Comments on "Clinical Value of Monitoring Plasma Octreotide Levels During Chronic Octreotide Long-Acting Repeatable Therapy inCarcinoid Patients"

To the Editor:

In the July 2008 issue of *Pancreas*, Woltering et al[1] have reported a decline in serum octreotide levels for 86 patients in their clinical practices compared with "historic" levels reported by Rubin et al[2] in 1999 and Woltering et al[3] in 2005. The authors state that their analysis was prompted by an apparent increase in episodes of flushing, diarrhea, and wheezing among their patients receiving stable or increasing doses of Sandostatin LAR (octreotide acetate). Among the hypotheses presented to explain their observation of lower octreotide levels, Woltering et al have suggested that a change in the drug formulation or its preparation has "dramatically decreased" the bioavailability of Sandostatin LAR. In response to the questions raised by Woltering et al, we conducted an extensive review of the authors' data, other published reports, and internal records. This review shows that

- Sandostatin LAR quality and efficacy have remained consistent since approval;
- all Sandostatin LAR released for distribution has met specifications for all process parameters and Good Manufacturing Practice (GMP) requirements;
- the authors' data are incomplete, and their conclusions cannot be verified; and
- the purported decline in octreotide levels between 2005 and the present is very likely an anomaly caused by selection bias and/or the effect of patient characteristics described below.

Since Sandostatin LAR was approved in the United States in 1998, tens of thousands of patients have used the medication to control the symptoms of carcinoid tumors as well as acromegaly. In acromegaly, efficacy is strongly correlated with octreotide plasma level, whereas no such relationship exists for carcinoid syndrome as noted by Woltering et al[3] in their 2005 publication. This published finding is inconsistent with the authors' present assertion that "Early in our clinical experience

TABLE 1. Mean ± SD Trough Octreotide Level (in pg/mL) After Monthly Doses of 30 mg Sandostatin LAR

	SMSE351		C2239	
Third dose	4430 ± 4370	n = 20 (14 M/6 F)	3430 ± 2320	n = 25 (13 M/12 F)
Fourth dose	3093 ± 2590	n = 19 (14 M/5 F)	4200 ± 2820	n = 18 (9 M/9 F)

M indicates male; F, female.

with octreotide level measurement, we noticed that patients who had increasing symptoms also had significant decreases in their octreotide plasma levels." In current clinical practice, carcinoid patients are dosed to control symptoms, not to a target octreotide level. Data from validated physician surveys beginning in 2003 and continuing until the present time have shown consistent satisfaction with Sandostatin LAR for the treatment of both carcinoid syndrome and acromegaly. In addition, a review of published data from multiple independent sources has shown consistent clinical efficacy with Sandostatin LAR in the treatment of patients with either carcinoid syndrome or acromegaly.

Novartis Oncology has attempted to understand the Woltering et al observations by conducting our own inquiry into this matter. Our first step was to perform a detailed and comprehensive review of the data generated for the Sandostatin LAR product's batch release and stability monitoring. This investigation determined that all data for drug product released since 1998 and until the present time met all specifications. Furthermore, all GMP requirements for the manufacturing, holding, distribution, and monitoring of the product for this same period were met. There is no evidence of a pre- versus post-2005 change in manufacturing and quality control procedures that would affect the product's bioavailability.[4]

Woltering et al have reported that in their patients who received 30 mg/mo of octreotide by continuous subcutaneous infusion, plasma octreotide levels were 5819 ± 3105 pg/mL. In the 2 pivotal studies in acromegaly patients (C201 and C202) conducted by Novartis, the relative bioavailability of Sandostatin LAR in comparison to subcutaneous octreotide was 43%[5]; other studies showed the range to be 50% to 60% in healthy subjects. The relative bioavailability of Sandostatin LAR in carcinoid patients is not known but should parallel that observed in acromegalic patients rather than healthy subjects. Therefore, the data of Woltering et al support an expectation of approximately 2500 pg/mL (0.43 × 5800) in the *average* octreotide steady-state level of intramuscularly administered Sandostatin LAR. In the authors' patients, monthly dosing with 30 mg intramuscular Sandostatin LAR produced trough levels of 2205 ± 1793 pg/mL. Clinical data show that trough levels of Sandostatin LAR are 10% to 12% lower than average levels. Therefore, the expected trough level based on the subcutaneous infusion data of Woltering et al would be 0.9 × 2500 = 2250 pg/mL, demonstrating no decline in the product's bioavailability.

