Symposium article
The development of tropisetron in its clinical perspective

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Summary

This review discusses the development of tropisetron as an antiemetic drug with the patient in mind. The original aims of the programme and the progress achieved towards them to date are described. The efficacy and safety data from two dose-ranging studies and four comparative-treatment studies with tropisetron were combined in a prospectively planned meta-analysis of 799 patients. An integrated safety summary is presented which includes all patients from the six studies. Tropisetron at a dose of 5 mg once daily is an effective and well-tolerated, single-agent, antiemetic treatment, which can be given without special precautions to all patients receiving highly emetogenic chemotherapy. In comparison with metoclopramide, tropisetron is more effective in the prevention of nausea and vomiting. When compared with the most potent cocktail treatments currently in use (containing high-dose metoclopramide, dexamethasone and lorazepam or diphenhydramine), tropisetron is equally effective in the prevention of acute vomiting and somewhat less effective in the prevention of nausea. Overall, tropisetron is an effective and well-tolerated antiemetic treatment that is simple to administer, comparing well with currently available antiemetic cocktails. Tropisetron remains effective for the prevention of nausea and vomiting during multiple chemotherapy courses. The simple dosing schedule (5 mg i.v. day 1; one 5 mg capsule daily, days 2–6) makes tropisetron ideal for both inpatient or outpatient use.

Key words: antiemetic, cancer chemotherapy, nausea, 5-HT3 receptor antagonist, tropisetron, vomiting

Introduction

It is essential for any new chemical entity to undergo a thorough investigation before being accepted by regulatory and medical authorities. This review will discuss the clinical development of a new 5-HT3 receptor antagonist, tropisetron (Navoban® Sandoz Pharma Ltd), as an effective antiemetic drug, undertaken with the patient in mind. The original aims of the clinical programme and the progress towards them until the submission of the registration dossier will be described. At the beginning of the clinical development of tropisetron, there were no 5-HT3 receptor antagonists in usage; therefore, tropisetron was mainly compared with antiemetic cocktails based on high-dose metoclopramide. As tropisetron has now entered clinical practice, this review will be extended to include the efficacy and safety results for the drug to date, set against the original objectives, and its future potential in the treatment of drug-induced emesis.

Early development objectives

Following successful dose-finding and tolerability studies with tropisetron, the clinical development proceeded to Phase III. Given the therapeutic burden that cancer patients normally have to bear, it was decided, at the outset, that studies with tropisetron would be designed from the patient's perspective. The ideal antiemetic drug should be:

- well tolerated;
- effective;
- simple to administer;
- universally applicable;
- better than existing therapies.

Initially, a careful selection needed to be made of patients, efficacy and tolerability endpoints, and of appropriate comparative treatments for the evaluation with tropisetron. Furthermore, a significant consideration of the study design was the selection of the correct efficacy endpoint criteria. Most importantly, it was essential to distinguish between observations of symptoms made by investigators and those made by the patients themselves. It was decided that patients should become involved in recording episodes of nausea and vomiting as well as adverse events in their diaries, throughout the development programme.

Clinical studies for the registration dossier

Methodology

Trial design of antiemetics is limited by the need to prevent nausea and vomiting in all patients receiving can-
cer chemotherapy. The major problems are caused by moderate-to-severely emetic chemotherapy, and high-dose cisplatin was chosen as standard chemotherapy for the dose-finding and comparative-treatment studies in the tropisetron programme. This precluded the inclusion of a placebo-control group in these studies. Since, ethically, it is difficult to carry out placebo-controlled studies in patients receiving anything other than mildly emetogenic chemotherapy. Since, without antiemetic treatment, almost 100% of patients would suffer nausea and vomiting following highly emetogenic chemotherapy, the efficacy of tropisetron was represented by the number of patients not suffering nausea and vomiting during antiemetic treatment.

**Comparative treatments**

The choice of comparative treatment depended largely on the type of chemotherapy the patients were receiving. In some cases, high-dose metoclopramide was chosen, and in others, antiemetic cocktails, containing high-dose metoclopramide, high-dose corticosteroids and benzodiazepines, were considered to be the best alternative treatment at that time, even though extrapyramidal side effects, especially in the young, could be expected to occur frequently [1]. The difficulty in maintaining impartiality amongst experienced investigators who, in many cases, could recognize antiemetics from their side effects was the main reason for not using double-blind, controlled studies in our trial programme. Therefore, tropisetron was clinically evaluated in randomized, open, parallel-group studies.

**Definition of criteria of antiemetic response**

Total control of vomiting was defined as no vomiting, and partial control as the occurrence of one to four vomits. Sometimes partial control was divided further into major (one or two vomits) and minor (three or four vomits) control. No control was defined as the occurrence of five or more vomits. A single episode of nausea was defined as one ‘clock hour’ in which nausea occurred. Total control of nausea was defined as zero episodes of nausea in a 24-hour period, and partial control as the occurrence of 1–4 episodes of nausea in the same time period. No control of nausea was defined as the occurrence of 5 or more episodes of nausea. The choice of duration of nausea, rather than of severity, was made in order to eliminate subjective interpretation of nausea by patients or observers and to allow a simple quantification for the statistical analysis.

