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Early View

Research letter

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Inhaled Corticosteroids for Outpatients with Covid-19: A Meta-Analysis

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To the Editors:

Inhaled corticosteroids have received substantial interest as treatments for non-hospitalized patients presenting with symptomatic SARS-CoV-2 infections, following two open label randomized controlled trials (RCTs). STOIC (Steroids in COVID-19, n=146) [1] reported budesonide was effective at improving time to recovery and reducing the composite outcome of urgent care, emergency room visits, and hospitalization. PRINCIPLE (Platform Randomized Trial of Treatments in the Community for Epidemic and Pandemic Illnesses, n=1719 concurrent) [2] replicated the findings for time to recovery and detected a reduction in hospitalization, primarily in those older than 65. However, previous work has demonstrated that, with respect to respiratory symptoms, inhaled medications can have important placebo effects [3]. By contrast, both the recent CONTAIN trial (Inhaled Ciclesonide for the Treatment of COVID-19 in Non-hospitalized Adults, n=203) [4] and an industry-sponsored ciclesonide trial (Covis Pharma, n=400) [5] were placebo-controlled and failed to demonstrate a benefit in time to recovery, with conflicting findings on hospitalizations. We conducted a meta-analysis to inform clinical practice by contextualizing the totality of the data.

Methods:

We searched PubMed and Clinicaltrials.gov on November 1st, 2021 (updated December 30th, 2021) for completed RCTs of inhaled corticosteroids for outpatients with COVID-19. Four trials were identified: STOIC [1], PRINCIPLE [2], CONTAIN [4], and Covis Pharma [5]. We used the secondary outcome of complete resolution of symptoms by Day 14 which was conserved between them. We also compared the outcome of hospitalization; for STOIC, only the composite of urgent care visits and hospitalizations was available. Using *metan* for STATA version 17, we performed a random effects meta-analysis for these outcomes stratified by the presence of placebo control with a pooled overall estimate. With the estimates for risk ratio (RR) and the accompanying 95% confidence interval, we calculated the probability of any benefit (RR>1 for symptom resolution, RR<1 for hospitalization) as well as for a 5% (NNT of 20) and 2% (NNT 50) absolute difference based on the overall control event rates (29.3% for symptomatic improvement; 10.2% for hospitalization) by integrating the area under the probability density curves [6]. The NNT represents the number of patients who needed to be treated for 1 additional patient with symptom resolution by day 14 or 1 fewer hospitalization, respectively. We repeated the above with a fixed effects model as a sensitivity analysis.

Results:

The four trials included 2317 patients, summarized in Table 1 along with the pooled relative risk and 95% confidence intervals for complete symptom resolution by day 14 and hospitalization. The average age in the STOIC, CONTAIN and Covis Pharma studies was similar (range 37 to 45), whereas the average age of patients in the PRINCIPLE trial was higher (64). The effect size for symptomatic improvement was numerically increased in the open-label trials (RR 1.39;

95%CI 1.22-1.58) compared to the placebo-controlled studies (RR 1.15; 95%CI 0.95-1.38), but with overlapping confidence intervals. However, even the placebo-controlled studies suggested a 92.5% probability of any benefit and a 78.1% probability of an NNT ≤50. There was little heterogeneity, thus the random and fixed effects models were very similar. Whereas the open label studies individually suggested a high probability of reduction in hospitalization (RR 0.44; 95%CI 0.12-1.70; 89.3% probability of any effect), the placebo-controlled estimate was more modest (RR 0.90; 95% CI 0.22-3.71; 54.7% probability of any effect). There was moderate heterogeneity, with the fixed effect model showing higher probability of any effect (99.0% vs 89.3%) with similar probability of an NNT ≤50 (78.2% vs. 72.9%) a lower probability of an NNT ≤20 (0.7% vs. 26.7%).

Discussion:

Our results support the use of inhaled corticosteroids (ciclesonide or budesonide) for the resolution of symptoms at day 14 of treatment. While there is likely some placebo effect, the probability of an objective effect remains high in the placebo-controlled subgroup at 92.5% probability for any effect and 78.1% probability of an NNT ≤50. Overall, inclusive of any placebo effect, there is at least a 93.1% chance that the NNT is ≤20. With respect to hospitalization, the effect is promising, but less clear due to the large influence of the PRINCIPLE trial, which included a much older population. This is important given older adults have a much higher risk of hospitalization. While the statistical test for heterogeneity in PRINCIPLE was not significant, there was a notable and plausible difference in the subgroup of patients older than 65 (aOR 0.60; 95%CI 0.40-0.90) when compared to younger participants (aOR 1.03; 95%CI 0.59-1.80). Also of note, STOIC combined urgent care visits with hospitalizations. Though urgent care visits are still a clinically important outcome, this may have inflated the estimated effect on hospitalizations. Still, the probability of a clinically significant effect on hospitalization (NNT ≤50) was only 72.9% (78.2% in the fixed model) which may be an overestimate because the pooled control event of 10.2% was driven by PRINCIPLE and STOIC. If using inhaled corticosteroids to prevent hospitalization, the yield will be higher with greater patient risk.