This conclusion is further supported by the octreotide levels observed in an ongoing clinical trial, CRAD001C2239, a prospective, well-controlled study comparing the efficacy and safety of Novartis' developmental compound RAD001 in combination with Sandostatin LAR in the treatment of neuroendocrine tumors. The following table (Table 1) compares the steady-state trough octreotide levels in this study with SMSE351, the registration study for Sandostatin LAR, which was conducted in 1996/1997 and reported by Rubin et al[2] in 1999.

There was no meaningful difference in steady-state octreotide levels between the 2 studies. Novartis Oncology considers this finding to be significant because C2239 was conducted at the same time as the observations of Woltering et al. It is unlikely that RAD001 would affect octreotide levels, because the 2 compounds are cleared from the systemic circulation by different mechanisms and are not extensively bound to plasma proteins.

In the study of Woltering et al[1] in 2008, the authors have suggested that the patient composition in their report is similar to that in "2 previously published reports." However, the authors provided no data pertaining to patient characteristics to support this statement. Their clinical practices include many clinically challenging patients who have been referred by other physicians throughout the United States, resulting in a level of self-selection that can reinforce the influence of interpatient variability. This is very significant because high interpatient variability in octreotide levels has been recognized since the earliest trials of Sandostatin LAR in patients with carcinoid syndrome. Women and older patients had higher mean levels of octreotide than men and younger patients, and the rise to steady-state octreotide level was slower for women than for men.[2]

In their 2005 study, Woltering et al[3] noted the impact of sex and body weight on octreotide levels. However, they have not categorized patients in their 2008 study according to these criteria. We have confirmed the significance of these demographic covariates in a mixed-effects modeling analysis of 767 patients in 7 Sandostatin LAR studies conducted between 1996 and 2007, including the abovementioned studies SMSE351 and C2239. In our analysis, we observed that, in addition to sex and body weight, a patient's age, hepatic function, renal function, and lean body weight affect octreotide levels.[6] Therefore, the variation in mean octreotide levels when grouped by time into small data sets of as low as 8 or 10 patients per set (see tables 1–3 of Woltering et al[1]) may be explained by interset differences in these important patient covariates. The authors' data set of 162 octreotide level determinations in 86 patients, of whom 60 provided "multiple measurements," is clearly too small to derive meaningful conclusions based on intrapatient values.

Our analysis suggests that the unusually high "historic" octreotide level of 5200 pg/mL with 30 mg Sandostatin LAR in the 2005 study of Woltering et al,[3] which is used as a comparator to the 2008 study of Woltering et al,[1] may be due to the preponderance of female patients in this data set. Other patient variables as well as the analytical characteristics of the ISI radioimmunoassay to measure octreotide could also have contributed

to the apparently lower current octreotide values in comparison to the "historic" values. Thus, the assertion of Woltering et al in 2008 of no statistically significant change in the ISI octreotide assay between 2005 and their present study requires further substantiation, given the clearly lower levels for the current analyses, some by more than 20%, in all but one of the specimens analyzed (see figure 1 of Woltering et al[1]).

When first informed of the Woltering et al[1] 2008 observations, we requested the data for inclusion in our mixed-effects model analysis. The data set provided to us by Woltering et al contained numerous inconsistencies and was missing information that we have not been able to reconcile despite our many requests for assistance. We therefore have not been able to accurately reproduce from their data set the means and SDs shown in tables 1 to 3 of Woltering et al.[1] Despite these limitations, the incomplete data set provided by Woltering et al suggests that sex effects and the other abovementioned patient characteristics could explain at least some of the apparent differences between the authors' current and "historic" data.

