Prevention of COPD exacerbations: a European Respiratory Society/ American Thoracic Society guideline

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ABSTRACT This document provides clinical recommendations for the prevention of chronic obstructive pulmonary disease (COPD) exacerbations. It represents a collaborative effort between the European Respiratory Society and the American Thoracic Society.

Comprehensive evidence syntheses were performed to summarise all available evidence relevant to the Task Force's questions. The evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluation approach and the results were summarised in evidence profiles. The evidence syntheses were discussed and recommendations formulated by a multidisciplinary Task Force of COPD experts.

After considering the balance of desirable (benefits) and undesirable consequences (burden in the form of adverse effects and cost), quality of evidence, feasibility, and acceptability of various interventions, the Task Force made recommendations for mucolytic, long-acting muscarinic antagonist, phosphodiesterase-4 inhibitor (roflumilast) and macrolide therapy, as well as a conditional recommendation against fluoroquinolone therapy. All of the recommendations were conditional, except for a strong recommendation for the use of a long-acting antimuscarinic agent *versus* a long-acting β_2-adrenergic, indicating that there was uncertainty about the balance of desirable and undesirable consequences of the intervention, and that well-informed patients may make different choices regarding whether to have or not have the specific intervention.

The guideline summarises the evidence and provides recommendations for pharmacological therapy for the prevention of COPD exacerbations.

Introduction

Prevention of exacerbations is a key objective in chronic obstructive pulmonary disease (COPD) management. There are patients with COPD that are prone to suffer from recurrent exacerbations [1] and they experience a more severe impairment in health status [2, 3]. Moreover, patients with recurrent hospitalisations for exacerbations have a reduced survival [4]. Although no definitive evidence exists about the impact of prevention of exacerbations of COPD in reducing mortality, treatments that effectively reduce the frequency and/or severity of exacerbations may have an impact on quality of life, the progression and ultimately the prognosis of COPD.

This guideline was a collaborative effort between the European Respiratory Society (ERS) and the American Thoracic Society (ATS). It employed a systematic review of the literature followed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [5] approach to develop recommendations that answer the following five questions:

1) Should mucolytics be prescribed to patients with stable COPD to prevent COPD exacerbations?
2) Are long-acting β-agonists (LABAs) or long-acting muscarinic antagonists (LAMAs) preferable in patients with stable COPD to prevent COPD exacerbations?
3) Should roflumilast be prescribed to patients with COPD associated with chronic bronchitis and exacerbations to prevent subsequent exacerbations?
4) Should fluoroquinolones be prescribed to patients with stable COPD to prevent COPD exacerbations?
5) Should macrolides be prescribed to patients with stable COPD to prevent COPD exacerbations?

This ERS/ATS guideline focuses on the prevention of COPD exacerbations. A separate ERS/ATS guideline was recently published that addresses the management of COPD exacerbations [6]. We accepted other evidence-based evaluations of certain established therapies and did not seek to repeat the analyses already undertaken. Our role is to update and address gaps in the existing evidence. Other therapies are effective and might be preferred to those we address here, *e.g.* smoking cessation or dual bronchodilator therapy, which were not considered within the time frame of this Task Force.

Methods

The methodology followed for the development of this document regarding formulation of questions, rating the important outcomes, study selection, evidence synthesis, and formulating and grading the evidence has been described in detail in the previous ERS/ATS guideline on management of COPD exacerbations [6], and can also be found in the supplementary material. Some important aspects of the methodology are summarised in the following subsections.

Group composition

The Task Force co-chairs (J.A. Wedzicha and J.A. Krishnan) were selected by the ERS and ATS. They led all aspects of project management and selected the panellists, which included 11 clinicians with experience in COPD management and research. In addition, there were two methodologists (T. Tonia and D. Rigau) and a clinician-methodologist (K.C. Wilson). The lead methodologist (T. Tonia) identified and collected the evidence, performed the evidence syntheses, constructed the evidence profiles, and ensured that all the methodological requirements were met, with assistance from the other methodologists. Thresholds for clinically important differences between treatment groups (used to judge imprecision) included the following relative risk reductions: mortality 15%, exacerbations 20%, hospitalisations 20% and adverse

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events 15%. They also included the following absolute reduction: St George's Respiratory Questionnaire score change of 4 points.

The co-chairs and panellists discussed the evidence and formulated the recommendations; the methodologists did not participate in the development of recommendations. All panel members were required to disclose their conflicts of interest. Being an author of a publication reporting the effect of an intervention in prevention of exacerbations was considered as a conflict of interest. At least 50% of the co-chairs and 50% of the panel were required to be free from conflicts of interest. Individuals with potential conflicts of interest took part in the discussions about the evidence but did not participate in the formulation of recommendations.

