Sandostatin LAR

Use in GEPET
Types of GEPET

- VIPoma*
- Carcinoid tumor*
- Gastrinoma
- Insulinoma
- Glucagonoma
- GRFoma
- Somatostatinoma

* = Approved indication for Sandostatin and Sandostatin LAR in Canada
VIPoma

- Major peptide/hormone
  - VIP

- Syndrome/symptom
  - Verner-Morrison syndrome or pancreatic cholera syndrome (watery diarrhea, hypokalemia and achlorhydria)
  - Hypercalcemia, glucose intolerance and flushing

- Percent malignant
  - 80

- Main sites (%)
  - Pancreas (90); Adrenal (10%)
Ultimate Goals for the Treatment of Neuroendocrine Tumours

- Total eradication by surgery *(not possible in most cases)*
- Abrogation of tumour growth and/or amelioration of clinical symptoms
- Improving and maintaining a good quality of life
Carcinoid Tumour

- **Major peptide/hormone**
  - Serotonin

- **Syndrome/symptom**
  - Carcinoid syndrome
    - diarrhea, flushing - most common
    - endocardial fibrosis, respiratory complications, pellagra, and arthropathy and myopathy

- **Percent malignant**
  - 2-60 (site-dependent metastases)

- **Main sites (%)**
  - Appendix (40); small intestine (27); rectum (13); bronchus (11.5)
<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid Tumours</td>
<td>1: 150 000</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>1: 1 000 000</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>1 : 1 000 000</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>1: 20 000 000</td>
</tr>
<tr>
<td>VIPoma</td>
<td>1: 10 000 000</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>1: 40 000 000</td>
</tr>
</tbody>
</table>
Treatment of GEPET
Types of Treatments for GEPET

- Surgery
- Liver dearterialization
- Irradiation
- Medical Therapy
  - Chemotherapy
  - Somatostatin analogues
  - Interferon
Mechanism of Action of Sandostatin

- Suppress the release of peptides and amines from the tumors
- Inhibit the actions of these mediators on target tissues
- Affect tumour growth?
Carcinoid Syndrome
(approved in Canada)

- Response rates are generally between 60-100%
- Control of diarrhea is usually accompanied by
  - increase in appetite and weight gain
  - increase in Karnofsky performance score
  - improved quality of life
- Life-saving effect in reversing carcinoid crisis have been documented by several investigators
- Reduces urinary 5-HIAA excretion (doesn’t always predict response to treatment)
Sandostatin in Carcinoid Syndrome
Diarrhea


Bar chart showing the percentage of patients with diarrhea normalized, improved > 50%, unchanged, or worse after treatment with Octreotide 200-500 µg TID. The chart includes data for Month 3 (n=28) and Month 12 (n=20).
Sandostatin in Carcinoid Syndrome

Flush

% of Patients with Flush

- Normalized
- Improved > 50%
- Unchanged
- Worse

Octreotide 200-500 µg TID

VIPoma
(approved in Canada)

- Sandostatin provides rapid short- and long-term control of diarrhea in approximately 70-100% of patients
- Reduces plasma VIP concentrations in approximately 60-89% of patients
- Weight gain often accompanies control of diarrhea
- Quality of life can be improved with relief of symptoms
Octreotide Acetate Long-Acting Formulation Versus Open-Label Subcutaneous Octreotide Acetate in Malignant Carcinoid Syndrome

Rubin J et al. Journal of Clinical Oncology
Vol 17, No. 2:600-606, 1999
93 patients with carcinoid syndrome due to a carcinoid tumor

Double-blind for octreotide LAR and open-label for SC, randomized (after 2 week screening with SC Sandostatin, followed by 3-5 day washout)

LAR 10mg  LAR 20mg  LAR 30mg  SC 0.3-0.9 mg/d

The primary efficacy endpoint was treatment response. Other efficacy endpoints were daily stool frequency, flushing episodes, rescue medication and 5-HIAA levels.
## Study Objectives

### Primary
- Compare once-monthly IM Sandostatin LAR to Sandostatin for control of diarrhea and flushing associated with carcinoid syndrome

### Secondary
- Evaluate safety and tolerability of Sandostatin LAR
- Assess 5-HIAA urinary excretion as biological indicator of response
- Measure octreotide levels at 10-, 20-, and 30-mg doses of Sandostatin LAR
Octreotide LAR vs SC in Carcinoid Syndrome
Study Design

- Patients experienced control of symptoms with sc
- Continued to show symptom control for at least a 2-week screening period
- Washout period of 3-5 days
- Patients then randomly assigned to receive one of the four treatments
  - LAR 10, 20 or 30 mg or sc at the same dose as screening
- Assignment to LAR was double-blind
- All patients received LAR on day 1, but continued to receive concomitant sc every 8 hours at the previous dose
Serum Octreotide and GH Concentrations After Sandostatin LAR Injection

Mean Serum Octreotide and GH Concentrations After Injection of a Single 30-mg Dose in a Typical Patient

Serum Octreotide and GH Concentrations After Sandostatin LAR Injection

Mean Serum Octreotide and GH Concentrations After Injection of a Single 30-mg Dose in a Typical Patient

- Days After Injection: 0, 7, 14, 21, 28, 35, 42, 49, 56, 63
- 12 hour-mean Octreotide (ng/L): 0, 200, 400, 600, 800, 1000, 1200
- 12 hour-mean GH (ug/L): 0, 2, 4, 6, 8, 36, 38, 40, 42
- Growth hormone less than 2 ug/L until 34 Days

Patients

- Histologically, confirmed carcinoid tumor with carcinoid syndrome

- Symptoms of flushing and diarrhea had to have been well controlled by sc
  - two or fewer flushing episodes per day
  - average stool frequency of three or fewer per day (maximum of five stools on any one day)

