UAMS EM Journal Club
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Inhaled Budesonide in the Treatment of Outpatients with COVID-19 Infection

Clinical Bottom Line:
The STOIC and PRINCIPLE trials suggest that inhaled budesonide may be beneficial for some outpatient COVID-19 patients, particularly older, unvaccinated patients. There was statistically significant evidence that early administration of inhaled budesonide in COVID-19 infection decreases time to reported recovery by 2-3 days. The benefit of reduced ED visits or hospitalizations was conflicting. Both trials are subjected to placebo effect as they were open label. The patient populations studied were also largely unvaccinated, older, and over >90% Caucasian which may limit the studies' generalizability. Although inhaled budesonide is a well-tolerated medication, its limited availability and price may limit its practicality.

In outpatients with acute COVID-19, does inhaled budesonide improve clinical outcomes compared with usual care?
P – Outpatients with COVID 19
I – Inhaled budesonide
C – Usual care
O – Improved clinical outcomes

Study 1

Yu LM, Bafadhel M, Dorward J, et al. PRINCIPLE Trial Collaborative Group. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet. 2021 Sep 4;398(10303):843-855. doi: 10.1016/S0140-6736(21)01744-X. Epub 2021 Aug 10. Erratum in: Lancet. 2021 Aug 18;: PMID: 34388395; PMCID: PMC8354567.

Pubmed Link: https://pubmed.ncbi.nlm.nih.gov/34388395/

The Basics:
PRINCIPLE is a multi-center, open-label, randomized, controlled, adaptive platform trial evaluating the efficacy of inhaled budesonide in treating high-risk patients diagnosed with COVID-19 infection. The primary outcomes assessed were time to reported recovery and COVID-19 related admissions and deaths. This study is the first randomized pragmatic trial to report effectiveness of inhaled budesonide in COVID-19 patients.

Inclusion Criteria: PRINCIPLE included patients diagnosed with COVID-19 infection who were age 65 years and older or 50 years and older with comorbidities such as heart disease, hypertension, and chronic lung disease.

Exclusion Criteria: Excluded if already taking systemic or inhaled corticosteroids.

Methods: Patients were randomized using a web-based system; the trial team was masked to randomization whereas participants were aware of their group assignment. Participants were followed up through an online symptom diary and electronic medical records. The two primary endpoints, time to reported recovery and COVID-19 related hospital admissions and death, were measured within 28 days of randomization. Several secondary outcomes including oxygen administration, intensive care unit admission, and mechanical ventilation were also assessed. The primary outcomes were analyzed using the Bayesian piecewise exponential and logistic regression models. The secondary outcomes were analyzed using the Cox proportional hazard and logistic regression models.

Results**:**
Out of 38,520 patients screened, 4700 were selected for the study. Enrollment into the budesonide group started on April 2, 2020 and the trial was closed early on March 21, 2021 as time to recovery met the superiority criterion. In the primary analysis population, the observed median time to recovery was 11 days in the inhaled budesonide group and 15 days in the usual care group. The estimated median benefit was 2.94 days (95% Bayesian criteria interval [BCI], 1.19-5.11). The probability of superiority was >0.999, which met the prespecified superiority criterion. Furthermore, 9% of the inhaled budesonide group and 11% patients in the usual care group were admitted to the hospital or died; the odds ratio was 0.75 (95% BCI, 0.55-1.03). The probability of superiority was 0.963, which did not meet the prespecified superiority criterion of 0.975. In terms of secondary outcomes, there was evidence of benefit in the budesonide group in early sustained recovery, daily illness severity rating, time to sustained alleviation of all symptoms, and time to reduction of symptom severity.

Limitations/Bias:
Although this study provides evidence that inhaled budesonide reduces time to recovery for high-risk patients with COVID-19, there is as risk of placebo effect in the budesonide group due to the study being open-label. The study population was not ethnically diverse as over 90% of participants were Caucasian. Furthermore, this trial was conducted in the early stages of vaccination administration and only 11-13% of the study population received one dose of the vaccine. It is unclear if inhaled budesonide would be clinically beneficial in today's high-risk populations, as the vaccination rate is much higher. Overall, this trial can be safely applied to our unvaccinated high-risk patients, however further double blinded studies on more representative population groups may be warranted to further evaluate the efficacy of inhaled budesonide.

Study 2

Sanjay Ramakrishnan, Dan V Nicolau, Beverly Langford, Mahdi Mahdi, et.al. Inhaled Budesonide in the Treatment of Early COVID-19 (STOIC): a Phase 2, Open-Label, Randomized Controlled Trial. The Lancet Respiratory Medicine, Volume 9, Issue 7, 2021, pages 763-772

Link: https://doi.org/10.1016/S2213-2600(21)00160-0

The Basics
Open-label, parallel-group, phase 2 randomized controlled trial of inhaled budesonide, compared with usual care in adults within 7 days of onset of mild COVID-19 symptoms. Participants included 146 individuals who were 18 or older and randomly assigned to either inhaled budesonide group or usual care. Primary end point was COVID-19 related urgent care visit, emergency department assessment or hospitalization.

Inclusion Criteria: Individuals 18 years old and older who were within 7 days of onset of mild COVID-19 symptoms from July 16 to December 9, 2020.

Primary Outcome: COVID-19 related urgent care visit, emergency department assessment or hospitalization

Secondary Outcomes:

- self-reported clinical recovery (symptom resolution)
- viral symptoms measured using the Common Cold Questionnare (CCQ) and the InFLUenza Patient Reported Outcome Questionnaire (FLUPro)
- body temperature
- blood oxygen saturations
- SARS-CoV-2 viral load.

Results: Investigators found a clinically significant decrease in the primary outcome in the budesonide group with relative risk reduction of 91%, absolute risk reduction of 13%, and NNT of 8. Budesonide improved self-reported clinical recovery by about 2-3 days and they had improved number of fever free days. Additionally, they found significantly better CCQ and FLUPro scores over 14 days in the Budesonide group. There were no significant changes in blood oxygen saturations and SARS-CoV-2 viral load.

Limitations/ Biases: This was an open-label study which allows various biases since participants know what their treatment was and many of the end points were subjective. There was limited racial and ethnic diversity, especially compared with our patient population. The sample size was also small. Regarding the primary outcome, an ED/urgent care visit is not the same as a hospitalization, so lumping them together is difficult to interpret, and the breakdown was not provided. Lastly, Budesonide is expensive in the United States and may be cost-prohibitive for some patients.