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Letter to the editor

Re: 'Cost-effectiveness of 5-hydroxytryptamine$_3$ receptor antagonists: a retrospective comparison of ondansetron and granisetron'

Rob Thwaites, TV Parasuraman and Walter Paska
Glaxo Wellcome Research and Development Ltd; Greenford Road, Greenford, Middlesex UB6 0HE, UK.
Tel: (+44) 181 422 3434; Fax: (+44) 181 426 8243.

The article by Johnson and Bosanquet (Cost-effectiveness of 5-hydroxytryptamine$_3$ receptor antagonists: a retrospective comparison of ondansetron and granisetron. *Anti-Cancer Drugs* 1995; **6**: 243–49) raises an important issue—cost-effectiveness—in the decision over which 5-HT$_3$ receptor antagonist to select for prevention of chemotherapy-induced emesis (CIE). Not only is CIE a distressing problem with potentially serious clinical implications if not treated but, as the authors highlight, it can also have important cost consequences. *The authors' conclusion that granisetron is more cost-effective than ondansetron is not, however, supported by the clinical results and it would be inappropriate to infer that granisetron is the more cost-effective drug in clinical practice.*

The authors incorrectly state that the Noble study, one of the two clinical studies used in their cost-effectiveness analysis, was financed by Glaxo. The Noble study was conducted by the Granisetron Study Group and was not funded by Glaxo.

We also disagree with the authors on several main points in the article including the method of economic evaluation, the inappropriate application of rescue costs, the use of an outdated ondansetron dosing regimen and the interpretation of the preference data. These shortcomings are discussed below.

The significant differences in effectiveness required for a cost-effectiveness analysis have not been demonstrated between the two drugs

The clinical studies (Bonneterre *et al.* and Noble *et al.*) upon which the economic evaluation was based both concluded that there was no statistically significant difference in efficacy between ondansetron and granisetron. Despite this, the Johnson and Bosanquet analysis uses the numerical differences in efficacy to build the central cost-effectiveness analysis. This is not supportable: in the absence of any clinical conclusions that the products are different in terms of efficacy, the appropriate method of economic evaluation is a cost-minimization analysis (i.e. analysis and comparison of costs where two or more interventions have been demonstrated or assumed to be equivalent in terms of the outcome or consequence).

Other head-to-head studies comparing ondansetron and granisetron have typically found no statistically significant differences in efficacy between the two drugs. (See, for example, Ruff *et al.* Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced emesis: a multicentre double-blind, randomized, parallel-group study. *Oncology* 1994; **41**: 113–8; which found no difference in efficacy between ondansetron and granisetron in acute emesis, and Roila *et al.* Ondansetron vs granisetron, both combined with dexamethasone in the prevention of cisplatin-induced emesis. *Proc ASCO* 1995; **14**.) Jantunen *et al.* in an open, crossover study, did find statistically significant better control of acute vomiting with granisetron (80%) than with ondansetron (69%), but commented that 'the observed differences in the control of emesis, although statistically significant, may not have clinical significance' (Jantunen *et al.* 5-HT$_3$ receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy —a randomized study. *Eur J Cancer* 1993; **29A**: 1669–72).

With no differences in effectiveness the appropriate decision rule is cost-minimization analysis. If, despite the lack of evidence for differences in effectiveness, it is expected that variations in the efficacy

rates might affect the conclusions, then the impact of any numerical differences in efficacy should be explored in a sensitivity analysis.

The study inappropriately ignores the costs of rescue medication

In their main analysis, Johnson and Bosanquet ignore the costs of rescue medication (i.e. costs of additional medication to treat nausea and/or vomiting). These costs are, however, a critical factor in the relative costs associated with the ondansetron and granisetron regimens. If rescue for the granisetron failures was not made with the same drug as rescue with the ondansetron failures, then there may be cost differences between the treatment arms that must be evaluated:

- In the abstract from the Bonneterre study (Bonneterre *et al.* Granisetron iv compared with ondansetron iv plus tablets in the prevention of nausea and vomiting induced by a moderately emetogenic chemotherapy regimen: a randomized, cross-over study. *SmithKline Beecham Satellite Symp Anti-emetic Control: Maximizing the Benefits*, November 14, 1993 at *ECCO 7*), only limited information is given about the approach to treatment and rescue: 'Ondansetron was given i.v. (8 mg) before chemotherapy followed by an 8 mg tablet every 8 h for 3 days. Granisetron was given as one i.v. 3 mg injection before chemotherapy; one or two rescue administrations were allowed but these patients were considered failures'. It appears that the ondansetron patients were simply continued on their ondansetron regimen if they suffered nausea or vomiting, while the (failed) granisetron patients were given up to two i.v. rescue administrations of granisetron.

- In the Noble study (Noble *et al.* A double-blind, randomized, crossover comparison of granisetron and ondansetron in 5-day fractionated chemotherapy: assessment of efficacy, safety and patient preference. *Eur J Cancer* 1994; **30A**: 1083–88), 'patients who experienced breakthrough nausea and/or vomiting on any chemotherapy day received up to two further blinded doses of granisetron 3 mg i.v. (patients receiving granisetron) or placebo granisetron (patients receiving ondansetron)'. Granisetron patients were rescued with granisetron, ondansetron patients were 'rescued' with only placebo. Only subsequent uncontrolled nausea and vomiting was treated with a standard anti-emetic of the physician's choice.

Clinical practice in the treatment of patients who are rescued will, of course, vary and may well differ from the approaches used in the design of these studies. Nevertheless, both the incidence and method of rescue are central factors to consider in the cost comparison of granisetron and ondansetron, and should be incorporated in any economic evaluation.

The analysis is based on three times daily dosing for ondansetron, whereas in all European countries, the approved regimen is twice daily

Although the clinical trials upon which the Johnson and Bosanquet analysis is based used three times daily dosing for ondansetron, ondansetron has been registered in all countries in Europe for twice daily dosing for some time now. Using the current data sheet regimen for ondansetron rather than the out-of-date regimen significantly reduces the cost of ondansetron compared with granisetron. [Importantly, the use of twice daily dosing with ondansetron does not increase the need for rescue medication compared with three times daily dosing. In the Dicato study which demonstrated that oral ondansetron given twice daily or three times daily was equally effective in controlling nausea and emesis, the proportion of patients defined as failures or requiring rescue was the same (10%) in both treatment arms (Dicato *et al.* Efficacy of twice daily versus three times daily oral ondansetron in the prevention of chemotherapy induced emesis: a randomized, single-blind, multicentre study. *Clin Oncol* 1992; **4**: 275–9).]

There are no strong patient preference data in favor of granisetron

The authors conclude by pointing out that 'two recent studies [Noble *et al.* and Jantunen *et al.*] have found that a preference was expressed for granisetron' and suggest that 'as granisetron has been shown in this analysis to be the more cost-effective antiemetic, the addition of patient preference in a quantifiable way will simply serve to reinforce this economic advantage'.

This conclusion is not supported by the Bonneterre study, which found no statistically significant difference between the patients preferring ondansetron (34%) and the patients preferring granisetron (39%).

Nor is it supported in the Noble study which found more patients undecided (39.2%) than preferred either ondansetron (25.6%) or granisetron (34%). Because granisetron failures were typically rescued with an active antiemetic, whereas the ondansetron failures were typically rescued with placebo, this difference is perhaps not surprising.

In summary, with the paucity of preference data, there is little reason to believe that patients prefer one drug rather than the other. The question of which drug provides treatment for the lower overall cost hinges critically on the assumptions made and, as differences in effectiveness have not been shown, it is incorrect for the authors to state that one drug is more cost-effective than the other.