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Reassessing the Benefits and Risks of Alosetron

What is its Place in the Treatment of Irritable Bowel Syndrome?

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Abstract

Functional gastrointestinal disorders such as the irritable bowel syndrome (IBS) cause substantial morbidity and a high amount of healthcare utilisation. However, no direct mortality can be attributed to functional disorders. Hence, drug treatment of IBS must not only be highly efficient to relieve clinical symptoms but also very safe for the long-term use in humans with such chronic disorders. Alosetron is a potent and highly selective serotonin 5-HT_3 receptor antagonist that in large randomised controlled clinical trials has been shown to be clinically efficient in female patients with diarrhoea-predominant IBS. The efficacy data along with a low number of serious adverse effects in the preclinical and clinical trials suggested a favourable benefit/risk profile that led to US FDA approval of alosetron in early 2000. However, postmarketing experience has proven that several serious adverse effects, including death, occurred in the treated patient population, which resulted (for a time) in the withdrawal of alosetron from the US market by the producer (GlaxoSmithKline). In the meantime, both public pressure and the proposal of a careful postmarketing surveillance have led the FDA to re-approve alosetron to the US drug market under severe restrictions. These restrictions aim to ensure a safer use of the drug with a more favourable safety profile. Under these restrictions, however, it is not very likely that alosetron will become a major treatment option for many patients, but presumably the continued use of this first selective serotonin antagonist will open an avenue for the development of similar drugs with more favourable benefit/risk profiles in the near future.

Several previous experimental and clinical studies have shown that afferent and efferent neural pathways are directly involved in the modulation of gut sensory and motor function. Disturbances of the neural sensory and motor gut-brain axis are believed to be involved in clinical symptom generation in functional bowel disorders such as the irritable bowel syndrome (IBS) and functional abdominal pain.[1] Functional gastrointestinal disorders such as IBS are very common and exert substantial impact on patients' quality of life and the use of medical resources.[2] Estimates of the prevalence of IBS in the general Western population are as high as 20%, with a clear predominance in female patients.[1] Effective treatment of IBS and other functional syndromes remains a challenge to primary care physicians and gastroenterologists. Evaluating the 'true' efficacy of single treatment measures such as the use of a single

drug for IBS is difficult, since IBS represents a heterogenic group of disorders that produce a multitude of patient symptoms. Furthermore, assessment of therapy is complicated by the significant placebo responses of patients observed in all clinical trials. At present, there is still no agent or treatment measure that effectively controls the multiple symptoms in IBS, suggesting that new treatment strategies should be much more based on novel insights into the pathophysiology of IBS and related syndromes, for example targeting directly the brain-gut-axis.

Serotonin, is an important neurotransmitter in the brain-gut axis and is involved in several functions of the gastrointestinal tract, including, among others, the peristaltic reflex.[3,4] Serotonin is found primarily within the gastrointestinal tract (95% of body serotonin stores), where it is mainly stored in gut enterochromaffin cells (95%) and partly in enteric neurons (5%).[5,6] Serotonin plays a pivotal role in the modulation of multiple gut functions such as motility, sensation, and secretion.[5,6] However, serotonin also acts as a neurotransmitter in the CNS.[7] Released from enterochromaffin cells in response to luminal mechanical, neuronal, or chemical stimulation, serotonin acts via a variety of serotonin 5-HT receptors either directly, for instance on the muscle or enterocytes themselves, or indirectly through, for instance, extrinsic vagal afferent fibres and on intrinsic enteric neurones to modulate gastrointestinal function.[5,6,8,9] The receptors involved in its functions consist of 5-HT_3, 5-HT_4, and 5-HT_{1p}.[5,6] Spinal 5-HT_3 receptors in the rat are involved in the mediation of endogenous pain inhibition in response to noxious colorectal distension.[10] Binding of a specific 5-HT_3 ligand has been shown in the area postrema in the brain and in various limbic regions.[11]

Taken together, these findings indicate that the serotoninergic pathway network appears to play a key role in the neuro-humoral gut-brain-gut axis in health and disease.

