POEMs

Patient-Oriented Evidence That Matters

Single Maintenance and Reliever Therapy More Effective Than Inhaled Corticosteroids and Beta Agonists for Asthma

Clinical Question

Is single maintenance and reliever therapy (SMART) more effective than inhaled corticosteroids with or without long-acting beta agonists (LABA) as the controller and short-acting beta agonists (SABA) as relief therapy for asthma?

Bottom Line

When compared with standard therapy (inhaled corticosteroids with or without LABAs and SABAs as relief therapy), SMART is associated with a reduced risk of acute asthma exacerbations in patients 12 years or older. Evidence is limited for children four to 11 years of age. Fifteen of the 16 studies evaluated SMART vs. standard therapy using a combination of budesonide and formoterol (Symbicort) in a dry powder inhaler as needed to a maximum of 10 inhalations daily. (Level of Evidence = 1a–)

Synopsis

Until recently, standard therapy consisted of inhaled corticosteroids with or without LABAs as the controller therapy for patients with asthma, augmented with SABAs for as-needed quick relief of symptoms. These investigators thoroughly searched multiple sources, including Medline, Embase, the Cochrane databases, clinical trial registries, manufacturers' data, and bibliographic references, for studies that compared standard therapy with SMART, in which the combination of inhaled corticosteroids and LABA is used as the controller and quick relief therapy. No language restrictions were applied. Two reviewers independently evaluated potential studies for inclusion and used a standard scoring tool to assess methodologic quality. Disagreements were resolved by consensus discussion with a third reviewer. A total of 16 randomized controlled trials (N = 22,748 patients) met inclusion criteria. Of these, 15 evaluated SMART as a combination of budesonide and formoterol in a dry powder inhaler. Six of the studies were considered to have a high risk of bias; the rest were considered at low risk of bias. Asthma exacerbations included a composite outcome of requiring systemic corticosteroids, hospitalization, or emergency department visits.

Among patients at least 12 years of age, SMART was significantly associated with a reduced risk of asthma exacerbations compared with standard therapy with either the same or a higher dose of inhaled corticosteroids alone (number needed to treat [NNT] = 12.3; 95% confidence interval [CI], 8.7 to 22.2; and NNT = 9.1; 95% CI, 6.8 to 13.9, respectively). Similarly, SMART was significantly associated with a reduced risk of asthma exacerbations compared with standard therapy with either the same or a higher dose of inhaled corticosteroids and LABAs (NNT = 15.6; 95% CI, 9.8 to 38.5; and NNT = 37.0; 95% CI, 19.2 to 33.3, respectively). ▶

There was no significant difference in SMART vs. standard therapy in overall quality-of-life scores. Limiting the analysis to only studies at low risk of bias did not change the results. Only one trial evaluated SMART vs. standard therapy in children four to 11 years of age, and the results were inconclusive. A formal analysis for publication bias was not possible because of the small number of studies. Formal testing found minimal evidence of significant heterogeneity of results.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Government

Setting: Various (meta-analysis)

Reference: *Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis.* JAMA. *2018;319(14):1485-1496.*

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HPV Testing Better Than Cytology for Women Vaccinated Against HPV

Clinical Question

What is the best means of cervical cancer screening in women who have received the human papillomavirus (HPV) vaccination?

Bottom Line

In women who had received the HPV vaccine, screening for HPV every five years, with cytology and colposcopy follow-up as needed, resulted in higher rates of identification of high-grade precancerous disease (cervical intraepithelial neoplasia grade 2 or higher [CIN2+]) than standard liquid-based cytology every 2.5 years with HPV follow-up cotesting as needed. (Level of Evidence = 1b)

Synopsis

In Australia, where this study was performed, all women included in this aspect of the study had been offered the HPV vaccination, either at age 12 or 13 years or later as a catch-up, with an estimated 50% to 77% of women receiving all three doses. In this study, 1,078 women younger than 33 years who had been offered the HPV vaccine were randomized, using concealed allocation,

to cervical cancer screening using one of three strategies: (1) liquid-based cytology (ThinPrep) every 2.5 years with follow-up HPV cotesting if the results were abnormal; (2) HPV testing every five years with follow-up cytology or colposcopy if the results were abnormal; or (3) HPV testing every five years with follow-up cell staining for oncogenic markers in women with identified oncogenic HPV (HPV 16 or 18) on initial screening (further details of follow-up testing and confirmation is available at https://goo.gl/J3MX4V). Rates of identification of high-grade precancerous disease (CIN2+) were higher in women in each HPV testing arm (2.6% and 2.9%) than with cytology (0.5%; $P = .05$). The researchers do not know the percentage of eligible women who received the vaccine, and most of the women had been screened at some point before the study was started, biasing the sample toward lower rates of disease.

Study design: Randomized controlled trial (nonblinded)

Funding source: Foundation

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Canfell K, Caruana M, Gebski V, et al. Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: results of the Compass pilot randomised trial.* PLoS Med. *2017;14(9):e1002388.*

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Febuxostat Increases All-Cause and Cardiovascular Mortality Compared with Allopurinol

Clinical Question

Do febuxostat (Uloric) and allopurinol differ with regard to cardiovascular safety?

Bottom Line

For patients with gout who require treatment to lower their uric acid level, allopurinol is a safer option than febuxostat. (Level of Evidence = 1b–)

Synopsis

Because gout is an independent risk factor for cardiovascular events, manufacturers of medications for gout, such as febuxostat, have been asked to perform safety trials. The authors of this trial recruited 6,190 patients with known cardiovascular disease and gout with a serum uric acid level greater than 7.0 mg per dL (420 µmol per L), or greater than 6.0 mg per dL (360 µmol per L) if the gout was poorly controlled. The uric acid level was measured after a one- to three-week washout period. The mean age of participants was 64 years, 84% were men, and 70% were white. This was a noninferiority study comparing febuxostat with allopurinol, with noninferior defined as a less than 30% increase in the risk of a combined cardiovascular end point. The dose was titrated using an investigator-masked computer system based on renal function and the amount of drug needed to achieve a serum uric acid level of less than 6.0 mg per dL. Although the data safety monitoring board saw noninferiority with regard to the composite outcome, they saw a trend toward an increase in mortality rates, so the study ran until its conclusion. The mean duration of treatment was approximately two years, and the mean duration of follow-up was just less than three years. Notably, more than one-half of the patients discontinued the study drug, with similar rates between the study groups. Near five years, the mortality curves separated, with higher cardiovascular and all-cause mortality in the febuxostat group. Specifically, cardiovascular mortality was 3.2% in the allopurinol group and 4.3% in the febuxostat group ($P = .03$; number needed to treat to harm [NNTH] over 2.7 years = 90), while the all-cause mortality was also higher in the febuxostat group compared with the allopurinol group (7.8% vs. 6.4%; $P = .04$; NNTH over 2.7 years = 71). The overall dropout risk was 56%, which is a concern. Notably, febuxostat was not any better for symptom control, with episodes of flare-ups similar between the groups (0.68 episodes per year for febuxostat vs. 0.63 for allopurinol).

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Uncertain

Setting: Outpatient (any)

Reference: *White WB, Saag KG, Becker MA, et al.; CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout.* N Engl J Med. *2018;378(13):1200-1210.*

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