In summary, there is no evidence supporting the claims of Woltering et al suggesting a change in the bioavailability of Sandostatin LAR. Given this, the overall tone of the Woltering et al article is regrettable because it could create confusion for physicians and undue anxiety among patients who are being treated successfully with Sandostatin LAR.

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Reply:

We appreciate the opportunity to respond to the letters to the editor that our recent article engendered. In response to the letter from Drs Schran and Hager, we would like to make the following points.

We are happy that our article prompted an extensive review of changes in the manufacturing practices for octreotide LAR that occurred after 2004 and are delighted that you can assure the readers that the changes in drug levels that we observed are not due to changes in your manufacturing processes. Unfortunately, this is only one of several potential conditions that could account for our observations. We feel that we also must investigate the other proposed potential mechanisms for lower plasma drug levels before attributing these changes to patient selection bias and "incomplete" data. Unfortunately, the Novartis team did not help shed light on these other possible causes of the current plasma levels of octreotide that we are currently observing.

The Novartis Oncology team criticizes our calculation based on bioavailability of expected plasma drug levels for LAR at a dose of 30 mg/mo. In the Novartis retort, they claim that our calculation of theoretic plasma levels based on bioavailability and a monthly dose of 30 mg of octreotide obtained prospectively in patients undergoing continuous administration of octreotide by subcutaneous infusion of 1 mg of octreotide per day (30 mg/mo) was not correct. They claim that bioavailability of LAR when compared with immediate-release octreotide should be 43%, not the 60% figure we used for our calculation. In our article, we have noted that patients receiving octreotide by subcutaneous infusion had a mean octreotide level (not trough because the infusion was constant) of 5819 ± 3105 pg/mL. When this is multiplied by a 63% bioavailability, the theoretic plasma level should be 3666 pg/mL, not 2500 pg/mL, as claimed by the Novartis team.[1] The data provided by Novartis with every dose of LAR and approved for distribution as a package insert by the FDA claim that the bioavailability of LAR is 60% to 63% when LAR was compared with immediate-release octreotide.[2] We used these data for our calculations, assuming that it was accurate.

Schran and Hager claim that "the analytical characteristics of the ISI radioimmunoassay to measure octreotide could also have contributed to the apparently lower current octreotide values in comparison to the 'historic' values." To determine if this statement might be true, we investigated the performance of our current assay versus previously published Novartis/Sandoz octreotide assays. One of our authors (T.M.O.) published the octreotide radioimmunoassay using the Marbach-Sandoz octreotide antibody in 1987.[3] We repeated our assays using identical parameters for incubate volumes and compared the results of the current day assay with the historic Sandoz-Novartis assays. The curves were essentially identical (r^2 = 0.997), ruling out a defect in our current assay as the cause of the low plasma octreotide levels that we are currently observing.

We will have to assume that RAD 001 has no effect on the plasma levels of octreotide because there are no published data on this drug-drug interaction to confirm these Novartis claims.

The Novartis Oncology team states that differences in our study's sex split may be responsible for our observations. A 50/50 sex distribution is noted in their C2239 study, and a 70% preponderance of males is seen in the SMSE351 study; despite these differences, the SMSE had a numerically higher octreotide level after 3 doses than the C2239

study with a higher percentage of females. Despite this, they claim that "there was no meaningful difference in steady-state octreotide levels between the 2 studies (C2239 and SMSE351). Novartis Oncology considers this finding to be significant because C2239 was conducted at the same time as the observations of Woltering et al." Our current study has a 53% female versus 47% male sex split, essentially identical to the C2239 study.