Hence, it has been proposed that serotoninergic pathways may be implicated in the underlying pathophysiology of functional bowel diseases particularly via 5-HT_3 and 5-HT_4 receptors that have been shown to be involved in many motor and sensory processes in the gastrointestinal tract.[5,6,12] 5-HT receptors have therefore emerged as a new therapeutic target and treatment approach to the management of functional disorders such IBS, functional dyspepsia, also known as non-ulcer dyspepsia, and non-cardiac chest pain.[8,13,14]

1. Pharmacological Features and Properties

Alosetron (figure 1) is a potent and highly selective antagonist of the 5-HT_3 receptor. The drug is administered orally at a dosage of 1mg once to twice daily and rapidly absorbed with a mean bioavailability of approximately 50–60%. Following oral administration of alosetron 1mg, the peak plasma concentration occurs at 1 hour. There is no accumulation of the substance after repeated oral intake of 1mg twice daily.[15,16]

Alosetron is extensively metabolised in the liver and then mainly eliminated by renal excretion (about 70%). Its elimination half-life is approximately 1.5 hours. The metabolism of alosetron involves the human microsmomal cytochrome P450 (CYP) system, shown *in vitro* to involve enzymes CYP2C9 (30%), CYP3A4 (18%), and CYP1A2 (10%). Non-CYP mediated phase I metabolic conversion also contributes to an extent of about 11%. The biological activity of at least 13 metabolites of alosetron is unknown.[15,16]

Analysis of patient subgroups revealed pharmacokinetic gender differences with plasma concentrations of alosetron being about 27% lower in men compared with women.[17] This may partly explain the higher drug efficacy of alosetron in female patients which was observed in clinical trials.

A variety of *in vitro* as well as *in vivo* animal-studies reveal some insights into the pharmacodynamic profile of alosetron.[18] Radioligand binding studies and 5-HT_3 receptor function studies demonstrated that alosetron possesses a high 5-HT_3 receptor-selectivity as well as affinity.[19-21] The latter is

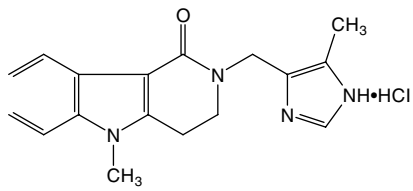

Fig. 1. Chemical structure of alosetron ($C_{17}H_{18}N_4O$•HCl).

about 10-fold higher than that of ondansetron, another known 5-HT_3 receptor antagonist which is in clinical use for the treatment of chemotherapy-associated emesis.

The high receptor affinity of alosetron is supposed to be responsible for the long pharmacodynamic half-life of approximately 6–10 hours, which is obviously differing from the elimination half-life of only 1.5 hours. In humans, an oral dose of alosetron 1mg was able to block the cutaneous flare response to intradermal serotonin in volunteers and sustain the inhibition for up to 10 hours.[22]

Gastrointestinal studies in animals have focussed on the effect of alosetron on colorectal distension evoked vasomotor responses and *c-fos* expression in the spinal cord. In rats, alosetron potently inhibited the vasodepressor response as well as the number of *c-fos* immunoreactive nuclei in the lumbosacral spinal cord following noxious colorectal distension.[23,24] These effects very likely reflect a visceral antinociceptive activity of alosetron.

Further pharmacodynamic properties of alosetron in the gastrointestinal tract have been evaluated in humans.[25] In healthy volunteers alosetron significantly delayed the whole gut transit time. However, this was only accounted for by the increase in colonic transit time alone, whereas the oro-caecal transit time remained unaffected. In IBS patients the delayed colonic transit was demonstrated to be caused by prolonging left colonic transit.[26,27]

In a study of patients with diarrhoea-predominant IBS, alosetron did not only significantly delay the overall colonic transit with almost a doubling of the ascending colonic emptying, but it also retarded the small bowel transit. The effect seemed to be greater in women.[28]

In colonic distension studies carried out in IBS patients, alosetron treatment was shown to significantly increase the colon compliance to distension. While there was no effect on the perception and pain thresholds on isobaric distension, the alosetron treatment was associated with higher volume perception and pain thresholds, supporting changes in colonic compliance.[29]

In contrast, analysis of gastric isobaric and isovolumetric distension data in healthy volunteers did not reveal any significant influence of alosetron on gastric compliance or gastric sensation scores.[30]

Another study evaluated the effect of alosetron on intestinal fluid and electrolyte absorption compared with placebo. Alosetron treatment resulted in a significant increase of basal jejunal fluid and sodium absorption, whereas the transport of other electrolytes (potassium, chloride or bicarbonate) was not affected.[31]

