Inhaled Corticosteroids for Ambulatory Patients with Mild-to-Moderate COVID-19

Background

Limited studies have been conducted regarding the use of inhaled budesonide to treat ambulatory patients symptomatic with COVID-19 or suspected COVID-19. Inhaled budesonide may be considered for use in mild-to-moderate, symptomatic, ambulatory (non-hospitalized) patients with confirmed or suspected COVID-19 infection as an alternative or adjunct to COVID-19 monoclonal antibody therapy.

Recommendation

Based upon literature review, inhaled corticosteroid can be considered for adult ambulatory patients with mild-to-moderate COVID-19 within 10 days from symptom onset.

Studies were conducted with inhaled budesonide; however, the IUH/Eskenazi Health COVID-19 Therapeutics Workgroup endorses use of any inhaled corticosteroid, based on insurance coverage. See the below chart for equivalent inhaled corticosteroid dosing:

Inhaled Corticosteroid	Dosing
Budesonide (Pulmicort Flexhaler®) 180 mcg/actuation	4 puffs (720 mcg) inhaled twice daily x 7 days
Ciclesonide (Alvesco®) 160 mcg/actuation	2 puffs (320 mcg) inhaled twice daily x 7 days
Fluticasone propionate (Flovent ™HFA) 220 mcg/actuation	2 puffs (440 mcg) inhaled twice daily x 7 days
Fluticasone propionate (Flovent ™ Diskus) 250 mcg/blister	2 puffs (500 mcg) inhaled twice daily x 7 days
Mometasone furoate (Asmanex® HFA) 200 mcg/actuation	2 puffs (400 mcg) inhaled twice daily x 7 days

*For Medicare, evaluate individual prescription benefit plans for preferred agents

Literature Support

Two studies have been conducted evaluating inhaled budesonide as a potential treatment for patients with mild-to-moderate COVID-19.

The STOIC Trial, a randomized, open-label, parallel-group phase 2 clinical trial, evaluated efficacy of inhaled glucocorticoids for early COVID-19:

- Patients were randomized to receive either budesonide 800 mcg inhaled twice daily for up to 14 days or usual care with antipyretics, NSAIDs, and other agents for symptom management. Participants with confirmed COVID-19 included in analysis: 94% in both groups.
- Rates of hospitalization or emergency department attendance due to COVID-19 at 28 days were lower in the budesonide group (1%), compared to patients receiving usual care (14%) [0.131, 95% CI 0.043–0.218; p = 0.004].
- Self-reported clinical recovery was 1 day shorter with budesonide compared with UC [median 7 days [95% CI 6–9] vs. 8 days (7–11); p = 0.007].

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- Day 14 self-reported symptoms were present in 10% of participants randomly assigned to budesonide compared with 30% of participants randomly assigned to usual care [95% CI 0.075–0.334; p = 0.003].
- Proportion of days patients reported a fever (p = 0.051) or required PRN antipyretics (p = 0.025) were lower in patients receiving budesonide.
- Reported rates of adverse events with budesonide use were low.

The PRINCIPLE study, a platform trial investigating community-based interventions for COVID-19, including inhaled budesonide:

- Patients were randomized to receive either budesonide 800 mcg inhaled twice daily for 14 days or usual care with agents for symptom management. Participants with confirmed COVID-19 included in analysis: 78% in the budesonide group vs. 57% in the usual care group.
- Co-primary endpoints measured within 28 days of randomization included time to first recovery, defined as the first instance that a participant reports feeling recovered and hospitalization or death related to COVID-19.
- There was benefit in time-to-first-recovery in the budesonide arm versus usual care (HR 1.208; 95% BCI 1.076–1.356, estimated median benefit of 3.011 (95% BCI [1.134 – 5.410] days). The probability that median time to recovery was shorter in budesonide versus usual care (i.e., probability of superiority) was 0.999, which met the pre-specified 0.99 superiority threshold).
- Among those who contributed to the data for 28-day follow-up, the point estimate of the proportion of COVID-19 related hospitalizations/deaths was slightly lower in the budesonide group compared to usual care (59/692 [8.5%] vs 100/968 [10.3%]; estimated percentage difference 2.1%; 95% BCI -0.7 -4.8%). The probability that COVID-19 hospitalizations/deaths were lower in the budesonide versus usual care (probability of superiority) was 0.928, which did not meet the predefined superiority threshold of 0.975.
- There was evidence of benefit with budesonide in early sustained recovery, 32.2% in the budesonide arm compared to 22% in the usual care arm, 95% BCI 1.46 (1.23-1.74); P-value <0.0001.
- 79.9% of participants reported using budesonide for at least 7 days.
- At 14 and 28 days, the WHO-5 Wellbeing Index showed benefit with budesonide; mean (SD) [n] at day 14; 42.6(24.9) [673] in budesonide arm, 39.1(24.6) [689] in the usual care arm; 95% BCI 3.37(0.97-5.76; p-value 0.006.at day 28; 54.9(25.2) [612] in budesonide arm, 51.2(24.9) [620]; 95% BCI 3.34 (0.87-5.81]; p-value 0.008.
- Minimal adverse effects noted.
- Overall, inhaled budesonide improved the time to recovery by a median of 3 days compared to usual care alone.

