A SYSTEMATIC LITERATURE REVIEW OF THE EFFICACY AND SAFETY OF OCTREOTIDE LONG-ACTING REPEATABLE (LAR) AT HIGHER THAN FDA-APPROVED DOSES AND/OR FREQUENCIES FOR TREATMENT OF NEUROENDOCRINE TUMORS

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BACKGROUND

- Octreotide long-acting repeatable (LAR) is FDA approved for alleviating severe diarrhea or flushing associated with metastatic carcinoid tumors at doses ≤30mg every 4 weeks. [1]
- In clinical practice, octreotide LAR is sometimes prescribed at above-label doses, but evidence for this practice has not been systematically assessed. [2]

OBJECTIVE

- We reviewed published literature on efficacy and safety of octreotide LAR at doses >30mg/month for treatment of neuroendocrine tumors (NETs).

METHODS

Data Sources

- Databases: PubMed and Cochrane Library
- Conferences: American Society of Clinical Oncology (ASCO), Endocrine Society (ENDO), European Neuroendocrine Tumor Society (ENETS), European Society for Medical Oncology (ESMO), North American Neuroendocrine Tumor Society (NANETS)
- Bibliographies of included articles

Search Strategy and Timeframe

- Database searches from 1998-2012 were conducted on 12/9/12. Conference years were 2000-2013.
- MeSH terms and key words used were: neuroendocrine tumors, neuroendocrine carcinoma, carcinoid tumor, carcinoma, neuroendocrine, carcinoid syndrome, octreotide, and sandostatin.

Inclusion and Exclusion Criteria

- Studies published before 1998 or not reporting data on human subjects, above-label dosage of octreotide LAR, neuroendocrine tumors, efficacy, safety, or expert opinion were excluded.
- For duplicate studies, only the full-length articles (not the conference abstracts) were included in the review.

Outcomes

- Efficacy: disease markers, quality of life, tumor response, time to progression of disease, requirements for additional intervention, survival
- Safety: frequency of various adverse effects

RESULTS

Search and Screening

- Of 1086 identified publications, 238 underwent full-text review (20 following translation into English), and 18 (10 articles, 8 conference abstracts) were included (weighted-kappa: 0.94).

Description of Included Studies

- Study designs of included studies were: 12 clinical studies (chart studies, case series, clinical trials),[3-14] 1 modified Delphi process,[15] 1 claims analysis,[16] 3 literature reviews,[17-19] and 1 letter to the editor.[20]
- Oxford's Centre for Evidence-based Medicine Levels of Evidence ratings ranged from 2b to 5 for the included studies, with 10 studies scoring 4 or 5, indicating a relatively low quality of evidence (grade C).
- 9 studies were performed in the US,[3,4,9,11,13-16,20] 2 in Italy,[6,18] 1 in both the US and Europe,[19] 1 in the US, Europe, Canada, and Singapore,[12] and the location for the remaining 5 was not reported.[5,7,8,10,17]
- Patients in these studies had a variety of NETs, including carcinoid tumors and pancreatic NETs.
- High doses of octreotide LAR studied ranged from a minimum of either 40 mg per month or 30 mg per 3 weeks up to a maximum of 120 mg per month.
- Studies reported a variety of reasons for dose increase of octreotide LAR: 1 reported lack of efficacy,[3] 11 reported symptom control,[4,6,8-15,17] 7 tumor treatment,[4-9,15] 3 biochemical markers,[6,9,11] and 1 radiographic progression.[11]

RESULTS

Efficacy

- Efficacy was reported in 11 studies describing 260 subjects with doses ranging from 40mg/month or 30mg/3 weeks up to 120mg/month.
- There appears to be a trend supporting the use of higher dose octreotide LAR to control symptoms and tumor progression, although the data on symptom improvement are limited by lack of quantitative measurements of symptom severity and absence of formal quality of life analysis.