In order to recognize the importance of delayed nausea and vomiting, these parameters were assessed on days 2 to 7 after chemotherapy. This posed a practical problem, since many patients left hospital the day after their chemotherapy. Therefore, the information kept by the patients in their diaries during the entire observation period formed the basis for the efficacy analysis.

**Efficacy assessment**

**Pilot studies**

Pilot studies of tropisetron in cytostatic drug-induced emesis were performed by three groups who determined that the drug was effective over a wide dose range and that a single dose was effective for up to 24 hours [2–4]. In general, tropisetron was well tolerated.

**Dose-finding studies**

Two dose-finding studies, involving 217 patients, showed that a single dose of tropisetron was effective as an antiemetic for at least 24 hours after highly emetogenic chemotherapy. In the first study (Van Belle et al., unpublished data), a 5 mg dose was shown to be as effective as a 10, 20 or 40 mg dose, and more effective than a 2 mg dose (Stamatakis et al., unpublished data) used in the second study. Following a single, 5 mg dose of tropisetron, 66% of patients were free from acute nausea and vomiting, and this dose was selected for the comparative-treatment studies.

**Comparative-treatment studies**

For registration purposes, there were four comparative-treatment studies, in addition to the two dose-finding studies described above, which focused on efficacy and on providing an integrated summary of safety. Overall, 582 patients were studied, of whom 309 received tropisetron. All patients had a proven malignancy and were treated de novo with highly emetogenic chemotherapy, often based on high-dose cisplatin. Patients were followed up for one to three chemotherapy courses of 1 to 7 days' duration.

In study I, tropisetron was compared with metoclopramide given either as monotherapy (1.5–4 mg/kg) or in combination with lorazepam (2–4 mg) in patients receiving non-cisplatin therapy. Tropisetron was more effective than metoclopramide (with or without lorazepam) in preventing nausea and vomiting (Fig. 1). In studies II–IV, tropisetron was compared with antiemetic cocktails (metoclopramide 4 or 7 mg/kg, dexamethasone 20–24 mg and lorazepam 1 mg or diphenhydramine 50 mg) in patients receiving cisplatin therapy. Tropisetron was equally effective as the antiemetic cocktails in preventing acute vomiting but somewhat less effective in preventing acute nausea (Fig. 2). When patients were followed up for more than one treatment course, however, the antiemetic cocktails proved to be no longer superior to tropisetron, and more adverse events, especially extrapyramidal reactions, were observed than with the 5-HT\textsubscript{3} receptor antagonists.

A prospectively planned meta-analysis of the efficacy and safety data from all of the above studies was obtained by combining data from the two dose-finding studies and studies I–IV, in a total of 799 patients; of these, 417 patients received the recommended regimen of tropisetron 5 mg once daily.
Integrated safety summary

For the purpose of the safety aspects of tropisetron in the meta-analysis, an adverse event was defined as any event reported during the study, without necessarily being causally related to antiemetic treatment. A side effect was defined as an adverse event considered related to drug treatment. Tropisetron (5 mg once daily) was well tolerated for the 6-day period. Headache, constipation and diarrhoea with abdominal pain, fatigue and dizziness were the most frequently reported adverse effects (Table 1). Headache, which was generally mild, and constipation with abdominal pain were the only adverse events that recurred in the same patients during repeated courses of tropisetron and must, therefore, by definition, be considered to be side effects of tropisetron. Only one patient out of 417 receiving tropisetron discontinued treatment because of headache. Extrapyramidal adverse events were absent following tropisetron treatment. The adverse-event profile of tropisetron did not change during repeated administration over two or three courses. It was concluded that treatment with tropisetron (5 mg once daily) for the prevention of cytostatic drug-induced emesis did not present the patient with any undue risk.

The side-effect profile of tropisetron compared favourably with that of metoclopramide monotherapy (Table 1). Whilst tropisetron was associated with a greater incidence of headache and constipation, the antiemetic cocktail comparators were associated with a greater incidence of diarrhoea, fatigue, and particularly, extrapyramidal reactions. Furthermore, eight out of 222 patients in the antiemetic cocktail group were withdrawn from treatment during the comparative trials because of extrapyramidal reactions.

Further clinical studies

During the evaluation and acceptance procedure of the registration dossier on tropisetron and in preparation for its entry into clinical practice, a number of new studies were initiated and partially completed. Once again, these studies departed from the patients’ needs and were tailored to clinical oncology practice. This
The combination of tropisetron and dexamethasone and equally effective as the tropisetron monotherapy in patients with an incomplete response in the first course proved superior to that of tropisetron and placebo in the tropisetron plus rescue treatment of the investigators' choice. With an antiemetic treatment failure received tropisetron continued on tropisetron monotherapy and patients cisplatin [8]. Patients with a complete emesis control subsequent identical chemotherapy course with high-dose dexamethasone for six days during a sub-sequent high-dose dexamethasone for six days during a sub-
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sequential antiemetics [5-7] or to tropisetron itself [8]. Furthermore, studies were performed for radiotherapy-induced nausea and vomiting in patients with metastasised gynaecological tumours [9], for chemotherapy-induced emesis in children [10-12] and for post-operative emesis [13]. Some of the results are presented elsewhere in these proceedings [5, 6, 10, 13].