Literature searches

Our literature searches used the National Institute of Health and Clinical Excellence (NICE) guidelines as a starting point [7]. For questions that were addressed in the 2004 NICE guidelines, we conducted literature searches in Medline, Embase and the Cochrane Database of Systematic Reviews beginning in 2003. For questions that were addressed in the 2010 NICE guidelines, we conducted literature searches in the same databases beginning in 2009. Initial searches were conducted in January 2012, and then updated in June 2012, February 2013 and September 2015. We used the same or similar search strategies as those used by NICE. To search Embase and Medline, we searched only the English-speaking literature using the search strategy shown in the supplementary material, whereas to search the Cochrane Database of Systematic Reviews, we used the search term "chronic obstructive pulmonary disease".

Manuscript preparation

The initial draft of the manuscript was prepared by the co-chairs, methodologists and one panellist (M. Miravitlles). The lead methodologist wrote the content for the supplementary material, which was edited by the co-chairs. Both the manuscript and the supplementary material were reviewed, edited and approved by all panel members prior to submission.

Results

Should mucolytics be prescribed to patients with stable COPD to prevent COPD exacerbations?

Summary of the evidence

We identified one relevant systematic review [8], which included four trials that met our inclusion criteria [9–12]. Our own systematic review identified two additional trials [13, 14]. These six trials collectively informed the Task Force's judgements [9–14].

All six trials were randomised, placebo-controlled trials conducted in patients with COPD. 93% of patients had moderate or severe airflow obstruction, defined as a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <0.70 and an FEV_1 % pred of 30–79%. Three trials enrolled patients with COPD who had a history of at least two exacerbations per year during the previous 2 years [9, 12, 14], one trial enrolled patients with COPD who had a history of at least one exacerbation per year during the previous year [10] and two trials enrolled patients with COPD regardless of whether or not they had any exacerbations during the previous year [11, 13]. Mucolytic agents included *N*-acetylcysteine in four trials [9, 11, 13, 14], ambroxol in one trial [10] and carbocisteine in one trial [12]. Four trials administered mucolytic therapy for 1 year [10, 12, 14, 15] and two trials administered mucolytic therapy for 3 years [11, 13].

The Task Force identified *a priori* four outcomes as "critical" to guide the formulation of treatment recommendations; three other outcomes were considered "important". The critical outcomes included the rate of COPD exacerbations, proportion of patients having at least one COPD exacerbation, hospitalisations and quality of life, while the important outcomes included mortality, adverse events and amount of sputum production.

When the data were pooled *via* meta-analysis (see evidence profile 1 in the supplementary material), mucolytic therapy decreased the likelihood of hospitalisation (14.1% *versus* 18.1%; risk ratio 0.76, 95% CI 0.59–0.97), indicating that 25 patients needed to be treated with mucolytics to prevent one hospitalisation. When we segregated the analysis based upon dosage, the absolute and relative decreases in hospitalisations were similar among patients who received high-dose or low-dose mucolytic therapy compared with both doses pooled together, but due to smaller numbers of patients in each group, the confidence intervals widened to include no significant effect of the drug.

The effect of mucolytic therapy on COPD exacerbations varied according to the method of measurement. Mucolytic therapy reduced the relative rate of exacerbations when assessed as the number of exacerbations per patient-year (rate ratio 0.79, 95% CI 0.65–0.95), although the absolute rate reduction was small (rate

difference of 0.38 fewer exacerbations per patient-year, 95% CI 0.23 fewer to 0.54 fewer). The reduced rate of COPD exacerbations was largely attributable to high-dose mucolytic therapy (rate ratio 0.69, 95% CI 0.50–0.94), as trials that used low-dose mucolytic therapy did not find a significant relative rate reduction (rate ratio 0.87, 95% CI 0.66–1.14). Mucolytic therapy had no effect on COPD exacerbations when assessed as the proportion of patients who remained exacerbation-free (34.1% *versus* 32.4%; risk ratio 1.06, 95% CI 0.95–1.19).

Mucolytic therapy had no demonstrable effect on mortality (1.3% *versus* 1.1%; risk ratio 1.15, 95% CI 0.55–2.43) or adverse events (26.9% *versus* 24.2%; risk ratio 1.11, 95% CI 0.91–1.35). The effect on quality of life could not be estimated *via* meta-analysis and the individual studies provided inconsistent results. For all outcomes, the estimated effects did not change substantially when the trials were pooled according to whether or not a history of exacerbations was required for enrolment.

Of note, we were unable to review one potentially relevant trial [15]; as this study included patients with chronic bronchitis, and we were not able to assess it ourselves, we decided not to include it in the evidence tables. We conducted sensitivity analyses to determine if the trial would have significantly affected the results and determined that the measured outcomes did not differ substantially whether the trial was included or excluded.