Finally, we completely agree with Drs Hager and Schran that further substantiation of our observations is required and believe that an unbiased prospective phase IV clinical trial of plasma octreotide levels, symptoms, tumor growth, and biochemical markers should be conducted.

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Octreotide LAR in Carcinoid *How to Dose?*

To the Editor:

In the July issue of *Pancreas*, Woltering et al[1] described their experience with the measurement of octreotide blood levels among patients with carcinoid syndrome. The authors described a decline of octreotide level in the blood, which was observed at various dosages of octreotide LAR. We read the article with interest but are troubled by a number of observations and conclusions made by the authors.

Based on in vitro studies, the authors have concluded that octreotide acetate binds to the sst2 receptor with an affinity of approximately 1 nM and that it is desirable to achieve a trough octreotide blood level of 10,000 pg/mL among patients with carcinoid syndrome. This line of reasoning, however, is not based in data.

First, none of the cited articles used human neuroendocrine tumor cells, and none claimed the calculated K_D was for sst2 receptor.[2–4] These studies, using breast cancer, neuroblastoma, and pituitary adenoma models, were conducted before full characterization of 5 known somatostatin receptor subtypes. In fact, a wide range of K_D for octreotide has been reported in the literature. For example, some have reported a K_D for octreotide as high as 80 nM using a pituitary tumor cell line.[5] However, in a model where only the human sst2 receptor was expressed, investigators have reported a K_D of 0.057 nM for octreotide.[6]

With a greater than thousand-fold difference in K_D reported in the literature, it is evident that there is considerable variation in the expression profiles of somatostatin receptor subtypes. Clinical experience with indium In 111 pentetreotide scintigraphy also suggests tremendous heterogeneity. We believe that it is not possible to estimate the blood concentration needed to achieve complete saturation of the sst2 receptor based on existing data.

Indeed, there are no clinical data to suggest that complete saturation of somatostatin receptors is even desirable or needed. Existing data suggest somatostatin receptors are transmembrane G protein–coupled receptors that most likely signal by inhibiting adenocyclase, Ca^+ influx, and stimulating phosphotyrosine phosphatase.[6,7] The system likely interacts in a complex and dependent way with other cellular pathways. There are no data to suggest that 100% of membrane somatostatin receptors need to be saturated to trigger downstream events.

Furthermore, tissue concentrations of drugs frequently differ substantially from plasma concentration. There are no data to tell us what intratumoral concentration of octreotide would be achieved by a plasma level of 10,000 pg/mL.

Since the original publication by Rubin et al,[8] octreotide LAR has been effectively used for the control of carcinoid syndrome in thousands of patients. We have not noted any recent changes in the rate of symptom control among our patients treated with octreotide LAR. While the authors quoted blood levels achieved in the study of Rubin et al,[8] the authors should also remind readers that in the cited study, there was no association between drug dose and symptom control rates.

As for the reported changes in octreotide blood levels, we are disappointed that the known factors associated with the variability in octreotide blood levels including age, sex, and weight have not been reported in the present study. The high proportion of patients requiring dose escalation or receiving a dose greater then 30 mg every 4 weeks suggests that the study involved a resistant population. Development of drug resistance among patients with malignant cancer is common. Data from such a population should not be compared with initial registration study involving patients who have never been exposed to octreotide LAR. In general, control over known covariates is especially important in small single-arm studies. The lack of pertinent information in a small retrospective study that involved multiple cohorts with less then 30 patients is unfortunate.

Analyses from the Surveillance, Epidemiology, and End Results database have shown improvements in survival of patients with advanced neuroendocrine tumors contemporaneous with the commercial introduction of octreotide.[9] We

believe this, to a large part, is due to the improved control of carcinoid syndrome, which changed the natural history of neuroendocrine tumors (NETs). For example, carcinoid crisis with severe flushing, diarrhea, and hemodynamic instability, which was a major cause of morbidity and mortality in the past, now occurs rarely. Organ failure, which tends to occur later in the course of illness, is now the major cause of mortality. Whereas many researchers have speculated that octreotide has a disease-stabilizing effect in patients with NETs, conclusive data from randomized human studies are lacking.

