Evidence-Based Policy in Practice: Management of Carcinoid Syndrome Diarrhea
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The Burden of Neuroendocrine Tumors and Carcinoid Syndrome

Neuroendocrine tumors (NETs), or carcinoid tumors, are functional secretory tumors that arise in neuroendocrine cells throughout the body, most often in the gastrointestinal system but also in the pancreas, lungs, and other organs.1–2 NETs are relatively rare, with an incidence of 70 cases per one million people, although their prevalence has increased steadily over the past 20 years due to improvements in identification and characterization.3–5 Neuroendocrine tumors are known to produce hormonal factors, including serotonin, histamine, bradykinin, and prostaglandins, that induce a subsequent hormonal, or carcinoid, syndrome (CS), which is characterized by diarrhea, flushing, hypotension, tachycardia, and bronchoconstriction that may include cardiovascular and/or pulmonary complications.6–9 As many as 35% of patients with NETs may develop CS, and 80% of them are likely to have associated diarrhea (CSD).10,11 When systemic serotonin is elevated, carcinoid heart disease (CaHD) is likely to develop, primarily from endocardial fibrotic plaques that form on the right side of the heart.9 Among patients with CS, up to 70% may develop CaHD during the course of their disease.12,13

Carcinoid syndrome has been shown to affect tumor characteristics and advancement, causing substantial morbidity and reducing patients’ quality of life and survival.14–17 In a recent clinical trial, almost all (97%) patients with CS reported bowel movement-related issues at baseline, along with flushing (83%), abdominal pain (63%), and low energy (63%), among other symptoms.11 Carcinoid syndrome symptoms reduced quality of life for the majority of patients (80%), and negatively impacted work productivity for almost half of them (43%).15 Another study showed statistically significant reductions in energy (71%), personal finances (59%), and emotional health (58%) among patients with NETs, as well as missed work days (62%), changes to working arrangements with employers (30%), and reduced hours (21%).18

In addition to patient morbidity, the economic costs associated with CSD have proved substantial.16 In adults with CS below 65 years of age, an analysis of commercial claims showed that patients with CSD have more hospitalizations, emergency department visits, and CS-related office visits (6.9 vs. 4.1)—all at a statistically significant rate—within one year of diagnosis, compared to their peers without diarrhea (all P < 0.001; Table 1).19 This greater utilization of resources remained after adjusting for demographic and clinical factors, and it extended to higher total annual costs for patients with CSD ($81,601) compared with patients who had CS and no diarrhea ($51,729; P < 0.001).19 An analysis of Medicare claims from elderly patients showed that most (83%) survived with continuous enrollment through one year after CS diagnosis, and that they incurred much higher total monthly costs compared to their peers without CS.3 Both inpatient and outpatient costs were higher among survivors with CS after adjusting for demographic and clinical factors. The successful management of CS has demonstrated cost savings among patients whose symptoms have improved.20,21

Management of Carcinoid Syndrome

As NETs express varying magnitudes of G-protein-coupled transmembrane somatostatin receptors based on the type and differentiation of the underlying tumor, somatostatin analogs (SSAs) historically have been the first approach for the medical management of CS symptoms.4,22,23 Somatostatin analogs are more potent inhibitors of growth hormone, glucagon, and insulin than somatostatin, and they inhibit the release of serotonin, vasoactive intestinal peptide, and pancreatic polypeptide.24 Intramuscular octreotide was the first SSA to be approved for the management of diarrhea and flushing in patients with NETs, followed by the monthly formulation, octreotide LAR,24 then subsequently the monthly subcutaneous lanreotide.25 Although SSAs have been shown to provide temporary relief for patients, the loss of their effect over time eventually causes increased CS symptoms, which is considered to be refractory CS.26–28 As many as 40% of patients with CSD may be unresponsive to SSA LAR therapy.20 Challenges associated with the self-administration of SSAs, such as the sturdiness and/or clogging of the device, may contribute to patient/caregiver difficulty with self-injections, particularly in the case of octreotide LAR, and have been reported among nurses.29

In the absence of more targeted therapy, common approaches to managing refractory CSD and CS symptoms have included increasing the frequency of administration and escalating the SSA dose.19,30,31 Escalating SSA therapy well beyond the dosing and administration recommended in the approved regulatory labeling has become common practice for addressing refractory CS, so much so that increasing doses of SSA are considered to be markers for inadequate response to therapy.20,32 The quality of evidence supporting progressive dose escalation has