Additional studies are ongoing to further evaluate the efficacy of inhaled glucocorticoids as a potential treatment for mild-to-moderate COVID-19 in ambulatory patients.

Additional FAQs

Q: What was the impact of the study results?

Inhaled budesonide was shown to reduce COVID-19 related emergency department visits and hospitalizations in both the STOIC trial, and the ongoing PRINCIPLE trial. Inhaled budesonide plus supportive care was shown to reduce the time to recovery by 2-3 days in patients who tested positive for COVID-19.

Q: How should inhaled corticosteroides be used in COVID-19 positive patients?

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While studies evaluated inhaled budesonide alone, an alternative inhaled corticosteroid would be appropriate treatment options in the event insurance does not cover budesonide.

Q: When should treatment be initiated?

Treatment should be initiated as soon as possible. Studies demonstrated that initiating therapy within 3 days of symptom onset showed maximum benefit; however, treatment can be initiated up to 10 days after symptom onset.

Q: What should I talk to patients about?

Monitor the patients for potential side effects including sore throat, oral candidiasis (thrush) and headache. Patients will need to be educated on proper steroid inhaler technique.

References

1. Ramakrishnan S, Nicolas Jr DV, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomized controlled trial. *Lancet Respir Med*. 2021; https://doi.org/10.1016/s2213-2600(21)00212-5

2. Yu L, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE Trial. *medRxiv* 2021.04.10.21254672; doi:https://doi.org/10.1101/2021.04.10.21254672

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Reference / Link to study	Study design	Number of pts		Treatment regimen	Severity of Symptoms/ age	Endpoints	Outcomes	Outcome summary	ADR reported	Limitations/issues
		Inhaled budesonide	Usual care							
STOIC Ramakrishnan S, et al. https://www.thelancet.com/action/showPdf?pii=S2213-2600%2821%2900160-0	RCT, Phase II, Open label, parallel group, randomized 1:1	70	69	Budesonide dry powder inhaler at a dose of 400 mcg per inhalation (two puffs to be taken twice per day; total dose 1600 mcg) for up to 14 days. Usual care was supportive therapy advising patients to take antipyretics or NSAIDs for symptoms of fever and honey for symptoms of cough.	Most prevalent symptoms present at baseline were cough (75%), fever (67%), headache (56%), fatigue (39% - more prevalent in the budesonide arm), and loss of smell or taste (39% - more prevalent in the usual care (UC) arm). The median duration of symptom onset prior to randomization was 3 days mean age of 45 years old.	Primary Endpoint: Hospitalization or emergency department attendance due to COVID-19 in 28 days Secondary Endpoints: Clinical recovery, as defined by: Self-reported time to symptom resolution; Viral symptoms measured by the Common Cold Questionnaire (CCQ) and the InFLUenza Patient Reported Outcome (FLUPro) questionnaire at days 14 and 28. Body temperature at day 14. Blood oxygen saturation level at day 14. Nasal/throat swab SARS-CoV-2 viral load at day 0, 7 and 14.	Primary Endpoint: For the ITT population, the primary outcome occurred in 11 (15%) participants in the UC group and two (3%) participants in the budesonide group (difference in proportion 0.123, 95% CI 0.033–0.213; p=0.009). In the per-protocol analysis, the primary outcome occurred in ten (14%) participants in the UC group and one (1%) participant in budesonide group (difference in proportions 0.131, 95% CI 0.043–0.218; p=0.004). Secondary Endpoints: In the per-protocol population, self-reported clinical recovery was **1 day quicker** with budesonide compared with UC (median 7 days [95% CI 6–9] vs 8 days (7–11); log-rank test p=0.007). Day 14 self-reported symptoms were present in seven (10%) participants randomly assigned to budesonide compared with 21 (30%) participants randomly assigned to UC (difference in proportion 0.204, 95% CI 0.075–0.334; p=0.003). Median time to symptom resolution as measured by the FLUPro was 3 days (95% CI 2 to 5) in the budesonide group and 4 days (3 to 6) in the usual care group (log-rank test p=0.080; appendix p 12). The mean change in CCQ total score between days 0 and 14 in the budesonide group was –0.49 (95% CI –0.63 to –0.35) and in the usual care group was –0.37 (–0.51 to –0.24; mean difference –0.12, 95% CI –0.21 to –0.02; p=0.016).	NNT w/ inhaled budesonide to reduce COVID-19 is low at 8. Minimal adverse effect profile. Low mortality, hospitalization and ED visits seen with budesonide use compared to supportive care alone. Potential greater benefit seen with supportive care plus inhaled budesonide use. PRN antipyretic medication was required for fewer days in the budesonide group compared to UC (difference 0.204, 95% CI 0.075-0.334; p= 0.003). Fewer budesonide patients had persistent symptoms at days 14 and 28.	Adverse events reported in 5 participants (4 had sore throat; 1 had dizziness). Each of these were self-limiting and fully resolved on cessation of budesonide.	93% of study participants were white. 146 participants total, small sample size. Trial stopped early after determining study outcome would not change due to increased participant enrollment. Budesonide may be an effective treatment of early COVID-19, but not rapidly deteriorating COVID-19.