Although octreotide has proven to be a safe and efficacious drug for carcinoid syndrome, it nonetheless can cause adverse events including steatorrhea, cholelithiasis, and hyperglycemia. Until conclusive data from randomized studies are available to show that octreotide has a disease-stabilizing effect and at what dose this effect occurs in humans, we advocate titrating the octreotide LAR dose according to symptoms rather than to an arbitrary blood level. Moving back to intermittent subcutaneous dosing or continuous infusion delivery of octreotide is a major step backward. We believe such a move would decrease the quality of life experienced by these cancer patients and cannot be justified based on existing data.

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Reply:

Thank you for also allowing us to comment on the letter from Drs James C. Yao and Larry K. Kvols regarding our article.

We have clearly stated that the measurement of plasma octreotide levels should be undertaken when the patient's symptoms are poorly controlled, or the patient's biomarkers are progressively rising, or the patient's tumor is growing.[1] These are essentially the same conditions that would prompt any reasonable clinician to consider increasing the octreotide long-acting release (LAR) dose. We believe that understanding the relationship between plasma octreotide levels and the clinical/radiological/biochemical scenarios helps the physician determine if increasing symptoms or biomarkers are due to progressive disease or inadequate drug therapy. Currently, rescue medications are used for patients on LAR therapy who have poorly controlled symptoms.

In contrast to our observations that recently patients have had increasing symptoms on stable doses of LAR, Kvols and Yao claim that "We have not noted any recent changes in the rate of symptom control among our patients treated with octreotide LAR." In a recent study by Anthony and Vinik in 392 patients with carcinoid, just over 65% (n = 256) of the total population changed octreotide treatment (dosing) during the study period (2000–2006). Lack of efficacy was cited as a reason for modification in most patients (65.5%) who changed regimens (personal communication with Drs Arthur Vinik and Lowell Anthony, July 2008). Thus, it seems that others have seen the same change in symptoms that we have reported.

Drs Yao and Kvols imply that administering octreotide by subcutaneous infusion is "a major step backwards" and imply that these patients would have an inferior quality of life. We disagree totally and have observed a significant decrease in symptoms and concomitant increase in the quality of life experienced by patients receiving octreotide by continuous infusion. This is worsened by our inability to achieve consistent blood levels of more than 10,000 pg/mL even when the patient is given 30 mg of LAR weekly (120 mg/mo). In fact, if one looks carefully at the drug registration trial by Rubin et al,[2] 70% of patients needed rescue (octreotide administered subcutaneously 3 times a day for 2 days) at some point in the trial, and 40% required subcutaneous octreotide at least weekly. Our use of subcutaneous infusions is consistent with the subcutaneous dosing patterns of octreotide that was required in this drug registration trial. This does not seem to us as "going backwards" especially if this method of drug administration provides significant improvement in symptoms and allows us to adjust drug doses until plasma octreotide levels of greater than 10,000 pg/mL can be reached.

Finally, we agree with Drs Yao and Kvols that there must be variations in the K_d among human tumors; however, we know of no studies that measured the K_d of each individuals tumor and used these data to adjust the clinical octreotide drug dose. Those of us who have been active in this clinical field for the last several decades use a 1 nM K_d and IC_{50} as reasonable estimates of these numbers. Higher K_d values would only strengthen our argument that drug levels of 10,000 to 15,000 pg/mL or higher (if K_d is higher) are required to saturate the sst2 receptor.

We appreciate the opportunity to respond to this review of our article and hope that these interchanges promote further studies of octreotide levels and how they affect drug dosing, tumor growth, symptoms, and biomarker levels. We believe that an unbiased prospective phase IV clinical trial correlating plasma octreotide levels with biochemical markers, tumor growth rates, and symptom control should be conducted.

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