Benefits

Mucolytic therapy reduced hospitalisations. Mucolytic therapy also reduced the number of COPD exacerbations per patient-year (an effect largely attributable to high-dose therapy), but not the proportion of patients who remained exacerbation-free.

Harms

None identified; there was no evidence that mucolytic therapy increased adverse events.

Other considerations

The overwhelming majority of patients had moderate or severe airflow obstruction; few patients had mild or very severe airflow obstruction. There was no information in any of the trials on the quantity of sputum production. In addition, the outcomes were limited by imprecise estimates, inconsistent results among the primary studies or both; these limitations diminished the panel's confidence in the estimated effects. A systematic review was published following the completion of our evidence synthesis [16]. The results support that mucolytic therapy may reduce the frequency of COPD exacerbations, but raised the possibility that patients with more severe obstruction may require higher doses than those with less severe obstruction.

Conclusions and research needs

Mucolytic therapy (*N*-acetylcysteine, ambroxol or carbocisteine) reduces the likelihood of hospitalisation and, when given in high doses, may also reduce COPD exacerbations. No effect on mortality was shown, although there were low numbers of deaths in the trials to definitively determine the effect on mortality. Similarly, there is no evidence that mucolytic therapy increases adverse effects or alters quality of life. Determining the effects of mucolytic therapy in patients with mild or very severe COPD is an important research need, as the findings will help define the patient population most likely to benefit from mucolytic therapy. Since most of the trials used *N*-acetylcysteine, additional research is needed to determine if ambroxol and carbocisteine have similar effects. As some of the studies included patients who were not on optimal inhaled therapy, the efficacy of mucolytics on top of maximal inhaled treatment has yet to be clearly established.

What others are saying

The 2010 NICE guidelines [7] recommended not to use mucolytic drugs routinely to prevent exacerbations in patients with stable COPD. The 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document [17] stated that "Regular treatment with mucolytics such as carbocysteine and *N*-acetylcysteine may reduce exacerbations and modestly improve health status in patients not receiving ICS". The 2015 American College of Chest Physicians (ACCP)/Canadian Thoracic Society (CTS) guidelines [18] recommended *N*-acetylcysteine treatment for patients with moderate to severe COPD and a history of two or more exacerbations during the previous 2 years [18].

ERS/ATS recommendation

For patients who have COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy, we suggest treatment with an oral mucolytic agent to prevent future exacerbations (conditional recommendation, low quality of evidence).

Remarks

Moderate or severe airflow obstruction is defined as a post-bronchodilator $FEV_1/FVC < 0.70$ and an FEV_1 % pred of 30–79%. The beneficial effect of mucolytic therapy on the rate of COPD exacerbations was driven by trials that administered high-dose mucolytic therapy (*e.g. N*-acetylcysteine 600 mg twice daily).

Values and preferences

This recommendation places a high value on avoiding hospitalisations, and a lower value on the cost and burden of taking daily medication.

Are LABAs or LAMAs preferable in patients with stable COPD to prevent COPD exacerbations?

Summary of the evidence

Our systematic review identified two relevant trials [19, 20]. The first trial compared once-daily tiotropium (LAMA) with once-daily indacaterol (LABA) [19]. The second trial compared once-daily tiotropium (LAMA) with twice-daily treatment with salmeterol (LABA) [20]. Both trials were conducted over 1 year and required that patients had at least one COPD exacerbation during the past year. The overwhelming majority of patients had moderate or severe airflow obstruction, defined as a post-bronchodilator $FEV_1/FVC < 0.70$ and an FEV_1 % pred of 30–79%.

The Task Force identified *a priori* six outcomes as "critical" to guide the formulation of treatment recommendations; two other outcomes were considered "important". The critical outcomes included mortality, frequency of COPD exacerbations, hospitalisations, adverse events, quality of life and FEV_1, while the important outcomes included dyspnoea and exercise tolerance.

When the trials were pooled *via* meta-analysis (see evidence profile 2 in the supplementary material), patients who received a LAMA were less likely to have one or more moderate to severe COPD exacerbations (30.9% *versus* 34.6%; risk ratio 0.89, 95% CI 0.85–0.94). In addition, there was a trend in patients who received a LAMA to have fewer severe adverse effects (14.7% *versus* 16.1%; risk ratio 0.91, 95% CI 0.84–1.0). There was no difference in mortality.

One of the trials additionally reported that patients who received a LAMA were less likely to have a severe COPD exacerbation requiring hospitalisation (7.1% *versus* 9.2%; risk ratio 0.77, 95% CI 0.66–0.90) and had greater improvement in their FEV_1 from baseline (mean difference +19 mL, 95% CI +11.34 mL to +28.66 mL) [20]. The trial also found no difference in the quality of life, magnitude of improved dyspnoea or proportion of patients with less dyspnoea.