Reference	Change in symptoms, disease markers, quality of life (QOL), tumor response, or survival with increased dose/frequency octreotide LAR?
Anthony 2011	**Markers**: 5-HIAA in 41%; CgA in 48%. **Tumor Response:** by dose of total 698 doses given: Complete: S-LAR 20mg 2% (n=224), S-LAR 30mg 1% (n=316), S-LAR 40mg 0% (n=78), S-LAR 60mg 2% (n=42); Partial: S-LAR 20mg 6% (n=224), S-LAR 30mg 8% (n=316), S-LAR 40mg 4% (n=78), S-LAR 60mg 10% (n=42); Stable disease: S-LAR 20mg 57% (n=224), S-LAR 30mg 57% (n=316), S-LAR 40mg 55% (n=78), S-LAR 60mg 50% (n=42); Progression: S-LAR 20mg 21% (n=224), S-LAR 30mg 25% (n=316), S-LAR 40mg 18% (n=78), S-LAR 60mg 29% (n=42).
Chadha 2009	**Survival**: 1-year survival was 0.77 in conventional dose S-LAR versus 0.88 in high dose S-LAR (p>0.4).
Costa 2006	**Tumor Response**: partial response "after evidence of objective progressive disease in liver, a second response with disease stabilization was achieved with octreotide dosage increase to 30mg and to 40mg/4 weeks."
Ferolla 2012	**Symptoms**: complete normalization in 40% and symptom control in 60%; flushing normalized in 71.4%, improved/controlled in 28.6%; diarrhea normalized in 70%, improved/controlled in 30%; bronchospasm improved/controlled in 100%; hypoglycemia improved in 100%; pain improved/controlled in 67%, disappeared/normalized in 33%. **Markers**: significant response to high dose S-LAR in 57% of those with elevated 5-HIAA, 30% with elevated CgA, and 100% with elevated Gastrin; 30% of those with elevated markers responded to higher dose. **QOL**: weakness and well-being improved in all patients. **Tumor Response:** complete response in 0%, partial in 7.2%, and stable disease in 92.8%.
Koumarianou 2010	**Tumor Response**: partial response in 69.2% with >50% reduction in tumor size by CT; stable disease in 23.1%.
Markovich 2012	**Tumor Response**: tumor growth was controlled in 83.9% of subjects, and median time to progression in the total group was 18 months, however, the study did not report these results by doses of S-LAR.
Valle 2001	**Symptoms**: symptom control was noted as "improvement" of flushing, diarrhea, and bronchospasm. **Markers:** "patients who required continued dose-escalation of S-LAR showed evidence of increased urinary 5-HIAA suggesting increased disease activity."
Weber 2012	**Symptoms**: flushing improved in 56%, diarrhea improved in 62%.
Wolin 2013	**Symptoms**: 21% with symptom response in the pasireotide-LAR group and 27% in the S-LAR group.
Woltering 2005	**Symptoms**: complete normalization in 38%, symptom control in 47%; the study did not report results by doses of S-LAR.
Woltering 2006	**Symptoms**: out of control flushing in 0% for 20mg, 11.1% in 30mg, and 7.1% in 60mg S-LAR groups; out of control diarrhea in 0% for 20mg, 27.8% in 30mg, and 30.8% in 60mg S-LAR groups; 1 subject in each of the groups had wheezing (5 episodes/week in 20mg, 7/week in 30mg, 1/week in 60mg S-LAR). **Markers:** mean CgA 56.6 ng/mL in 20mg, 66.2 ng/mL in 30mg, and 65.2 ng/mL in 60mg S-LAR.

Octreotide LAR (S-LAR)

Safety

- Safety was reported in 8 studies. Five supported the tolerability of higher dose octreotide LAR and 3 did not report results by dose, although study sample sizes may have been too small to identify rare events.

Reference	Safety Results
Anthony 2011	AEs not broken down by dose.
Chadha 2009	No treatment related toxicities were reported.
Ferolla 2012	Diarrhea in 1/28 (3.5%), abdominal pain in 1/28 (3.5%), cholelithiasis in 2/28 (7%), pyrexia/fever in 1/28 (3.5%).
Koumarianou 2010	Patients had no significant symptoms related to treatment AEs (neutropenia in 2; thrombocytopenia in 1).
Ludlam 2011	AEs were balanced between 30 mg/month vs. 40 mg/month groups.
Markovich 2012	Tolerability of long-acting octreotide in a dose of 30-40 mg was satisfactory for all patients.
Valle 2001	All patients found the long-acting analogue acceptable and none requested a change back to conventional daily octreotide.
Wolin 2013	Pasireotide LAR (P) and octreotide LAR showed a similar safety profile except for the higher frequency of hyperglycemia in P.

Adverse events (AE)

Expert Opinion

- Expert opinion in 8 studies supported dose escalation up to 60mg/month for symptom control and suggested increased doses may be effective for tumor progression.
- Expert opinions regarding the use of octreotide LAR at doses >30 mg/4 weeks were reported in 8 articles.[2,4,5,15,16,18-20]
- In general, expert opinions supported the use of octreotide LAR dose escalation above standard dose.
- 2 studies supported the use of increasing octreotide LAR dose up to 60 mg/month for control of symptoms.[15,19]
- 3 studies further suggested that increased doses of octreotide LAR may be effective in controlling tumor progression.[4,5,18]
- Strosberg (2013) reported above-label dosing of octreotide LAR is common in NCCN institutions, and the primary indication is refractory carcinoid syndrome.
- Yao (2008) cautioned that until there are appropriate studies (i.e., RCTs) completed, escalating doses of octreotide LAR should be done only for control of symptoms.
- Xu (2012) reported that a substantial number of patients in this study required doses greater than the FDA approved dose of 30 mg/month.

LIMITATIONS

- Included studies varied in designs, patients, and definition of outcomes, so heterogeneity of these data prevented us from conducting meta-analysis.

CONCLUSIONS

- This was a comprehensive review and synthesis of global literature published in peer-reviewed journals and presented at a variety of international and national professional congresses.
- The review indicated that above-label doses of octreotide LAR for symptom and tumor control of NETs are being used frequently for management of NETs in clinical practice and that no excess toxicity has been observed.
- In most cases, the use of high dose octreotide LAR (i.e., dose escalation) appears to be prescribed in those with increased symptoms or tumor progression on standard dose therapy.
- Expert opinion supports escalation of somatostatin analogs for patients with refractory hormonal symptoms.
- However, given the overall scarcity of published evidence on this topic, no conclusive statements can be made on the safety and efficacy of above label dose and/or frequency of octreotide LAR in treatment of NETs.

References

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