In an open study 231 patients with a previous antiemetic treatment failure were randomised to receive either tropisetron monotherapy (5 mg/day for 6 days) or the best alternative non-5HT3-receptor antagonist treatment of the investigators' choice during a subsequent identical chemotherapy course [5]. Tropisetron monotherapy completely prevented acute vomiting in half of the patients with a previous treatment failure, whereas the alternative treatment only prevented it in one-quarter (p = 0.001). Tropisetron also prevented the vomiting on subsequent days in a higher proportion of patients than the alternative treatments (p = 0.001). Moreover, when vomiting occurred, it was less severe in the tropisetron group than in the alternative treatment group (median number of vomiting per entire treatment course 1 vs. 7, respectively, p = 0.001). The superiority of tropisetron over alternative treatment was also apparent with respect to nausea but the differences were less striking.

In a double-blind, placebo-controlled study 160 patients with a previous incomplete emesis control on tropisetron monotherapy were randomised to receive either tropisetron plus placebo or tropisetron plus high-dose dexamethasone for six days during a subsequent identical chemotherapy course with high-dose cisplatin [8]. Patients with a complete emesis control continued on tropisetron monotherapy and patients with an antiemetic treatment failure received tropisetron plus rescue treatment of the investigators' choice. The combination of tropisetron and dexamethasone proved superior to that of tropisetron and placebo in patients with an incomplete response in the first course and equally effective as the tropisetron monotherapy in patients with a complete response in the first course. The addition of open-label rescue treatment improved the response from failure to partial, but did not eliminate all emesis during the entire course, probably because the rescue treatment was limited to the first two treatment days only. In conclusion, tropisetron monotherapy is a good first-line antiemetic treatment; if patients are not fully controlled by monotherapy, dexamethasone should be added and given for six days for it to bring the full clinical benefit.

In many countries a compassionate need programme was set up as a national study in order to prospectively collect data on efficacy and safety. Patients were eligible if they had suffered an antiemetic treatment failure during previous chemotherapy or if they were expected to suffer side effects or to be inadequately controlled by conventional antiemetic treatments. Many of these programmes are still ongoing. The experiences to date from the Nordic countries and from Belgium are reported elsewhere in these proceedings [6, 7]. They show that tropisetron monotherapy prevents all further emesis in more than 60% of these high-risk patients and adequately controls it in another 25 to 35%. Importantly, only headache and constipation were reported as adverse events, but their frequency was considerably lower than those emerging from the comparative treatment studies.

The first experiences with children are promising as reported in these proceedings [10] and elsewhere [11, 12].

**Conclusions**

In conclusion, the question may be asked whether the goal was reached of developing the ideal antiemetic treatment. Since the complete absence of emesis in all chemotherapy-treated patients remains the ultimate goal of antiemetic treatment, the answer to the above question is 'not quite'; especially the control of delayed emesis remains a challenge. However, many of the objectives were accomplished in the development of

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**Table 1. Meta-analysis summary of adverse events, by antiemetic therapy.**

<table>
<thead>
<tr>
<th></th>
<th>Tropisetron monotherapy</th>
<th>Metoclopramide monotherapy</th>
<th>Antiemetic cocktail</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>417</td>
<td>51</td>
<td>222</td>
</tr>
<tr>
<td>No. (%) of patients</td>
<td>1 (0.2)</td>
<td>0</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Total no. of adverse</td>
<td>761</td>
<td>67</td>
<td>484</td>
</tr>
<tr>
<td>events</td>
<td></td>
<td></td>
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<tr>
<td>Percentage of adverse</td>
<td>3</td>
<td>4</td>
<td>16</td>
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<tr>
<td>events attributed to</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>antiemetic therapy</td>
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<td>(defined as side effects)</td>
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<td>Most frequent adverse</td>
<td></td>
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<td>events (% of treated</td>
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<tr>
<td>patients)</td>
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</tr>
<tr>
<td>Headache</td>
<td>27</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Extrapyramidal reactions</td>
<td>0.7c</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

a Relationship to antiemetic treatment uncertain or absent; b ataxia, agitation, dystonia, involuntary muscle contraction, teeth grinding, tremor, oculogyric crisis; c Two patients with muscle cramp, one patient with peripheral nerve damage and ataxia.
tropisetron: 5 mg once daily tropisetron is a simple, effective and well-tolerated antiemetic treatment that can be administered to all patients receiving emetogenic chemotherapy. Tropisetron is effective both as a first-line and as a rescue treatment. If tropisetron monotherapy does not offer complete antiemetic protection, its efficacy may be enhanced by the addition of dexamethasone. First clinical results suggest that this combination must be given for six days to also control the delayed emesis. The efficacy of tropisetron (with or without dexamethasone) will allow more freedom to apply the cytotoxic dose needed for optimal anti-cancer treatment. The simple dosing schedule of a single daily 5 mg injection or capsule renders tropisetron ideal for both in- and out-patient use.

References

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