Benefits

Patients who received a LAMA were less likely to have one or more moderate to severe COPD exacerbations, were less likely to have a severe exacerbation requiring hospitalisation and had greater improvement in FEV_1 than patients who received a LABA.

Harms

There were no significant differences in severe adverse events between both treatments.

Other considerations

The overwhelming majority of patients had moderate or severe airflow obstruction and there were no data from patients who had not had an exacerbation during the previous year. In addition, one outcome that the panel considered important (*i.e.* exercise tolerance) was not reported in either study. For several outcomes, the panel's confidence in estimating the relative effects of LABA *versus* LAMA treatment was diminished by imprecision (*i.e.* wide confidence intervals).

Conclusions and research needs

LAMA therapy reduces the likelihood of moderate to severe exacerbations compared with LABA therapy. It may be associated with fewer adverse events; however, additional data are needed to confirm or exclude this possibility. A differential effect of the agents on mortality has not been shown, although there were very few deaths in the trials to definitively confirm or exclude such an effect. The effects of LAMA *versus* LABA therapy in patients with mild or very severe COPD requires additional research. Additional data are also required to determine the difference in the effects of LAMA *versus* LABA therapy on mortality and adverse effects, as well as to determine the comparative effects of these two agents on other important clinical outcomes.

What others are saying

The 2010 NICE guidelines [7] state that "In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy: if FEV_1 ⩾50% predicted: either long-acting $beta_2$ agonist (LABA) or LAMA; if FEV_1 <50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA". The 2017 GOLD strategy document [17] recommend either a LAMA or a combination LABA/LAMA (but not LABA monotherapy) for patients with either two or more exacerbations per year or one or more exacerbations requiring hospitalisation. The 2015 ACCP/CTS guidelines [18] stated that "in patients with moderate to severe COPD, we recommend the use of long-acting muscarinic antagonists compared with long-acting β-agonists to prevent moderate to severe acute exacerbations of COPD".

ERS/ATS recommendation

In patients who have COPD with moderate or severe airflow obstruction and a history of one or more COPD exacerbations during the previous year, we recommend that a LAMA be prescribed in preference to LABA monotherapy to prevent future exacerbations (strong recommendation, moderate quality of evidence).

Remarks

Moderate or severe airflow obstruction is defined as a post-bronchodilator FEV_1/FVC <0.70 and an FEV_1 % pred of 30–79%.

Values and preferences

This recommendation places a high value on reducing the likelihood of a COPD exacerbation, and a lower value on symptomatic relief, the burden of taking daily medication and cost.

Should roflumilast be prescribed to patients with COPD associated with chronic bronchitis and exacerbations to prevent subsequent exacerbations?

Summary of the evidence

The Task Force made an *a priori* decision to look at the effects of a phosphodiesterase-4 inhibitor (roflumilast) exclusively in patients who had chronic bronchitis. The rationale for focusing on this patient population was that initial trials conducted in patients with or without chronic bronchitis found only a small decrease in the exacerbation rate [21, 22]; however, a subsequent subgroup analysis found a much larger reduction in the exacerbation rate among patients with chronic bronchitis [22].

Our systematic review identified three trials that compared roflumilast to placebo in patients with stable COPD, a history of COPD exacerbations and chronic bronchitis [23, 24]; two of the trials were reported together [23]. 68% of patients had severe airflow obstruction, defined as a post-bronchodilator FEV_1/FVC <0.70 and an FEV_1 % pred of 30–49%, and 31% of patients had very severe airflow obstruction, defined as a post-bronchodilator FEV_1/FVC <0.70 and an FEV_1 % pred of <30%. Two of the trials required participants to have had one or more COPD exacerbations during the previous year [23] and one trial required participants to have had two or more COPD exacerbations during the previous year [24]. All three trials administered roflumilast for 1 year [23, 24].

The Task Force identified *a priori* six outcomes as "critical" to guide the formulation of treatment recommendations; three other outcomes were considered "important". The critical outcomes included rate of COPD exacerbations, proportion of patients having at least one COPD exacerbation, time to first COPD exacerbation, mortality, adverse events and cardiovascular events; other important outcomes included changes in quality of life, FEV_1 and FVC.

When the data were pooled *via* meta-analysis (see evidence profile 3 in the supplementary material), roflumilast therapy decreased the number of moderate or severe exacerbations per patient-year (rate ratio 0.85, 95% CI 0.78–0.91), as well as proportion of patients who had an exacerbation (21.4% *versus* 25.2%; risk ratio 0.85, 95% CI 0.78–0.94). Roflumilast also increased time to next exacerbation (hazard ratio 0.88, 95% CI 0.81–0.96). While these effects were relatively modest when the three trials were pooled together and analysed, the largest and most recent trial found a larger reduction in the number of severe exacerbations (defined a severe exacerbation as one requiring hospitalisation or resulting in death) per patient-year despite concomitant therapy with an inhaled corticosteroid/LABA (rate ratio 0.76, 95% CI 0.60–0.95) [24].