Lately, functional brain imaging studies using positron emission tomography (PET) scan have been performed to asses the effects of alosetron on regional cerebral blood flow (and therefore on brain activity) during rectosigmoid distension in correlation to the associated perception ratings and to changes in IBS-related bowel symptoms.[32] Compared with placebo and baseline, alosetron treatment decreased brain activity in response to unanticipated, anticipated and delivered aversive rectal stimuli in cerebral regions of the emotional motor system. This finding was associated with a reduction in stimulus perception ratings and irritable bowel symptom scores. Results from a following PET study[33] demonstrated that alosetron treatment improved IBS symptoms and reduced brain activity in 5-HT_3-containing regions of the emotional motor systems, but not in structures directly activated by pain. Interestingly, the effects on cerebral blood flow reduction were greatest in the absence of a nociceptive input. These results suggest that symptom relief during alosetron treatment is not primarily caused by peripheral viscero-analgesic effects but may rather be due to a reduced activity of central 5-HT_3-containing structures of the emotional motor system possibly involved in the modulation of gut symptoms.

2. Clinical Profile

Previous trials consistently demonstrated that alosetron 1mg twice daily taken orally improves stool frequency, stool consistency, abdominal discomfort, and global IBS symptoms in the patients enrolled. Theoretically, symptoms of incomplete rectal evacuation or urgency may best respond to this pharmacological agent because it induces rectal relaxation, as suggested by preclinical trials.[34] To date, no clinical trial specifically aimed at this major outcome measure or targeted this problem in a systematic fashion.

Six large international, randomised, multicentre, double-blind, placebo-controlled studies with a minimum 12-week treatment phase provide information about the efficacy of alosetron for the treatment of diarrhoea-predominant IBS patients.[34-39] In phase II dose-ranging studies, alosetron 1mg taken twice daily showed the most favourable treatment response.[34] In female patients, alosetron was associated with significantly greater improvements in pain and in bowel function (urgency, stool consistency and stool frequency) compared with placebo. The response was seen within the first 2 weeks of treatment. In contrast, no significant effect over placebo was seen with alosetron in male patients in those few trials that also assessed the treatment response in both genders.[40] In a phase III trial, 647 female, non-constipated IBS patients were randomised to either alosetron 1mg twice daily or placebo in a 12-week treatment study,[37] similar in design to earlier phase II trials. In this trial, again, alosetron produced a modest but significant relief of abdominal pain and improvement in bowel function. The therapeutic effects were usually seen within the first 2 weeks of treatment and disappeared promptly after discontinuation of this drug. The therapeutic effect was most prominent in diarrhoea-predominant female patients, while a smaller treatment effect was seen in those with alternating bowel habit. The efficacy (absolute difference between alosetron and placebo response rates) was 10, 7 and 9% for months 1, 2 and 3, respectively.[37] The main outcome used was relief of pain or discomfort for at least 2 weeks in the month. Forty-one percent of patients reported adequate relief for all 3 months compared with 29% of those on placebo.[37] Stool frequency improved by 22%, while stool consistency also improved by 19% and bowel urgency of defecation by 16%. These beneficial effects were sustained over the 3-month treatment period.

A head-to-head comparison of alosetron with the peripheral smooth-muscle relaxant mebeverine[36] was conducted in 623 non-constipated IBS female patients. This trial had no placebo control. A significant benefit of alosetron over mebeverine was identified by the fourth week of treatment and was generally maintained over the 3-month period. However, symptoms returned to baseline when the drug was stopped.

Why the effects of alosetron appear to be gender specific remains unexplained. Similar results were obtained in other functional bowel disorders such as non-ulcer dyspepsia, supporting the suggestion of drug-specific gender differences. Those may be due to pharmacological differences regarding serum drug levels during treatment with alosetron.[17] On the other hand, experimental studies also suggest the existence of disease-specific gender differences. In brain imaging studies, the activation of cerebral areas involved in processing visceral stimuli has consistently been found to be greater in men compared with women in response to standard rectal pressure stimulus,[41] suggesting that females and males may process visceral pain differently. However, preliminary experiences with other drugs (e.g. cilansetron) suggest that this novel 5-HT_3 antagonist may also be more efficient than placebo, while no gender differences were observed.[42]

To date, no head-to-head clinical trials comparing alosetron with loperamide, an opioid antagonist that slows colonic transit, have been performed. Loperamide proved superior to placebo in the relief of diarrhoea in IBS but failed to relieve IBS-associated pain.[43] For this reason loperamide is not considered to be an IBS-specific treatment, while serotonin antagonists such as alosetron or cilansetron appear to have at least the potential to relieve IBS pain scores to a certain extent, which is also the case in functional dyspepsia. This statement is in keeping with the fact that alosetron not only improves global IBS symptoms but also the health-related quality of life[44] suggesting that alosetron may be more than a mere 'constipation-inducing agent'. This is also in line with the mechanistic preclinical trials that demonstrated effects of alosetron on rectal compliance and afferent CNS function.