Our analysis is limited by the granularity of the available data. An individual patient meta-analysis accounting for age and comorbidities might produce more accurate estimates, particularly in subgroups. Furthermore, individual patient date would facilitate time to event analyses which could have increased power. Additionally, approximately two-thirds of the data is open label and subject to the placebo effect with respect to symptom reporting. There is potentially bias in urgent care or emergency room utilization due to unblinded providers being less likely to refer to urgent care when the patient was on treatment, and/or a difference in care-seeking behavior for participants. Finally, these trials were performed in different waves of the global COVID-19 pandemic. Patients and providers may have been more likely to refer patients to the emergency department early in the pandemic when less was known about the natural history of the disease. If additional placebo-controlled trials become available, it will be important to update any meta-analysis. The strength of this analysis is that we have used all the available data in combination with a probabilistic presentation allowing for determination of a variety of clinically relevant effect sizes. Inhaled corticosteroids are widely available, inexpensive in many jurisdictions, have few reported severe side effects, and are likely beneficial based on the total evidence to date.

Overall, there is an ongoing need to identify available, affordable, and effective oral or inhaled medications that can be used early in the disease to prevent COVID-19 hospitalization. Inhaled steroids have several advantages over treatments such as antivirals (which are in short supply) and monoclonals (which require infrastructure for infusion). Furthermore, primary care providers are comfortable prescribing inhaled steroids, especially given familiarity with this drug class based on its use in asthma. Inhaled corticosteroids could be feasible to prescribe via, for example, virtual COVID-19 clinics. It is still unknown whether improving complete symptom resolution will have a meaningful impact on long term outcomes and the prevention of chronic symptoms However, earlier resolution of symptoms could have an important impact on the workforce, which has been substantially affected by more infectious variants, such as omicron. With respect to reduction in hospitalization, there is promise for inhaled corticosteroids, particularly in older adults; however, additional placebo controlled randomized trial evidence should still be sought to minimize bias and obtain more accurate estimates of effect size.

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Data Sharing
Statistical code available on request from Dr. Lee

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Table 1 - Trial descriptions and Meta-Analysis Results

Study	Timing and Primary Outcome	Total Patients	Average Age	Male (%)	Comorbidities	Symptom Free by Day 14		Hospitalized	
						Drug	Control	Drug	Control
CONTAIN (Placebo)	≤6 days of symptoms Resolution of cough, dyspnea, and fever day 7	203	37	46.3%	20.2% Overall 5.9%. HTN 2.5% Diabetes 0.5% CAD	57/105	44/98	6/105	3/98
Covis Pharma (Placebo)	≤72h of test Time to symptom free	400	43	44.8%	22% HTN 7.5% Diabetes	81/197	76/203	3/197	7/203
STOIC (Open label)	≤7d of symptoms Covid-19 urgent visits	139	45	42.4%	Median of 1 8.4% CAD 5% Diabetes	63/70	48/69	2/70	11/69
PRINCIPLE (Open label)	≤14d of symptoms Covid-19 related hospitalization or death	1719 (concurrent)	64	48.5%	80% (median of 1) 43-46% HTN 20-23% Diabetes 15-17% CAD	251/781	173/794	72/787	98/799

Analysis	Pooled Risk Ratio		Probability Any Benefit		Probability NNT ≤50		Probability NNT ≤20	
	Random	Fixed	Random	Fixed	Random	Fixed	Random	Fixed
Symptom Free Day 14 (I^2 30%)	1.29 (1.14-1.47)	1.31 (1.18-1.45)	100%	100%	99.8%	100%	93.1%	98.2%
Placebo-controlled (I^2 0%)	1.15 (0.95-1.38)	1.15 (0.95-1.38)	92.5%	92.7%	78.1%	78.2%	42.6%	43.4%
Open label (I^2 11.9%)	1.39 (1.22-1.58)	1.39 (1.23-1.56)	100%	100%	100%	100%	99.3%	99.8%
Hospitalization – Overall (I^2 49.2%)	0.64 (0.31-1.29)	0.72 (0.55-0.95)	89.3%	99.0%	72.9%	78.2%	26.7%	0.7%
Placebo-controlled (I^2 54.4%)	0.90 (0.22-3.71)	0.90 (0.35-2.33)	54.7%	57.6%	43.0%	40.1%	21.6%	12.3%
Open label (I^2 71.3%)	0.44 (0.12-1.70)	0.71 (0.59-0.94)	89.1%	99.8%	81.3%	85.3%	57.6%	0.3%