results is complicated because the study endpoints were changed after the first trial (B351) and there is a high rate of placebo response in this patient population. Also complicating the assessment of efficacy was that bulk forming laxatives and TCAs were permitted if the dose was stable for one month prior to study entry. Patients who met pre-defined criteria for severe constipation were allowed rescue laxative medication, while those with diarrhea were allowed use of loperamide. The trials and intent-to-treat results of each are summarized below (Table 3). The primary endpoints were assessed only during the final 4 weeks of each trial.

In Study B351, the Subject's Global Assessment (SGA) Relief was measured using a five point ordinal scale: complete relief, considerable relief, somewhat relieved, unchanged, or worse. No significant difference from placebo was seen in either category. Investigators altered the SGA Relief criteria of response for studies B301 and B307, liberalizing the definition of a responder. Investigators converted SGA Abdominal Discomfort and Pain to a secondary endpoint in the final two studies. Study B301 used the revised SGA Relief scale, showing both tegaserod 2mg bid and tegaserod 6mg bid significantly better than placebo, with NNT of 11.6 and 12.2, respectively. Only this study demonstrated a significant benefit of tegaserod over placebo. Yet, the altered criteria suggest the effect is quite modest. Study 307 used the revised SGA Relief and no significant difference was shown in either treatment group.

No treatment effect was apparent at any endpoint with tegaserod in male patients.[12] Finally, tegaserod demonstrated limited efficacy for females with approximately one female patient in twelve benefiting after three months.[13]

Adverse Effects

Diarrhea is the only adverse event that is clearly more frequent in tegaserod treated patients than placebo (Table 2). Discontinuation rates due to diarrhea were 2% (2mg bid dose) and 2.4% (6mg bid dose). No placebo patients discontinued use due to diarrhea.[11] Tegaserod should not be initiated in patients currently or frequently experiencing diarrhea and should be discontinued immediately in patients with new or sudden worsening of abdominal pain.[1]

An increase in abdominal surgeries, including cholecystectomy (n=2) and ovarian cysts (n=3), were observed with tegaserod during the clinical trials, but a causal relationship has not been identified. This was a major concern of the FDA advisory committee that prolonged review of the new drug application.

Table 2 – Adverse Event Rates

	Tegaserod 2mg bid	Tegaserod 6mg bid	Placebo
Diarrhea	11.40%	12.10%	5.40%
Abdominal Pain	19.90%	18.80%	18.20%
Flatulence	7.50%	7.10%	6.60%
Headache	21.40%	23.20%	21.10%
Nausea	9.20%	9.80%	8.60%

Dosing

The recommended dose of tegaserod is 6mg twice daily by mouth 30 minutes before meals for 4-6 weeks. An additional 4-6 week course can be considered for those who respond. The bioavailability of tegaserod decreases 40-65% when given with food. It is not recommended for patients with severe renal impairment (including hemodialysis) or moderate to severe hepatic impairment.

Place in Therapy

Although tegaserod will provide a new treatment option for constipation predominant IBS, the effectiveness of this agent appears highly suspect. The agent was not consistently more effective than placebo in studies conducted to date. When a statistical advantage over placebo was found, one could question the clinical significance, since only one in twelve patients receiving the drug exhibited a true drug response. At a cost of approximately $132 per month, tegaserod does not appear to offer a good value. Thus use of this agent is discouraged unless more compelling data become available to support its use.

It appears that tegaserod will be heavily advertised to consumers. Due to the high placebo response rates documented, expect marketing efforts to encourage a "therapeutic trial". While about 40% of patients will respond, most of this response can be attributed to placebo.

IBS is a chronic condition and there remains the unanswered question of efficacy and safety beyond 12 weeks. A study to assess the effect on gall bladder motility and biliary tract diameter on healthy patients is ongoing and due in the first quarter 2003. Novartis has also committed to study intermittent or long term efficacy with a final report due in 2005.[14]

IBS, while a prevalent and debilitating syndrome, is not life threatening. Another 5-HT_4 agonist, cisapride, was removed from the market because of life-threatening adverse events. Alosetron, recently reintroduced with restricted access for diarrhea predominant IBS, was withdrawn previously after reports of life-threatening events. The consumer group, Public Citizen, has raised concerns about the efficacy and safety profile of tegaserod.[15] Use of traditional therapy with bulk forming agents and osmotic laxatives is safe and recommended.

Reviewed by Michele Koder, Pharm.D., OSU College of Pharmacy

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Table 3 – Summary of Clinical Trials

Study #	Demographics	Drug Regimen	N=	Outcome	Response Rate	ARR	NNT
B351[12,13]	Caucasian 88% Female 87% Mean age 43 ± 30-56 yrs Duration of C-IBS 14.6 ± 10yrs	1. Tegaserod 2mg BID 2. Tegaserod 6mg BID 3. Placebo BID	265 267 267	Original SGA	1. 29.4% 2. 26.2% 3. 22.1%	NS NS	- -
				New SGA (retrospective analysis)	1. 38.9% 2. 45.7% 3. 33.3%	NS 12.40% (p=0.016)	- 8.1
				SGA of Abdominal Pain (primary endpoint)	1. 23.4% 2. 25.1% 3. 18.7%	NS NS	- -
B301[11,12,13]	Caucasian 98% Female 83% Mean age 46 ± 31-60 yrs Duration of C-IBS 13.2 ± 12 yrs	1. Tegaserod 2mg BID 2. Tegaserod 6mg BID 3. Placebo BID	299 294 288	Original SGA	1. 27.8% 2. 26.2% 3. 20.5%	7.3% (p=0.028) NS	13.7 -
				New SGA	1. 38.8% 2. 38.4% 3. 30.2%	8.6% (p=0.033) 8.2% (p=0.018)	11.6 12.2
				SGA of Abdominal Pain (secondary endpoint)	1. 29.8% 2. 29.9% 3. 22.6%	NS 7.30%	- 13.7
B307[12,13]	Caucasian 90% Female 84% Mean age 45 ± 32-58 yrs Duration of C-IBS 3.9 ± 10 yrs	1. Tegaserod 2mg BID 2. Tegaserod 2-6mg BID (dose titration) 3. Placebo BID	283 277 285	Original SGA	1. 25.5% 2. 26.5% 3. 28.2%	NS NS	- -
				New SGA	1. 38.3% 2. 42.2% 3. 37.0%	NS NS	- -
				SGA of Abdominal Pain (secondary endpoint)	1. 25.5% 2. 27.6% 3. 30.6%	NS NS	- -

ARR = Absolute Risk Reduction; NNT = Number Needed to Treat; Original SGA= Subject's Global Assessment at complete or considerable relief 50% of the time at study endpoint; New SGA= Complete or considerable relief 50% of the time at study endpoint, or Somewhat relieved 100% of the time at study endpoint; SGA of Abdominal Pain = 20mm or 40% reduction in mean visual analog scale at endpoint; NS = Data not significantly different

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840 SW Gaines Road MC 212
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Managing Editor: Kathy L. Ketchum
Ketchumk@ohsu.edu or 503-494-1589