One recent meta-analysis assessed the overall efficacy of all published evidence-based clinical studies,[45] as shown in figure 2. Specifically, the effect of alosetron on adequate relief of pain or global improvement of symptoms in IBS patients was analysed. A total of 1762 patients were randomised to alosetron treatment and 1356 to placebo. Seventy-five percent of patients included in all six trials had diarrhoea-predominant IBS and 93% of patients in all six trials were females. The overall

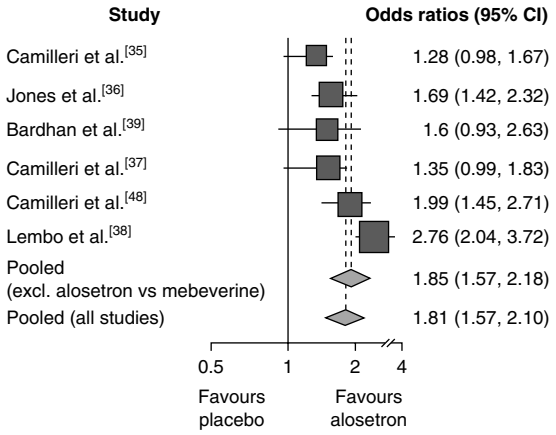

Fig. 2. Overview of the meta-analysis of key clinical trials regarding efficacy of alosetron in the treatment of diarrhoea-predominant irritable bowel syndrome. **excl.** = excluding.[45]

results were not too enthusiastic. The average number of patients needed to treat with alosetron for one patient to achieve improvement over placebo was seven (figure 3), while the pooled odds ratio for adequate relief of pain or global symptom improvement was 1.81 (95% CI 1.57, 2.1).

Besides IBS-symptom reduction, alosetron treatment has been demonstrated to improve health-related quality of life. Quality-of-life assessments during clinical trials showed improvement in all tested domains (emotional health, mental health, sleep, energy, physical functioning, food/diet, social functioning, role-physical, and sexual relations) in the alosetron treated patients compared with patients receiving placebo.[44] Moreover, alosetron therapy was associated with a reduction of work absenteeism, which is considered to be an important issue regarding the health economic impact of the IBS.[46]

3. Safety Profile

In the pre-marketing studies, the most important adverse effect of alosetron in all trials was constipation, which was clearly dose-dependent and more frequent in female patients and in patients with alternating bowel habits (20–30% of patients on alosetron 1mg twice daily were affected, compared with 3% on placebo).[35-37] This adverse effect is actually not surprising since one of the known pharmacodynamic actions of alosetron is the delay of colonic transit time.[47] The recently published meta-analysis[45] of all six high-quality clinical trials on alosetron confirmed that approximately one out of four patients may develop constipation during the treatment with alosetron administered as 1mg twice daily (number needed to treat = 3.9). The overall differences are shown in table I. Among those patients affected by constipation, the proportion of patients who had to withdraw from the study because of constipation was 10–43%. There was no difference between the placebo treatment group and the alosetron group when other adverse effects were assessed. However, in these six clinical trials, two cases of ischaemic colitis were reported in the alosetron-treated group of patients, with a calculated prevalence of 0.1%. Possible aetiological co-factors for the development of ischaemic colitis were possible infectious gastrointestinal disorder in one patient and protein C deficiency in another patient.

Hence, ischaemic colitis was recognised as an adverse effect prior to licensing. The estimated incidence of 1 out of 750–1000 treated patients proved to be reasonably accurate during the post-licensing period. However, after approval of the drug in February 2000 by the US FDA, growing concern about the safety profile of alosetron arose when there were several reports of severe complications of ischaemic colitis and severe constipation requiring hospitalisation and in some cases even inducing bowel perforation and requiring surgery, including colectomy. By the time of market withdrawal in November 2000, the FDA had registered 70 cases of severe complications (49 ischaemic colitis and 21 severe constipation), of which 44 resulted in hospitalisations, ten in