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PRINCIPLE Collaborative Group, et al. https://www.medrxiv.org/content/10.1101/2021.04.10.21254672v1.full.pdf	Multicenter, open-label, multi-arm, adaptive platform randomized clinical trial	805	1100	Usual care plus inhaled budesonide (Pulmicort Turbohaler) 800 mcg twice daily for 14 days.	Average age of participants was 62.8 years old. The median time to randomization was 6 days from symptom onset. The most common symptoms noted were fever (50%), cough (83%), dyspnea (53%), and myalgia (75%).	Primary Endpoint: Co-primary endpoints measured within 28 days of randomization: 1. Time to first recovery defied as the first instance that a participant reports feeling recovered 2. Hospitalization or death related to COVID-19 Secondary Endpoints: Time to sustained recovery. How well are you feeling today? Please rate how you are feeling now using a scale of 1 –10, where 1 is the worst and 10 is feeling the best you can imagine. Time to sustained alleviation of symptoms. Time to initial reduction of severity of symptoms, contacts with health services, hospital assessment w/o admission, oxygen administration, ICU admission, and mechanical ventilation. Adherence to study treatment.	Primary Endpoint: There was benefit in time-to-first-recovery in the budesonide arm versus usual care (hazard ratio, 1.208; 95% Bayesian Credible Interval [BCI] [1.076–1.356], estimated median benefit of 3.011 (95% BCI [1.134 – 5.410] days). The probability that median time to recovery was shorter in budesonide versus usual care (i.e., probability of superiority) was 0.999, which met the pre-specified 0.99 superiority threshold). Among those who contributed to the data for 28-day follow-up, the point estimate of the proportion of COVID-19 related hospitalizations/deaths was slightly lower in the budesonide group compared to usual care (59/692 [8.5%] vs 100/968 [10.3%]; estimated percentage difference 2.1%; 95% BCI -0.7 -4.8%). The probability that COVID-19 hospitalizations/deaths were lower in the budesonide versus usual care (probability of superiority) was 0.928, which did not meet the predefined superiority threshold of 0.975. Secondary Endpoint: 33.2% in the budesonide arm achieved early sustained recovery compared to 22% in the usual care arm, 95% BCI 1.46 (1.23-1.74); P-value <0.0001. 79.9% of participants reported using budesonide for at least 7 days. WHO-5 questionnaire, mean (SD) [n] at day 14; 42.6(24.9) [673] in budesonide arm, 39.1(24.6) [689] in the usual care arm; 95% BCI 3.37(0.97-5.76; p-value 0.006.at day 28; 54.9(25.2) [612] in budesonide arm, 51.2(24.9) [620]; 95% BCI 3.34 (0.87-5.81]; p-value 0.008.	The results in this table stem from the pre-print and is not a reflection of the final complete analysis. Minimal adverse effects noted. The time to recovery was **3 days sooner in the budesonide** group compared to usual care alone.	Two participants reported hospitalization unrelated to COVID-19 in the budesonide arm.	92% of study participants who were analyzed were white. Participants were either >65 years, or >50 with comorbidities, not accounting for younger age groups. Tried to provide a self-swab confirming PCR testing results, but due to capacity issues (early in pandemic) meant testing was unavailable for some patients. Participants w/ suspected COVID-19 were included in primary analysis.

						WHO-1 Well-Being Index.				

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