Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial

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Summary

Background Multiple early reports of patients admitted to hospital with COVID-19 showed that patients with chronic respiratory disease were significantly under-represented in these cohorts. We hypothesised that the widespread use of inhaled glucocorticoids among these patients was responsible for this finding, and tested if inhaled glucocorticoids would be an effective treatment for early COVID-19.

Methods We performed an open-label, parallel-group, phase 2, randomised controlled trial (Steroids in COVID-19; STOIC) of inhaled budesonide, compared with usual care, in adults within 7 days of the onset of mild COVID-19 symptoms. The trial was done in the community in Oxfordshire, UK. Participants were randomly assigned to inhaled budsonide or usual care stratified for age (≤40 years or >40 years), sex (male or female), and number of comorbidities (≤1 and ≥2). Randomisation was done using random sequence generation in block randomisation in a 1:1 ratio. Budesonide dry powder was delivered using a turbohaler at a dose of 800 µg per actuation. Participants were asked to take two inhalations twice a day until symptom resolution. The primary endpoint was COVID-19-related urgent care visit, including emergency department assessment or hospitalisation, analysed for both the per-protocol and intention-to-treat (ITT) populations. The secondary outcomes were 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, and SARS-CoV-2 viral load. The trial was stopped early after independent statistical review concluded that study outcome would not change with further participant enrolment. This trial is registered with ClinicalTrials.gov, NCT04416399.

Findings From July 16 to Dec 9, 2020, 167 participants were recruited and assessed for eligibility. 21 did not meet eligibility criteria and were excluded. 146 participants were randomly assigned—73 to usual care and 73 to budesonide. For the per-protocol population (n=139), the primary outcome occurred in ten (14%) of 70 participants in the budesonide group and one (1%) of 69 participant in the usual care group (difference in proportions 0·131, 95% CI 0·043 to 0·218; p=0·004). For the ITT population, the primary outcome occurred in 11 (15%) participants in the usual care group and two (3%) participants in the budesonide group (difference in proportions 0·123, 95% CI 0·033 to 0·213; p=0·009). The number needed to treat with inhaled budesonide to reduce COVID-19 deterioration was eight. Clinical recovery was 1 day shorter in the budesonide group compared with the usual care group (median 7 days [95% CI 6 to 9] in the budesonide group *vs* 8 days [7 to 11] in the usual care group; log-rank test p=0·007). The mean proportion of days with a fever in the first 14 days was lower in the budesonide group (2%, SD 6) than the usual care group (8%, SD 18; Wilcoxon test p=0·051) and the proportion of participants with at least 1 day of fever was lower in the budesonide group when compared with the usual care group. As-needed antipyretic medication was required for fewer proportion of days in the budesonide group compared with the usual care group (27% [IQR 0–50] *vs* 50% [15–71]; p=0·025) Fewer participants randomly assigned to budesonide had persistent symptoms at days 14 and 28 compared with participants receiving usual care (difference in proportions 0·204, 95% CI 0·075 to 0·334; p=0·003). The mean total score change in the CCQ and FLUPro over 14 days was significantly better in the budesonide group compared with the usual care group (CCQ mean difference –0·12, 95% CI –0·21 to –0·02 [p=0·016]; FLUPro mean difference –0·10, 95% CI –0·21 to –0·00 [p=0·044]). Blood oxygen saturations and SARS-CoV-2 load, measured by cycle threshold, were not different between the groups. Budesonide was safe, with only five (7%) participants reporting self-limiting adverse events.

Interpretation Early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19.

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Research in context

Evidence before this study

The majority of interventions studied for the COVID-19 pandemic are focused on hospitalised patients. Widely available and broadly relevant interventions for mild COVID-19 are urgently needed. We searched PubMed, and ClinicalTrials.gov between Jan 20 and Mar 23, 2020, for all studies about COVID-19, using the search terms "severe", "community", "COVID-19", "inhaled corticosteroids", "inhaled glucocorticoids", "asthma", and "COPD", published since Dec 31, 2019, in English or translated into English. From this search we identified no clinical trials examining the therapeutic intervention of inhaled glucocorticoids in early COVID-19. Available observational studies showed a reduced risk of severe COVID-19 in patients with asthma or chronic obstructive pulmonary disease and it was thus hypothesised that inhaled corticosteroids might have a protective role in SARS-CoV-2 infection. To date, no clinical trials evaluating the efficacy of inhaled corticosteroids have been published.