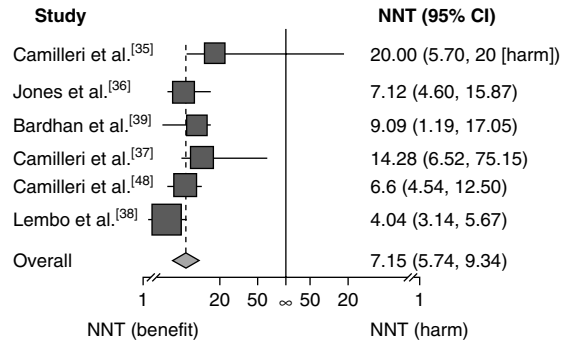

Fig. 3. Overview of the numbers of patients needed to treat (NNT) to achieve a clinical benefit from alosetron treatment in patients with diarrhoea-predominant irritable bowel syndrome. [45]

Table I. Odds ratios (95% CI) for adverse events in patients receiving alosetron versus patients receiving placebo or mebeverine

Study	All adverse events	Constipation
Camilleri et al.[35]		3.57 (1.92, 6.6)
Jones et al.[36]	1.22 (0.87, 1.69)	10.59 (9.15, 12.25)
Bardhan et al.[39]	1.21 (0.72, 2.02)	7.6 (2.19, 26.26)
Camilleri et al.[37]	1.69 (1.22, 2.32)	3.96 (3.24, 18.5)
Camilleri et al.[48]	2.54 (1.74, 3.58)	6.68 (4.99, 8.92)
Lembo et al.[38]	1.69 (1.22, 2.32)	3.96 (3.24, 4.8)
Overall	1.70 (1.42, 2.04)	5.64 (4.40, 7.33)

surgery and three in deaths. Two additional reports of death were not classified as being cases of ischaemic colitis or severe complications of constipation.[49] Although cases of ischaemic colitis were relatively rare and in most cases rather mild, it affected approximately 1 out of 750 patients receiving alosetron. Considering the pharmacological mode of action of alosetron, the possible mechanisms for this agent to cause ischaemic colitis are not known. However, those individuals affected were frequently relatively young and did not necessarily have any other predisposing illnesses or risk factors for developing ischaemic colitis. There was no clear relationship between ischaemic colitis and a current or past history of constipation and among those patients affected by severe serious adverse effects, not all had been prescribed the drug inappropriately. So far, there is one case report describing development of severe ischaemic colitis with the other experimental compound cilansetron, suggesting that this complication may indeed be an 'intrinsic' class effect of 5-HT_3 antagonists in general, which remains to be assessed in further clinical studies.

4. Marketing History

Alosetron was developed as a drug for functional gastrointestinal disorders such as the IBS based on its favourable combination of pharmacological effects on colonic motility, secretion, and possible afferent sensory mechanisms. Clinical trial data supported the drug's potential to alleviate visceral pain, discomfort, and bowel function disturbances such as urgency, straining and stool frequency especially in female patients with diarrhoea-predominant IBS.[35-37] These data finally led to the FDA approval of alosetron as the first IBS-specific pharmacological treatment in the US in February 2000, which resulted in many thousands of prescriptions made all over the US. Soon after marketing of the drug, however, several reports about serious adverse reactions such as severe constipation, ischaemic colitis, and death associated with this drug were published in medical journals and in newspapers. In a talk paper,[49] the FDA communicated details regarding 70 cases of severe reactions reported as of 10 November 2000 (see section 3). Because of these reports the drug company GlaxoSmithKline voluntarily withdrew the drug from the market within a short period of time. However, this decision was followed by thousands of letters to the FDA and GlaxoSmithKline written by patients who had experienced relief of symptoms and improvement of quality of life by taking alosetron. Finally, the FDA and GlaxoSmithKline agreed on a risk-management plan ensuring a restricted use in selected patients with severe IBS, providing a careful postmarketing surveillance and requiring further clinical research (e.g. on specific safety issues and on clinical efficacy with different dosage regimes). This agreement led to a new FDA policy, which finally re-approved the supplemental New Drug Application in June 2002 permitting alosetron back on the drug market under highly restricted conditions (see section 5) and putting the manufacturer GlaxoSmithKline in charge of the risk-management programme. This drug history is absolutely uncommon, since this is the first time that a drug has been withdrawn from the market and then returned to the market.