The meta-analysis also demonstrated that patients who received roflumilast therapy had a larger increase in their post-bronchodilator FEV_1 (mean difference +56.29 mL, 95% CI +45.45 mL to +67.14 mL) and FVC (mean difference +98.45 mL, 95% CI +79.35 mL to +117.55 mL). However, roflumilast also increased adverse events (67.4% *versus* 60.9%; risk ratio 1.11, 95% CI 1.06–1.15). Roflumilast therapy had no effect

on mortality (2.4% *versus* 2.4%; risk ratio 0.99, 95% CI 0.70–1.42) or cardiovascular events (5.4% *versus* 4.9%; risk ratio 1.11, 95% CI 0.88–1.40).

The panel was concerned that the adverse effects of roflumilast may have been underestimated by our analysis because studies <1 year had been excluded. The rationale was that whereas benefits may take a while to accrue, meaningful adverse effects often occur soon after the initiation of therapy and, therefore, would be detectable in the shorter trials. Thus, we sought additional data on adverse events from trials of roflumilast that were <1 year in duration. A Cochrane systematic review included all of the relevant trials [25]. Premature treatment discontinuation due to adverse effects was more common with roflumilast than placebo (14.9% *versus* 9.0%; risk ratio 1.80, 95% CI 1.58–2.04). The most common adverse effects were diarrhoea (9.7% *versus* 2.7%; risk ratio 3.96, 95% CI 3.20–4.89), nausea (4.8% *versus* 1.4%; risk ratio 3.54, 95% CI 2.63–4.78), weight loss (8.4% *versus* 2.3%; risk ratio 3.94, 95% CI 3.11–5.00), psychiatric disorders including anxiety and depressive symptoms (7.1% *versus* 3.5%; risk ratio 2.13, 95% CI 1.79–2.54), and sleep disturbance/insomnia (3.1% *versus* 1.1%; risk ratio 2.88, 95% CI 2.15–3.86). Mortality was rare, with no significant difference (<2% in both the roflumilast and placebo groups).

Benefits

Roflumilast therapy reduced the number of exacerbations per patient-year, an effect that was particularly strong for severe exacerbations. It also decreased the proportion of patients who developed an exacerbation, prolonged the time to next exacerbation, and modestly increased both FEV_1 and FVC.

Harms

Adverse events were increased in our systematic review. An independent systematic review that included trials with shorter durations supported our finding; it demonstrated that patients receiving roflumilast were more likely to prematurely discontinue treatment and develop diarrhoea, nausea, weight loss, psychiatric disturbances, insomnia or sleep disturbances.

Other considerations

The majority of patients had severe or very severe airflow obstruction, in contrast to the evidence reviewed for mucolytic therapy and LABA *versus* LAMA therapy that was predominately derived from patients with moderate or severe airflow obstruction. Several outcomes were limited by imprecise estimates, which diminished the panel's confidence in those estimated effects. None of the trials measured quality of life as an outcome.

Conclusions and research needs

Roflumilast therapy reduces COPD exacerbations, particularly severe exacerbations, and modestly improves lung function. No effect on mortality was evident, although there were too few deaths in the trials to definitively confirm or exclude an effect on mortality. Roflumilast therapy increases the risk of gastrointestinal, sleep and psychiatric adverse effects in up to 7.2% of patients. Determining the effect of roflumilast therapy in patients with mild or moderate airflow obstruction remains an important research need.

What others are saying

The 2010 NICE guidelines [7] did not address roflumilast therapy. The 2017 GOLD strategy document [17] mentioned that "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". The 2015 ACCP/CTS guidelines [18] suggests roflumilast for patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation during the previous year.

ERS/ATS recommendation

In patients who have COPD with severe or very severe airflow obstruction, symptoms of chronic bronchitis and exacerbations despite optimal inhaled therapy, we suggest treatment with roflumilast to prevent future exacerbations (conditional recommendation, moderate quality of evidence).

Remarks

Severe or very severe airflow obstruction is defined as a post-bronchodilator FEV_1/FVC <0.70 and an FEV_1 % pred of <50%.

Values and preferences

This recommendation places a high value on the prevention of exacerbations, and a lower value on the burden, cost and adverse effects of taking a daily medication.

Should fluoroquinolones be prescribed to patients with stable COPD to prevent COPD exacerbations?

