

INTRODUCTION

Hospices provide a suite of palliative and supportive services to manage pain and distressing symptoms at the end of life and to aid terminally ill patients (and their family and friends) pass through the dying process comfortably and with dignity.¹ Hospices that have been certified by the Centers for Medicare and Medicaid Services (CMS) to provide these services under the Medicare Hospice Benefit are reimbursed a set daily amount; in fiscal year (FY) 2016, the amount for routine home care was \$187 per day for days 1-60.²

According to the Medicare Hospice Benefit, hospices are responsible for covering all services, including medications, which are needed to care for the patient's terminal diagnosis and related conditions. Because of the per diem-based structure of Medicare's hospice payment system, it is up to each individual hospice to determine how to use their resources wisely in order to meet the needs of the patients under their care.³ For certain patients, the biomedical literature has demonstrated that therapies such as chemotherapy and radiation therapy may be of palliative benefit.³ However, the palliative benefit of roflumilast for a patient admitted to hospice services with a primary terminal diagnosis of advanced chronic obstructive pulmonary disease (COPD) has not been fully elucidated.

Decisions regarding whether a patient enrolled in hospice should receive roflumilast, for instance, should be made by the hospice interdisciplinary team, with participation from the patient, family/caregiver(s) and the patient's attending physician. This decision-making process includes, but is not limited to, determining: (1) how efficacious and safe the roflumilast would be in ameliorating the patient's symptoms, (2) the time until benefit of the roflumilast, and (3) the patient's remaining life expectancy.^{3,4} Other factors such as cost and availability of formulations may also be considered. A summary of the biomedical literature with respect to the efficacy, safety, time until benefit, cost, and available formulations of roflumilast is provided below; the patient's remaining life expectancy is assumed to be 6 months or less. This information is provided to assist the hospice with their decision regarding whether a patient enrolled in hospice should receive roflumilast.

EFFICACY AND TREATMENT TARGETS

- Based on the available evidence, the treatment targets of roflumilast are improvement in the forced expiratory volume in one second (FEV₁) and reduction in likelihood of exacerbations.^{5,6}
- The Global Initiative for Chronic Obstructive Lung Disease guidelines recommend that phosphodiesterase (PDE) inhibitors be reserved for patients with severe or very severe COPD with a history of exacerbations and chronic bronchitis and should always be used in combination with at least one long-acting bronchodilator. Roflumilast may also be useful for patients with FEV₁ <50% predicted.⁷
- In a Cochrane meta-analysis of 23 randomized trials, treatment with roflumilast or cilomilast (another PDE inhibitor, not currently on the market) was associated with a reduced likelihood of COPD exacerbation (OR 0.78; 95% CI 0.72 to 0.85) and a modest improvement in the forced expiratory volume in one second (FEV₁) (45.59 mL, 95% CI 39.1 to 52.03).
 - The subset of patients who experienced fewer exacerbations with roflumilast in clinical trials included: males, former smokers, current inhaled corticosteroid users, those with chronic bronchitis plus emphysema, those with chronic bronchitis plus emphysema using an inhaled corticosteroid, and those with a sputum score >1.⁸
 - The average age of patients receiving roflumilast in clinical trials was between 63 and 65 years old, however, patients up to 87 years of age have been evaluated.⁸

- Many patients in early clinical trials were concurrently treated with a long-acting beta-agonist (e.g., salmeterol (Serevent®)) and/or tiotropium (Spiriva®), and initial reports were uncertain whether roflumilast provided additional benefit when combined with other respiratory medications.⁶ Recent studies have shown the effects of roflumilast on lung function when administered alone and when added to long-acting bronchodilators.^{5,7}
- Roflumilast has no impact on mortality and little impact on quality of life or respiratory symptoms.^{5,6}

SAFETY

- Common adverse effects of roflumilast include gastrointestinal symptoms (e.g., diarrhea, nausea, vomiting), headache, loss of appetite and weight loss.^{5,9,10,11}
 - Gastrointestinal symptoms and headache are most evident in the first 4 to 12 weeks of therapy, were mostly mild to moderate in intensity, and are reversible.¹⁰
 - In general, weight loss appears to occur within the first 6 months of treatment, is small (<3% of baseline weight, average 2 kg), reversible, and primarily attributed to a reduction in fat mass.¹⁰ Although weight change appears to be more pronounced with obese patients, underweight patients do not show a more notable weight loss than patients in other body mass index categories.¹⁰
- Serious adverse effects of roflumilast include psychiatric disorders (e.g., depression, insomnia, anxiety, suicidal thoughts/suicide).¹⁰
 - In the COPD safety pool, roflumilast 500 mcg was associated with more cases of depression (1.21% vs. 0.82%) and suicidal ideation/attempt (0.03% vs. 0.02%) compared with placebo.¹⁰
 - The U.S. Food and Drug Association reports that currently the event rate is too low to draw conclusion about association of roflumilast with suicide/suicidal attempts but suggests that prescribers and patients should be warned of the higher incidence of psychiatric events, in general, in order to weigh the risk vs. benefits of treatment and if prescribed, the patient should be monitored for changes in psychiatric events.¹⁰

TIME TO BENEFIT

- Steady state is generally achieved within 4 days for roflumilast and 6 days for the active metabolite roflumilast N-oxide following the dosage of 500 mcg once daily.^{9,11}
- Based on clinical trials in patients with COPD, the time until benefit with roflumilast appears to be within 24-52 weeks.

COST

- The average cost of a 15-day supply of roflumilast is \$180.

AVAILABLE FORMULATIONS

- Roflumilast is available in a 500 mcg strength oral tablet.^{9,11}
- No information is available on crushing or splitting of the tablet.

CONCLUSION

- In summary, hospice care is a valuable service for terminally ill patients and their family and friends. The role of roflumilast in hospice and palliative care is ill-defined.
- Because roflumilast has minimal effect on quality of life or respiratory symptoms, it is reasonable to consider other therapies (e.g., opioids, corticosteroids) instead of roflumilast for respiratory symptoms associated with advanced COPD. However, consideration can be given for prescribing roflumilast for the purpose of reducing exacerbations in those patients who may have a longer prognosis, who might benefit most (i.e., males, former smokers, current inhaled corticosteroid users, those with chronic bronchitis plus emphysema, those with chronic bronchitis plus emphysema using an inhaled corticosteroid, or those with a sputum score >1) and for whom the benefits outweigh the possible adverse effects (namely psychiatric events and weight loss).
- For patients with continual respiratory symptoms or repeated exacerbations despite roflumilast therapy or who experience adverse effects associated with roflumilast (especially psychiatric events and weight loss), it is reasonable to consider discontinuation.

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