5. Restrictions of Use

The FDA has permitted marketing of alosetron only with severe restrictions and the implementation of a risk-management programme, which is conducted by the manufacturer GlaxoSmithKline. Those safety-measures include the following:

- The indication is now narrowed to the treatment of women with severe, diarrhoea-predominant IBS that is refractory to conventional IBS therapy trials. This measure aims to assure that only those patients receive alosetron who are the most likely to benefit from therapy and who may at the same time be deliberately willing to accept the risks of developing severe constipation or ischaemic colitis. Indications and contraindications defining the

criteria for patient selection are listed in table II.[16]

- GlaxoSmithKline is establishing an educational programme for alosetron. Physicians who want to prescribe alosetron have to report that they are qualified to diagnose IBS and to recognise and manage complications such as constipation or ischaemic colitis and they must enroll in GlaxoSmithKline's prescribing programme (http://www.Lotronex. com). In addition, they need to understand the full-scale risks of using alosetron in their clinical practice under the imposed restrictions which they confirm by signing the 'physician attestation form'. These physicians must also promise to educate the affected patients about the risks of adverse effects potentially developing during the treatment with alosetron, to have them sign a 'patient-physician agreement' (see http://www.fda.gov/cder/drug/infopage/Lotronex/Lotronex.htm) and to provide them with a copy of the FDA-approved medication guide. Finally, enrolled physicians must report all serious adverse events associated with alosetron to GlaxoSmithKline within a narrow time frame or to the FDA directly.
- A further measure to improve the safety of alosetron intake is a new dosage recommendation. Eligible patients should now first take 1mg alosetron per day for 4 weeks. If, after 4 weeks, the 1mg dose is well tolerated but does not adequately control IBS symptoms, it can be gradually increased to 1mg twice daily, the dosage used in controlled clinical trials.[35-37] The drug should then be discontinued if it does not provide adequate control of IBS symptoms after another 4 weeks of treatment at the 1mg twice daily dose to avoid serious adverse effects. Under no circumstances should the dosage of 1mg twice daily be increased, since no beneficial effects can be expected from further dosage escalation attempts in this clinical setting.
- Another FDA restriction measure concerns the pharmacists who are now to fill out only those prescriptions that display a prescribing programme sticker affixed by programme-enrolled physicians, and who are required to hand out to each patient a copy of the FDA-approved medication guide every time they dispense the drug.
- Finally, the drug company GlaxoSmithKline is obliged to conduct further clinical trials on alosetron including interaction studies, genetic studies concerning CYP enzyme polymorphism, studies on the pathomechanism of alosetron-induced ischaemic colitis, trials on the safety and efficacy of lower dosages and of an 'as-needed' administration and a large epidemiological study on the use and safety of alosetron in the US practice.

During this close surveillance period, the FDA advisory committee and GlaxoSmithKline are closely cooperating to be able to revisit and re-evaluate

Table II. Indications and contraindications defining the criteria for patient selection for treatment with alosetron in irritable bowel syndrome (IBS)[16]

Patients are eligible for alosetron treatment only, if all of the following criteria are met:
The patient is a woman
She has a severe form of IBS, which is diarrhoea-predominant and has produced continuous symptoms lasting for more than 6 months (severe is defined as frequent and severe abdominal pain, bowel urgency, faecal incontinence or restriction of daily activities)
Consequent conventional treatment attempts have clearly failed (e.g. with loperamide and dietary modifications)
No contraindications to the drug are present, particularly no ischaemic or inflammatory bowel disorders
The patient registers with the manufacturer (GlaxoSmithKline) to receive the drug
The patient is individually educated about this particular drug and signs a patient-physician agreement form (forms can be downloaded from the Internet at http://www.fda.gov/cder/drug/infopage/Lotronex/Lotronex.htm)
Patients are ineligible for alosetron treatment in any of the following cases:
The patient is a man
The patient has only a mild-to-moderate form of IBS
The subtype of IBS is not diarrhoea-predominant
Other treatment options have not yet been tested
Other therapies sufficiently improve symptoms
Any of the following contraindications to the drug are present:
chronic or severe constipation or history of sequelae from constipation
current or past inflammatory bowel disease or diverticulitis
a clinical history of intestinal obstruction, bowel stricture(s), toxic megacolon, gastrointestinal perforation, adhesions, ischaemic colitis, impaired intestinal circulation, thrombophilia, thrombophlebitis or a hypercoagulable state
patient is unable to understand or comply with the 'patient-physician agreement'
known hypersensitivity to any component of the product

the approval of alosetron in due course while under these conditions it is not yet known how many patients may be eligible for alosetron treatment and might potentially benefit from its long-term use.