Summary of the evidence

We identified one trial that met our inclusion criteria [26]. The trial was a randomised, placebo-controlled trial conducted in adults who had COPD (FEV_1/FVC <0.70), chronic bronchitis and at least two exacerbations per year during the previous year. 21% of patients had moderate airflow obstruction (pre-bronchodilator FEV_1 % pred 50–80%), 43.9% had severe airflow obstruction (pre-bronchodilator FEV_1 % pred 30–49%) and 26.0% had very severe airflow obstruction (pre-bronchodilator FEV_1 % pred <30%). Participants received either moxifloxacin 400 mg or placebo once daily for 5 days, repeated every 8 weeks for a total of six courses administered over 48 weeks. This trial informed the guideline panel's judgements.

The Task Force identified *a priori* five outcomes as "critical" to guide the formulation of treatment recommendations; two other outcomes were considered "important". The critical outcomes included time to first COPD exacerbation, the proportion of patients who had one or more COPD exacerbations, hospitalisations, mortality and adverse events, while the important outcomes included changes in quality of life and the airway bacterial load.

The trial found no definitive effects among patients who received the fluoroquinolone moxifloxacin. There were, however, trends toward all of the following: fewer patients developing COPD exacerbations (47.3% *versus* 50.9%; risk ratio 0.93, 95% CI 0.83–1.05), a longer duration to first exacerbation (p=0.062) and improved quality of life (mean difference −1.20, 95% CI −3.01 to 0.61) (see evidence profile 4 in the supplementary material). There were no differences in hospitalisations (23.0% *versus* 23.4%; risk ratio 0.98, 95% CI 0.80–1.21), mortality (2.6% *versus* 2.9%; risk ratio 0.901, 95% CI 0.45–1.78) or adverse events (82.1% *versus* 85%; risk ratio 0.97, 95% CI 0.92–1.02). When the outcomes were re-analysed using a per-protocol rather than an intention-to-treat approach, the results were similar.

The panel was concerned that its evidence synthesis underestimated the adverse effects of fluoroquinolone therapy since it included only a single trial. Therefore, the panel decided to look for additional evidence about the adverse effects, beginning with systematic reviews of fluoroquinolones in other populations since the panel had no reason to expect that the adverse effects of fluoroquinolones would be any different in patients with COPD. A systematic review comparing fluoroquinolone-containing regimens to fluoroquinolone-free regimens in patients with tuberculosis was identified [27]. In a meta-analysis of six randomised trials, adverse events were increased among patients who received fluoroquinolones (24.1% *versus* 15.7%; risk ratio 1.40, 95% CI 1.03–1.92). These results were limited by inconsistent results among the individual trials. The most common adverse effects were gastrointestinal effects, dizziness and joint pain.

Benefits

Fluoroquinolone therapy conferred no definitive benefits.

Harms

In the lone trial that met our selection criteria, fluoroquinolone therapy did not increase adverse events; however, analyses in other populations suggest that fluoroquinolones may increase adverse events.

Other considerations

The study reported a statistically significant improvement in COPD exacerbation rate when it was measured using an odds ratio; however, the same outcome showed only a trend toward improvement when measured using a risk ratio. The panel decided to use risk ratios to inform its judgements. The study also reported a decreased COPD exacerbation rate in the subgroup of patients with mucopurulent sputum, but not in the subgroup without mucopurulent sputum; insufficient data were reported for us to re-analyse the subgroups using risk ratios. Several outcomes were limited by imprecise estimates, which diminished the panel's confidence in the estimated effects.

Conclusions and research needs

Fluoroquinolone therapy has not been proven to prevent COPD exacerbations or improve other clinical outcomes, but it may increase adverse events. The estimated 3.6% absolute risk reduction and 7% relative risk reduction in COPD exacerbations would be clinically important if real, but these effects can be neither confirmed nor excluded due to the wide confidence intervals. Additional trials are necessary to determine the impact of fluoroquinolone therapy to prevent exacerbations. The panel concluded that patients who produce mucopurulent sputum are a particularly important subgroup to evaluate in future trials.

What others are saying

The 2010 NICE guidelines [7] did not address fluoroquinolone therapy. The 2017 GOLD strategy document [17] said that "Pulse moxifloxacin therapy in patients with chronic bronchitis and frequent exacerbations does not reduce exacerbation rate". The 2015 ACCP/CTS guidelines [18] did not address fluoroquinolone therapy.

ERS/ATS recommendation

Remarks

Fluoroquinolone therapy is not suggested as treatment for the sole purpose of preventing future COPD exacerbations (conditional recommendation, moderate quality of evidence).

Values and preferences

This recommendation places a high value on avoiding unproven therapies (particularly when there is a risk of adverse events and increasing bacterial resistance, which was of significant concern to the Task Force) and a lower value on the potential to prevent COPD exacerbations.

Should macrolides be prescribed to patients with stable COPD to prevent COPD exacerbations?

Summary of the evidence

We identified one relevant systematic review [28], which included three trials that met our inclusion criteria [29–31]. Our own systematic review identified an additional trial [32]. These four trials collectively informed the panel's judgements [29–32].

All four trials were randomised, placebo-controlled trials conducted in patients with COPD. Two trials reported the severity of airflow obstruction as the mean FEV_1 in each treatment arm, which ranged from 1.27 to 1.47 L [29, 30]. The remaining two trials reported that 0.4% of patients had mild airflow obstruction, 26.4% of patients had moderate airflow obstruction, 40.6% of patients had severe airflow obstruction and 32.6% of patients had very severe airflow obstruction, when defined as a post-bronchodilator FEV_1 % pred of $\geqslant$80%, 50–79%, 30–49% and <30%, respectively [31, 32]. One trial enrolled patients with COPD who had a history of at least three exacerbations during the previous year [32], one trial enrolled patients with COPD who had a history of at least one exacerbation during the previous year [31] and two trials enrolled patients with COPD regardless of whether or not they had any exacerbations during the previous year [29, 30]. Macrolide regimens included erythromycin 200–400 mg daily [29], erythromycin 250 mg twice daily [30], azithromycin 250 mg daily [31] and azithromycin 500 mg three times per week [32]. All of the trials administered the macrolide for 1 year [29–32].

The Task Force identified *a priori* five outcomes as "critical" to guide the formulation of treatment recommendations; two other outcomes were considered "important". The critical outcomes included the rate of COPD exacerbations, time to first exacerbation, mortality, hospitalisations and serious adverse events. Important outcomes included quality of life and acquisition of macrolide resistance.

When the data were pooled *via* meta-analysis (see evidence profile 5 in the supplementary material), macrolide therapy decreased the rate of COPD exacerbations (rate ratio 0.76, 95% CI 0.68–0.86), although the absolute decrease was modest (rate difference 0.40 fewer exacerbations per patient-year, 95% CI 0.24 fewer to 0.55 fewer). Macrolide therapy also increased the time to first COPD exacerbation (mean difference 81.53 more days, 95% CI 53.29 more to 109.77 more). Of note, the largest trial performed subgroup analyses and found that the increase in the time to first COPD exacerbation varied in patients on the basis of smoking status and age [33]. There was a significant reduction in the risk of COPD exacerbations among past smokers, but not current smokers (comparing azithromycin *versus* placebo in past smokers: relative hazard 0.65, 95% CI 0.55–0.77; comparing azithromycin *versus* placebo in current smokers: relative hazard 0.99, 95% CI 0.71–1.38; p=0.03 for interaction) and among patients >65 years, but not younger patients (>65 years: relative hazard 0.59, 95% 0.57–0.74; $\leqslant$65 years: relative hazard 0.84, 95% CI 0.68–1.04; p=0.02 for interaction) [31]. Although not a pre-specified outcome, macrolide therapy reduced the proportion of patients who developed an exacerbation (57% *versus* 68%; risk ratio 0.84, 95% CI 0.76–0.92) [31].

Macrolide therapy improved quality of life, measured using the St George's Respiratory Questionnaire score. The improvement was seen across all domains: total (mean difference 2.18 lower, 95% CI 1.53 lower to 2.82 lower), symptoms (mean difference 3.36 lower, 95% CI 2.42 lower to 4.29 lower), activity (mean difference 1.82 lower, 95% CI 1.03 lower to 2.62 lower) and impacts (mean difference 2.04 lower, 95% CI 1.28 lower to 2.81 lower). There was no demonstrable effect on mortality (2.7% *versus* 3.0%; risk ratio 0.90, 95% CI 0.48–1.69). Data on hospitalisations could not be pooled because the trials reported the outcome differently; individual trials found a trend toward a decreased rate of hospitalisation due to COPD exacerbations [31] and no difference in the time to first hospitalisation [32]. The effects of macrolide

therapy on acquisition of macrolide resistance and the proportion of exacerbations requiring hospitalisation were uncertain due to inconsistent results.

Our meta-analysis identified a trend toward fewer serious adverse events among patients who received macrolide therapy than among those who received placebo (28.3% *versus* 33%; risk ratio 0.86, 95% CI 0.74–1.01). While this suggests that macrolides are generally well tolerated, individual trials provide several reasons for caution. In the largest trial (the MACRO trial), the most common adverse event that led to premature treatment discontinuation was a hearing decrement measured using audiometry performed by clinical research staff (25.4% *versus* 19.7%; risk ratio 1.29, 95% CI 1.04–1.61) [31]. However, hearing as assessed by audiometry returned to baseline in about one-third of patients whether or not treatment was discontinued (21 out of 61 individuals (34%) after azithromycin was discontinued, six out of 19 individuals (32%) after azithromycin was not discontinued, 14 out of 37 individuals (38%) after placebo was discontinued and two out of eight individuals (25%) after placebo was not discontinued). These improvements in both the azithromycin and placebo groups, together with a lack of hearing-related adverse events in the COLUMBUS trial (which did not use audiometry to monitor participants) [32], raise questions about the clinical significance of the hearing decrements as measured by audiometry noted in the MACRO trial. Macrolides are known to cause ventricular arrhythmias that could be fatal [34], but the incidence with long-term azithromycin in COPD is unknown. The MACRO study demonstrated no increased risk of cardiac arrhythmias over a study period of 1 year with use of daily azithromycin compared with placebo; however; patients with baseline corrected QT (QTc) prolongation were excluded from participation in the study and other drugs known to increase the QTc interval were prohibited to be used during the conduct of the trial. Although not part of our systematic review, a well-known observational study that used a claims database suggests that the risk of a fatal ventricular arrhythmia due to a macrolide compared with amoxicillin is 1:4100 among individuals at high cardiovascular risk and <1:100 000 among individuals at low cardiovascular risk [35]; thus, the US Food and Drug Administration recommends careful review of patient-level risk factors for ventricular arrhythmias (*e.g.* a history of a prolonged QT interval, use of co-therapies that prolong the QT interval) when using azithromycin [36].

Benefits

Macrolide antibiotic therapy reduced the COPD exacerbation rate, reduced the proportion of patients who experience an exacerbation, increased the time to next exacerbation and improved quality of life.

Harms

There was no evidence that macrolide therapy increased serious adverse events collectively, but there was an increased incidence of a hearing decrement measured by audiometry. The effect of macrolide therapy on the acquisition of macrolide resistance was uncertain. The risk of ventricular arrhythmias with the use of macrolides has to be considered.

Other considerations

The overwhelming majority of patients had moderate, severe or very severe airway obstruction; few patients with mild airway obstruction were studied. One trial [31] was much larger than the others and, therefore, drove the pooled results. Reduction in the risk of exacerbations may be limited to former smokers or older patients based on *post hoc* analyses of one trial. The panel's confidence in the estimated effects for most outcomes was limited by inconsistency across trials or wide confidence intervals due to few events.

Conclusions and research needs

Macrolide therapy reduces the rate of COPD exacerbations and the proportion of patients who experience a COPD exacerbation. It also increases the time to next exacerbation and improves quality of life, although the magnitude of latter is smaller than what is typically considered clinically significant. No effect on mortality has been shown, but there were too few deaths in the trials to definitively confirm or exclude an effect on mortality. Similarly, there is uncertainty about the risk of serious adverse effects of chronic macrolide therapy in COPD (*e.g.* fatal arrhythmias) and its effect on the acquisition of macrolide resistance is uncertain. These effects of macrolide therapy need to be confirmed as most of the outcomes were driven by a single large trial. In particular, a better understanding of the impact of macrolide therapy on the acquisition of macrolide resistance and cardiovascular adverse effects is needed. In addition, it needs to be determined whether the effects are shared by all antibiotics or specific to macrolides. Also, head-to-head studies comparing the benefits and adverse effects of oral medications that reduce the risk of COPD exacerbations (*e.g.* long-term azithromycin *versus* roflumilast or *N*-acetylcysteine) are needed; previously published studies have been limited to comparisons with placebo. Finally, defining subgroups of patients who are more or less likely to benefit from macrolide therapy (*e.g.* by smoking status) is necessary

to refine the appropriate target patient population for therapy. In any case, macrolide therapy should not be a first-line treatment in COPD and should be considered in appropriately selected patients.

What others are saying

The 2010 NICE guidelines [7] did not address macrolide therapy. The 2017 GOLD strategy document [17] stated that "Azithromycin (250 mg/d or 500 mg three times per wk) or erythromycin (500 mg two times per d) for 1 year reduces the risk of exacerbations in patients prone to exacerbations. … Azithromycin use showed a reduced exacerbation rate in former smokers only and was associated with an increased incidence of bacterial resistance and impaired hearing tests". The 2015 ACCP/CTS guidelines [18] stated that "For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, we suggest the use of a long-term macrolide to prevent acute exacerbations of COPD".

ERS/ATS recommendation

For patients who have COPD with moderate to very severe airflow obstruction and exacerbations despite optimal inhaled therapy, we suggest treatment with a macrolide antibiotic to prevent future exacerbations (conditional recommendation, low quality of evidence).

Remarks

Moderate to very severe airflow obstruction is defined as a post-bronchodilator $FEV_1/FVC < 0.70$ and an FEV_1 % pred of <80%. Before prescribing macrolides, clinicians need to carefully consider patients' cardiovascular risk factors, particularly for ventricular arrhythmias. There is no data of efficacy and safety beyond 1 year of treatment.

Values and preferences

This recommendation places a high value on reducing COPD exacerbations, and a lower value on the suspected but unproven risk of inducing macrolide resistance and the cost and burden of taking daily medication.

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