- For patients efficacy to be assessable, symptoms must have returned during the washout period
  - three episodes of flushing in a single day and/or
  - an increase of at least tow stools daily for consecutive days above prewashout average
Procedures

- Patients receiving LAR who lost symptom control could use rescue sc until symptom were controlled to screening frequency
  - increased stool frequency by at least 2 per day for 2 consecutive days or flushing frequency increased to at least three episodes per day for 1 day
- Patients taking sc who required rescue could increase dose by 50%; patients on LAR - same dose used before washout
- After relief was achieved for 24 hours, d/c
- Rescue could be repeated a second time
- If first two episodes required more than 5 days total or if a third rescue episode was needed, patients received sc until the next visit.
Efficacy and Safety Assessments

- Primary efficacy assessment was treatment response
- Efficacy assessments included the daily frequency of stools and flushing episodes, number of patients using rescue medication, and 24-hours urinary 5-HIAA concentrations
- Number of safety assessments
Definition of Treatment Response

<table>
<thead>
<tr>
<th>Complete success</th>
<th>Partial success</th>
<th>Treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No supplemental medication (Sandostatin) needed</td>
<td>- Supplemental medication needed on no more than 2 occasions or for not more than 5 days</td>
<td>- Supplemental medication needed on 3 or more occasions or for 5 days or more days</td>
</tr>
</tbody>
</table>
Because of the low natural incidence of the carcinoid syndrome, only a limited number of patients were expected. Consequently, the study was designed to look at the equivalence between the sc and LAR formulations and not to detect statistically significant differences among groups. Conclusions were based on clinical rather than statistical findings.
Results
Patient Demographics and Clinical Characteristics

- 93 patients constituted the intent-to-treat population
- 79 patients constituted the efficacy-assessable population
  - 9 patients discontinued before week 24
  - 5 patients finished study but were later found not to have met the necessary inclusion criteria
- Demographic and clinical characteristics were comparable except for age
  - median age of patients in the 20-mg group was younger
## Discontinuations, Deaths, and Serious Adverse Events

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discontinuations</strong></td>
<td></td>
</tr>
<tr>
<td>Consent withdrawal</td>
<td>2</td>
</tr>
<tr>
<td>Failure to return</td>
<td>4</td>
</tr>
<tr>
<td>Adverse event</td>
<td>1</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td></td>
</tr>
<tr>
<td>Renal failure/hypotension/hypoglycemia</td>
<td>1†</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>1‡</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1‡</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>17</td>
</tr>
</tbody>
</table>

† 20-mg LAR group; ‡ 30-mg LAR group.

Data on file, Novartis Pharma AG.
Treatment Response

Percentage of Patients (Efficacy-Evaluable Population) With Treatment Success and Partial Treatment Success at Week 20 and/or Week 24 by Treatment Group

Data on file, Novartis Pharma AG.
Supplemental Medication Required

Percentage of Patients (Efficacy-Evaluable Population) Requiring Supplemental Medication in Each Treatment Group During the 24-Week Treatment Period

Data on file, Novartis Pharma AG.
Supplemental Medication Required

Median Number of Supplemental SC octreotide Doses Taken by Patients (Efficacy-Evaluable Population) Requiring Rescue During the Preceding 4-week Interval by Treatment Group.

Data on file, Novartis Pharma AG.
Symptomatic Control of Diarrhea

Median Number of Stools per Day in 47 Efficacy-Evaluable Patients Throughout Screening (SCN), Baseline (BASE), and 24-Week Treatment Period by Treatment Group

Data on file, Novartis Pharma AG.
Symptomatic Control of Flushing

Median Number of Flushing Episodes per Day in 33 Efficacy-Evaluable Patients Throughout Screening (SCN), Baseline (BASE), and 24-Week Treatment Period by Treatment Group

Data on file, Novartis Pharma AG.
**Urinary 5-HIAA Excretion**

Data on file, Novartis Pharma AG.
Pharmacokinetics of Sandostatin LAR

Mean Serum Octreotide Concentration (pg/mL) (Efficacy-Evaluable Population) After IM Administration of Sandostatin LAR at 10 mg (n=16), 20 mg (n=13), or 30 mg (n=19) Every 4 Weeks.

* Baseline levels > 160 pg/mL or 0 pg/mL were excluded. Data on file, Novartis Pharma AG.
## Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Sandostatin (n=26)</th>
<th>10 mg (n=22)</th>
<th>20 mg (n=20)</th>
<th>30 mg (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site inflammation</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal calculus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Data on file, Novartis Pharma AG.
# Newly Occurring Gallbladder Abnormalities

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Sandostatin (n=26)</th>
<th>10 mg (n=22)</th>
<th>20 mg (n=20)</th>
<th>30 mg (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstones</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Sludge</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dilatation of ductal system</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Data on file, Novartis Pharma AG.
Test dosing of subcutaneous Sandostatin for 2 weeks. Immediately after last subcutaneous injection, assess side effects, rule out acute toxicity, and verify symptom response.

Switch to Sandostatin LAR
Intragluteal injection 20 mg q 28 days (No washout period)

Continue sc Sandostatin for 2 weeks while awaiting the therapeutic level of the first injection of Sandostatin LAR

Evaluate after 2 months

Symptoms controlled

Consider trial period at 10 mg q 28 days. If symptoms recur, increase dose to 20 mg q 28 days

Symptoms not controlled

Maintain dose at 20 mg q 28 days

Increase dose to 30 mg q 28 days
Summary

- Sandostatin LAR provides efficacy, safety, and tolerability comparable to Sandostatin with the benefit of a once-monthly injection.

- A 20-mg initial dose is recommended.

- Monthly injections are preferred by patients and should increase compliance.