However, there are some critical aspects concerning the alosetron safety programme and the current benefit/risk ratio.

First, it remains a matter of continued debate, whether it was a good idea to set the manufacturer in charge of overseeing the risk-management programme. Presumably this was mainly a cost-related decision, since otherwise there would be the need for a government-funded programme. Now, the main responsibility of the risk-management programme lies with the manufacturer GlaxoSmithKline who have the duty to monitor and report the prescribing, the actual use and the potential adverse effects of alosetron and most importantly to react in cooperation with the FDA in case the collected information showed further safety concerns. Moreover, the safety programme relies on the 'goodwill' of the other concerned parties, i.e. the physicians, pharmacists and patients. Actually, there is no control system to verify the different safety measures, e.g. to evaluate whether patients have been fully and properly informed of the risks of alosetron treatment or whether adverse events are properly reported and thoroughly monitored.

Another critical point of the risk-management programme is the dosage reduction to 1 mg/day. In the preclinical and clinical trials, this dosage was not significantly more effective than placebo. In 12% of the first cases of ischaemic colitis reported to the FDA, patients had received a dose of 1 mg/day, i.e. the same dosage as has now been approved for the new marketing plan. Some of the early clinical trials also showed a significant increase in constipation rates at even this low dosage treatment with alosetron, which led to study termination in a fairly significant number of patients.

Finally, it could be argued that adverse events in the past had happened without any warning signs and even in correctly selected patients with diarrhoea-predominant IBS. Therefore, the current safety measures might not be able to prevent any new cases of ischaemic colitis or severe constipation. This issue leads to the major question of whether it could be tolerated that any medical treatment for a benign, non-life threatening disease may possess the risk to cause serious, potentially life-threatening adverse effects. This question has been widely discussed, and opponents of the re-approval of alosetron have criticised the FDA for the decision to allow this drug back on the market under the given circumstances.[50-54]

6. Conclusion

Alosetron was the first approved IBS-specific drug whose mode of action was based on the emerging knowledge of the potential pathophysiological relation between IBS symptoms and the serotoninergic system in the bowel and the brain-gut axis. However, first hopes of this 'new era' of IBS treatment approaches had been disappointing as severe adverse effects resulted in the market withdrawal of alosetron only a few months after its first approval in 2000. Following public pressure (mainly by IBS patient organisations) and the proposal of a careful postmarketing surveillance, alosetron was re-approved in 2002 under highly restricted conditions and is now given a second chance to prove a more favourable benefit/risk profile in a very selected subset of IBS patients. Under the new marketing limitations and severe therapeutic restrictions since re-approval in 2002, it is not yet known how many patients with IBS may still be eligible for alosetron treatment and might potentially benefit from its long-term use. Hence, it is rather difficult to assess the clinical significance of this drug in a greater clinical setting outside of carefully monitored studies. At best, the new approach of a restricted use of alosetron only in female patients with severe, refractory diarrhoea-predominant IBS (i.e. only in those patients who are most likely to benefit from this agent and least likely to experience adverse effects such as constipation) will emerge a much better benefit/risk ratio than its widespread and sometimes uncritical use in the recent past. In this case, alosetron could eventually emerge as an alternative medication for a distinct number of female patients with otherwise untreatable diarrhoea-predominant IBS. This number, however, is expectably small, since there are several strings attached before the treatment can be started (see section 5). In a worst-case scenario, on the other hand, alosetron could again be banned by the FDA in case more patients should

emerge who develop serious adverse effects even under the restrictions imposed by the FDA. This will be seen in the near future. At present, the use of alosetron is justified for carefully selected patients under close surveillance, where a favourable benefit/risk ratio could be expected. The re-release of alosetron, however, may in the near future also push the development of other 5-HT_3 antagonists that will hopefully have a better safety profile.

Taken together, the 'alosetron story' underlines once more the difficulty in developing an adequate drug for the treatment of the IBS; since functional disorders such as IBS cause substantial morbidity but no mortality, an 'ideal' drug must not only be efficient but also extremely safe for the long-term treatment of these chronic benign conditions. However, alosetron is about to get its 'second chance' of demonstrating its safety profile under controlled conditions in a clinical setting and the drug might still find a niche as a treatment option for selected and severely affected female IBS patients.

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