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Table 1 Annual Health Resource Use and Costs Among Patients With CS and Patients Without CS\(^{19}\)

<table>
<thead>
<tr>
<th></th>
<th>With CS (n = 534)</th>
<th>Without CS (n = 2,288)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total annual health care costs, mean</td>
<td>$82,032</td>
<td>$51,621</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total medical costs</td>
<td>$74,654</td>
<td>$47,083</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total pharmacy costs</td>
<td>$7,378</td>
<td>$4,538</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Patients with CS hospitalization, %</td>
<td>13.7</td>
<td>7.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Length of stay (days), mean (SD)</td>
<td>7.4 (7.1)</td>
<td>5.5 (3.6)</td>
<td>0.029</td>
</tr>
<tr>
<td>Annual inpatient costs, mean</td>
<td>$27,018</td>
<td>$16,609</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Patients with CS ED visits, %</td>
<td>11.0</td>
<td>4.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Annual ED costs, mean</td>
<td>$719</td>
<td>$334</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CS outpatient visits, mean (SD)</td>
<td>6.9 (7.8)</td>
<td>4.1 (6.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Annual outpatient costs, mean</td>
<td>$46,917</td>
<td>$30,140</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CS = carcinoid syndrome; ED = emergency department; n = number; SD = standard deviation

remained low, however, deriving primarily from retrospective case series or post hoc subgroup analyses.\(^{27,28}\) Extended SSA treatment has shown decreased absorption and tachyphylaxis, causing an even shorter duration of effect for subsequent SSA administration.\(^{29}\) Additional research suggests that saturation of somatostatin receptors may make doses exceeding 60 mg ineffective.\(^{33,34}\)

In addition to the clinical considerations of escalating SSA doses, a recent analysis of U.S. commercial claims showed substantially higher all-cause and CS-related health care costs after SSA dose escalations, driven primarily by increased ambulatory care.\(^{20}\) Total all-cause health care costs rose from $3,000 per month one year prior to SSA dose escalation to $8,000 per month one year after SSA dose escalation. The proportion of all-cause health care costs attributable to SSA were higher post-SSA dose escalation (86%) than pre-SSA dose escalation (77%).\(^{20}\) This was the first study to highlight the economic implications of the persistent challenge posed by refractory CS symptoms regarding treatment practices that are isolated to escalating SSA therapy doses.

In the presence of refractory CS symptoms, physicians have explored other options for the medical management of patients who received first-line SSA therapy, including interferon alfa, antidiarrheal drugs, and systemic therapy such as everolimus.\(^{35}\) Interferon alfa reduces flushing and diarrhea in roughly half of patients previously treated with SSA, but it often causes notable side effects including depression, fatigue, and flu-like symptoms.\(^{35,36}\) Physicians may prescribe the antidiarrheal drugs loperamide or diphenoxylate-atropine for mild refractory CSD only; for more severe diarrhea, the serotonin receptor antagonist ondansetron has been prescribed, despite little supporting evidence of its efficacy.\(^{11,37,38}\) The use of the immunosuppressant everolimus for CS symptoms is based primarily on case reports and series, as the phase 3 RADIANT-2 trial did not report CS symptom improvements with the drug.\(^{33,39}\)

Telotristat ethyl (TE) is a novel oral inhibitor of tryptophan hydroxylase (TPH) that mediates the rate-limiting step in serotonin biosynthesis.\(^{40}\) As serotonin plays an important role in the secretion, motility, and inflammation of the gastrointestinal tract and is elevated in patients with CS, TE reduces the frequency of CSD by reducing the production of peripheral serotonin.\(^{40}\) Telotristat ethyl is approved for treating CSD in combination with SSA therapy in adults who are not adequately controlled by SSAs alone.\(^{40}\) The drug demonstrated statistically significant reductions in daily bowel-movement frequency and improvements in other markers of disease among patients with refractory CSD in the randomized, controlled phase 3 TELESTAR trial.\(^{41}\) An open-label extension to TELESTAR showed the safety and tolerability of TE through one year.\(^{41}\) The cost-effectiveness and minimal budget impact of TE on U.S. health plans have also been demonstrated in published models.\(^{42,43}\) The combination of TE+SSA in patients with CSD who are inadequately controlled by SSA therapy is expected to be more cost-effective than continued SSA-only therapy, with incremental gains per quality-adjusted life-year (QALY) within both conventional and rare-disease value frameworks.\(^{43}\) The probability of TE+SSA’s cost-effectiveness is expected to be particularly high when considering willingness-to-pay thresholds that are more appropriate for rare (99.1%) and ultra-rare (99.9%) conditions such as CSD.\(^{43}\)

