

Oral glucocorticoids

Oral glucocorticoids have numerous side effects, including steroid myopathy⁽¹⁰¹⁴⁾ which can contribute to muscle weakness, decreased functionality, and respiratory failure in people with very severe COPD. Systemic glucocorticoids for treating acute exacerbations in hospitalized patients, or during emergency department visits, have been shown to reduce the rate of treatment failure, the rate of relapse and to improve lung function and breathlessness.⁽¹⁰¹⁵⁾ Conversely, prospective studies on the long-term effects of oral glucocorticoids in stable COPD are limited.^(1016,1017) Therefore, while oral glucocorticoids play a role in the acute management of exacerbations, they have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.

Phosphodiesterase-4 (PDE4) inhibitor

The principal action of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP.⁽¹⁰¹⁸⁾ Roflumilast is a once daily oral medication with no direct bronchodilator activity. Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations.⁽¹⁰¹⁹⁾ The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators,⁽¹⁰²⁰⁾ and in patients who are not controlled on fixed-dose LABA+ICS combinations.⁽⁷⁰⁶⁾ The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation.^(705,708) There has been no study directly comparing roflumilast with an inhaled corticosteroid.

Adverse effects

Roflumilast has more adverse effects than inhaled medications for COPD.⁽¹⁰²¹⁾ The most frequent are diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. Adverse effects have led to increased withdrawal rates from clinical trials. Adverse effects seem to occur early during treatment, are reversible, and diminish over time with continued treatment. In controlled studies an average unexplained weight loss of 2 kg has been seen and weight monitoring during treatment is advised, in addition to avoiding roflumilast treatment in underweight patients. Roflumilast should also be used with caution in patients with depression.

Antibiotics

In older studies prophylactic, *continuous* use of antibiotics had no effect on the frequency of exacerbations in COPD^(1022,1023) and a study that examined the efficacy of chemoprophylaxis undertaken in winter months over a period of 5 years concluded that there was no benefit.⁽¹⁰²⁴⁾ Later studies have shown that regular use of some antibiotics may reduce exacerbation rate.^(1025,1026)

Azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (250 mg two times per day) for one year in patients prone to exacerbations reduced the risk of exacerbations compared to usual care.^(704,1027,1028) Azithromycin use was associated with an increased incidence of bacterial resistance, prolongation of QTc interval, and impaired hearing tests.⁽⁷⁰⁴⁾ A *post-hoc* analysis suggests lesser benefit in active smokers.⁽⁷⁰⁵⁾ There are no data showing the efficacy or safety of chronic azithromycin treatment to prevent COPD exacerbations beyond one-year of treatment.

Pulse therapy with moxifloxacin (400 mg/day for 5 days every 8 weeks) in patients with chronic bronchitis and frequent exacerbations had no beneficial effect on the exacerbation rate overall.⁽¹⁰²⁹⁾ Long-term doxycycline did not reduce exacerbations, although there may be responder subgroups.⁽¹⁰³⁰⁾

Mucolytic (mucokinetics, mucoregulators) and antioxidant agents (N-acetylcysteine, carbocysteine, erdosteine)

In COPD patients not receiving ICS, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine