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CE - THE CUTTING EDGE: RESEARCH UPDATE

New evidence in pulmonary and preventive medicine

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Roflumilast reduces the exacerbations in patients with chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is increasing in prevalence and is usually associated with periodic exacerbations.

Roflumilast is an oral anti-inflammatory agent. The efficacy and safety of the phosphodiesterase-4 inhibitor roflumilast have been investigated in studies of unselected patients with moderate-to-severe COPD. This article was aimed to investigate whether roflumilast reduces the frequency of exacerbations requiring corticosteroids in patients with moderate to severe COPD.

Two placebo-controlled, double-blind, multicentre trials (M2-124 and M2-125) with identical design performed in two populations of outpatients with COPD older than 40 years, with severe airflow limitation [postbronchodilator forced expiratory volume in 1 s (FEV1) was 50% or less than the predicted value], bronchitic symptoms (chronic cough and sputum production), and a history of exacerbations (at least one recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital, or both, in the previous year).

Each trial had an initial 4-week run-in period, during which patients took a placebo once a day and recorded their use of shortacting bronchodilator drugs, and production of cough and sputum on their daily diary cards. Patients were then randomly assigned to oral Roflumilast 500 μg once a day or placebo for 52 weeks. Inhaled corticosteroid and longacting anticholinergic inhalators were not allowed. Patient recruitment began in February 2006, and the studies ended in July 2008. 1,523 patients and 1,568 were randomly assigned and treated, respectively, in the M2-124, and in M2-125 study. Change in prebronchodilator (FEV1) during treatment and the rate of COPD moderate or severe exacerbations were the primary endpoints. Analysis was by intention to treat.

In the pooled analysis, in this study on patients with moderate to severe COPD prebronchodilator, FEV1 increased by 48 mL with roflumilast compared with placebo ($p < 0.001$) and the estimated rate of exacerbations per patient per year was 17% lower in the roflumilast group than in the placebo group ($p < 0.003$). Roflumilast improved measures of lung function in prebronchodilator and postbronchodilator period (FEV1, forced vital capacity, and peak expiratory flow) regardless of use of longacting b2 agonists. Patient withdrawal and adherence were similar in all groups. Mortality rate was not different in the different groups.

The authors concluded that roflumilast reduced exacerbation rate and significantly improved lung function independently of the smoking status or concomitant medication. The authors outlined that this treatment is not suitable for all COPD patients since gastrointestinal effects or headache are more common in roflumilast group than in placebo group.

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Reference

Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ, For the M2-124 and M2-125 Study Groups (2009) Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 374:685–694

In oupatient setting roflumilast could become an important treatment in patients with COPD treated with salmeterol or tiotropium reducing the rate of exacerbations

The management of patients with chronic obstructive pulmonary disease (COPD) involves pharmacological and non-pharmacological treatments. Inhaled glucocorticosteroids are recommended in combination with longacting bronchodilators for patients with COPD that is severe to very severe who have recurrent exacerbations. The efficacy and safety of the phosphodiesterase-4 inhibitor roflumilast have been investigated in studies of patients with moderate-to-severe COPD, but not in those concomitantly treated with longacting inhaled bronchodilators. Two double-blind, multicentre studies performed in an outpatient setting investigated the effects of roflumilast on lung function in patients with moderate-to-severe COPD who were regularly treated with salmeterol or tiotropium. Each trial had an initial 4-week run-in period, during which patients took a placebo tablet once a day, and recorded their use of shortacting bronchodilator drugs, and production of cough and sputum on their daily diary cards. Patients older than 40 years with moderate-to-severe COPD were randomly assigned to oral roflumilast 500 μg or placebo once a day for 24 weeks, in addition to salmeterol (M2-127 study) or tiotropium (M2-128 study). The change in prebronchodilator forced expiratory volume in 1 s (FEV1) was the primary endpoint. Analysis was by intention to treat.

In the M2-127 study, 933 patients were recruited and 466 patients were assigned to and treated with rofumilast and 467 with placebo (744 patients concluded this study); in the M2-128 study, 743 patients were recruited, 371 patients were assigned to and treated with roflumilast and 372 with placebo (642 patients concluded this study).

Roflumilast improved mean prebronchodilator FEV1 by 49 mL ($p < 0.0001$) in patients treated with salmeterol, and 80 mL ($p < 0.0001$) in those treated with tiotropium and likewise postbronchodilator FEV1 increased.

Furthermore, the authors showed positive effects in other prebronchodilator and postbronchodilator measures of lung function like forced vital capacity (FVC), forced expiratory flow (FEF), peak expiratory flow (PEF) in both groups independently by the use of longacting $\beta 2$ agonist.

Gastrointestinal side effects, headache and the probability of treatment discontinuation were higher in patients treated with roflumilast.

The improvement in prebronchodilator and postbronchodilator FEV1 suggested that the additive effect of roflumilast on lung function occurred in patients who are already being treated with effective, longacting bronchodilators but who are not taking inhaled corticosteroidis. Whether the additive effect remains in patients concomitantly treated with longacting bronchodilators and glucocorticosteroids must be established.

Reference

Calverley PMA, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ, For the M2-124 and M2-125 Study Groups (2009) Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 374:695–703

Updated recommendations about cervical cancer to maximize benefit and reduce harms

On November 2009 new guidelines for cervical cancer screening were published by the American College of Obstetricians and Gynecologists (ACOG). The benefits of cancer screening (reduction of cancer-related morbidity and mortality) are well known and widely promoted, and could be increased by initiating screening early and repeating testing frequently. The cancer screening harms (expense, anxiety, and new diagnoses with unclear clinical significance) could be reduced by adopting a more focused approach for screening.

Three major changes had been made in order to reduce screening harms while increasing benefits:

1. the age at which to begin cervical cytologic screening is 21 and before that age screening should be avoided,
2. whereas annual screening has been standard practice for many decades, the new guidelines recommend testing every 2 years for women 21–29 years of age and every 3 years among women 30–65 or 70 years of age who have had three consecutive negative cytological tests (among women in this age group with previous normal tests the likelihood of underlying cervical neoplasia decreases),
3. it is rational to stop screening in women between 65 and 70 years of age at low risk (at least three consecutive normal tests and no abnormal results within the preceding 10 years).

There are still areas of uncertainty like the possible effects of HPV vaccination on cervical cancer screening, and the

appropriate management for women over 65 years considered at low risk but who have multiple sexual partners.

The new guidelines state that physicians should inform women that an annual gynaecologic examination "may still be appropriate".

Physicians should explain that the new guidelines, updated periodically, have not been modified for financial considerations but for maximizing benefits and minimizing harms of the cervical cancer screening. Physicians should also increase screening in unscreened and/or poor women.

Reference

Sawaya GF (2009) Cervical-cancer screening—new guidelines and the balance between benefits and harms. NEJM 361(26):2503 (24 December)

Update recommendations about screening of breast cancer

Breast cancer (BC) is the most common cancer in women in United States, with more than 190,000 women receiving a diagnosis of invasive disease annually and more than 40,000 dying of BC each year. Worldwide, more than 1 million women are diagnosed with BC and more than 500,000 die from it each year. In the past 20 years, BC mortality lowered for the improvements in early diagnosis and treatment.

On November 2009 US Preventive Services Task Force (USPSTF) published updated recommendations about BC screening. Regarding 40 women without high risk of BC, they recommend that benefits of mammography are balanced with adverse effects.

The two most recommendations were that mammography be eliminated as a "standard test" for women 40–49 years of age and that mammography be performed biannually (to reduce positive false) rather than annually (it has not better outcomes) in women from 50 to 74 years of age.

The authors list open problems about BC screening:

1. Mammography is an imperfect test, even if it remains the gold standard for the diagnosis of BC.
2. Women should be informed that the absolute benefit of mammography in women of 40 years of age is limited—more than 1,900 women should undergo a mammography to prevent a death for BC and there are about 60% of false positive and unnecessary biopsies more than if screening would begin in women aged 50.
3. There is a consensus about the fact that mammography gets a BC mortality reduction among 40–74 women; routine screening is extended until 74, mainly on the estimation of benefit from statistical models.
4. The experts agree that the failure of regular screening results from disparities in health care and inadequate education about the benefits of screening.

The authors stress that early diagnosis of BC can save lives. Education/information must be maintained and should be increased in some regions. Mammographic screening must be extended until 74 years in women, preserving the mammography as the gold standard for diagnosis of BC, and considering breast autopalpation as a useful element to bring timely manner to the attention of the medical findings of abnormalities of the breast.

Reference

Partridge AH, Winer EP (2009) On mammography—more agreement than disagreement. NEJM 361(26): 2499 (24 December)

Comment

In the same number of NEJM December 2009, an other article was published about the new recommendations from the US Preventive Services Task Force on screening for breast cancer (Robert D. Truog. Screening Mammography and the "R" Word). The author does not agree to delay the onset of routine screening mammography from 40 to 50 years of age, since screening for women in their 40 s is clearly effective, even if the benefit is small and expensive. Among women between 39 and 49 years of age, screening mammography results in a 15% reduction in the risk of death from breast cancer. A cost–benefit analysis showed that adherence to the current guidelines from the American Cancer Society costs more than $680,000 per quality adjusted life year (QALY) gained, as compared with the new recommendations by US Preventive Services Task Force costing only $35,000 per QALY. This author suggests that behind this new recommendation of USPSTSF there is the principle of reduction/rationalization of expenditure.

Conflict of interest None.