Clinical Practice Guidelines

Organizations that focus on evidence-based management of NETs and CS have included recommendations relating to CS management, although a stand-alone evidence review and guideline for CS symptom management does not yet exist. To address the unmet needs of patients with refractory CSD, TE’s demonstrated effectiveness has made it the recommended therapy in combination with SSA for persistent CSD in the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium.\(^{44}\) Telotristat ethyl is also a recommended treatment option in NCCN’s Guidelines for Neuroendocrine Tumors (V.3.2017) in combination with SSA for patients with persistent CSD.\(^{45}\) The North American Neuroendocrine Tumor Society’s (NANETS) consensus guidelines for the management of NETs (2013) recommend antidiarrheal agents and SSA as indicated, as well as considering SSA dose escalation, despite the lack of evidence from well-designed prospective trials.\(^{46}\) The 2017 NANETS consensus guideline for mid-gut NETs recommends the drug for patients with stable radiographic disease and refractory CS before escalating SSA doses, adding short-acting octreotide, or using antidiarrheals.\(^{47}\) The NANETS recommendations still suggest that clinicians consider above-label SSA dosing when refractory CS symptoms occur toward the end of an SSA dosing cycle.

Evidence-Based Policy in Practice

The approval of TE in the U.S. has provided a new option for managing refractory CS symptoms. Based on the availability of TE and its support in NCCN and NET clinical-practice guidelines, population health managers have the opportunity to apply more evidence-based policies than have been historically available to address the unmet needs of patients with refractory
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CSD. This has led to the development of a policy framework that prioritizes TE treatment in combination with SSA over above-label escalating doses of SSA in those patients.

Payer-based Management Strategies

Because the guidelines regarding treatment of CS are limited to grade D recommendations, it is difficult to implement consistent programs across multiple payers. Within payer communities, standard drug-management strategies (prior authorization, step therapies, preferred providers)—even if grade A recommendations are available—are not generally deployed for products used to treat CS or CSD that are provided in outpatient office and clinic settings. This is likely because the total expense of CS and CSD management is insubstantial relative to other cancer-related therapies. It may also be a result of infrequent diagnosis among the CS/CSD populations, as well as a lack of necessary tools.

Recently, some payers have adapted the prior authorization strategies for the pharmacy dispensing of CS- and CSD-related products used in office/clinic settings. There is limited experience on the impact of such programs for this disease state, but inconsistent program application may still occur because TE is based on the use of self-administered products dispensed in the outpatient setting. Thus, prior authorization, step therapy, and quantity limitations are more likely to be used to manage TE than the foundation treatment, SSAs.

A few payers have implemented tools that provide claims-based editing to manage the use of SSAs in office/clinic-based settings. These tools often apply dosing limits based on the doses provided in the peer-reviewed literature, considering grade A or B evidence for the recommendations. This can and does limit doses and/or frequencies to those that are documented in the approved label, because evidence supporting higher doses or increased frequencies derives primarily from retrospective case series or post hoc subgroup analyses. Therefore, coverage policies may not be broadly accepted by the provider community.

CONCLUSION

Population health managers should consider strategies that take advantage of approved SSA dosing with the addition of TE for patients who have CSD. At a minimum, this would permit the use of approved treatment applications before pursuing ones based on Grade-D bodies of evidence. Research on comparative effectiveness from real-world clinical experience is required to evaluate TE+SSA compared with escalating doses of SSA therapy. Meanwhile, policies and practices would benefit from reflecting the best evidence-based approaches to help patients with CSD receive the most effective and efficient care. Evidence supporting the clinical and cost effectiveness of TE+SSA for appropriate patients should be weighed for people with this rare but debilitating condition.

REFERENCES

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