Added value of this study

In this open-label, parallel-group, phase 2, randomised controlled trial, inhaled budesonide, when given to adults with early COVID-19, reduced the likelihood of requiring urgent care, emergency department consultation, or hospitalisation. There was also a quicker resolution of fever, a known poor prognostic marker in COVID-19, and self-reported and questionnaire-reported symptom resolution was faster. There were fewer participants with persistent COVID-19 symptoms at days 14 and 28 after budesonide therapy compared with usual care. To our knowledge, this is the first interventional trial to study the efficacy of inhaled corticosteroids in early COVID-19 illness.

Implications of all the available evidence

The STOIC trial potentially provides the first easily accessible effective intervention in early COVID-19. By assessing health-care resource use, the study provides an exciting option to help with the worldwide pressure on health-care systems due to the COVID-19 pandemic. Data from this study also suggest a potentially effective treatment to prevent the long-term morbidity from persistent COVID-19 symptoms.

Introduction

The COVID-19 pandemic is the most serious pandemic to have occurred in more than 100 years, with substantial mortality and morbidity worldwide. Other than age, obesity, and sex,[1,2] no clear predictors forecast who will need hospital-based care among patients with COVID-19. The onset of COVID-19 is usually mild,[3] providing a potential window to intervene before the development of severe disease.[1,2] To date, the majority of studies have focussed on investigating and treating patients admitted to hospital with severe COVID-19.[4] However, there is little knowledge about therapeutic targets in early COVID-19 to prevent progression and clinical deterioration, although targets such as monoclonal antibodies are being studied.[5]

In early reports from China,[1,2] Italy,[6] and the USA[7] describing patients with COVID-19 admitted to hospital, patients with asthma and chronic obstructive pulmonary disease (COPD) were significantly under-represented. We hypothesised that this under-representation might be due to the widespread use of inhaled glucocorticoids in these patients.[8] Furthermore, the main indication for the use of inhaled glucocorticoids in patients with asthma and COPD is to reduce exacerbations, which are often recognised to be viral in cause.[9] In-vitro studies have shown that inhaled glucocorticoids reduce the replication of SARS-CoV-2 in airway epithelial cells,[10] in addition to the downregulation of expression of *ACE2* and *TMPRSS2* genes, which are critical for viral cell entry.[11]

Here, we present the analysis of the Steroids in COVID-19 (STOIC) trial, a phase 2 trial designed to evaluate the efficacy of the widely used inhaled glucocorticoid budesonide in individuals with early COVID-19 in the community. We examined the effect of inhaled budesonide on likelihood of urgent care or hospitalisation, clinical recovery, and parameters of physiology such as temperature and oxygenation. We also evaluated the effect of inhaled budesonide on SARS-CoV-2 viral load.

For **study protocol** see www.stoic.ndm.ox.ac.uk

For more on **participant information** see www.stoic.ndm.ox.ac.uk

Methods

Study design and participants

STOIC was a randomised, open-label, parallel-group, phase 2 clinical trial done in the community in Oxfordshire, UK. The study was approved by the Fulham London Research Ethics Committee (20/HRA/2531) and the National Health Research Authority. The protocol is available online.

Adults aged older than 18 years with symptoms of COVID-19 (new onset cough and fever or anosmia, or both) within 7 days were eligible for inclusion. Participants were excluded if they had recent use (within 7 days) of inhaled or systemic glucocorticoids or if they had a known allergy or contraindication to inhaled budesonide. Recruitment for the study was via local primary care networks, local COVID-19 testing sites, and via multichannel advertising. Volunteers were able to contact the study staff via the advertised phone numbers or email, and all participant information was publicly available on the study website.

All participants provided written informed consent.

Randomisation

Participants were randomly allocated to usual care or budesonide, stratified by participant age (≤40 years or >40 years), sex, and number of comorbidities (≤1 or ≥2). The randomisation sequence was created using a random number generation function and allocation to each group was done through block randomisation in a 1:1 ratio. The budesonide was open label.

Procedures

Participants who met the inclusion criteria were randomly assigned to usual care or intervention with budesonide dry powder inhaler (Pulmicort Turbuhaler, AstraZeneca, Gothenburg, Sweden) at a dose of 800 µg (two puffs) twice per day. Usual care was supportive therapy, with the National Health Service (NHS) advising patients with COVID-19 symptoms to take anti-pyretics for symptoms of fever (products containing paracetamol, or non-steroidal anti-inflammatories such as aspirin and ibuprofen) and honey for symptoms of cough.

Participants were seen at their homes at randomisation (day 0), day 7, and day 14 by a trained respiratory research nurse to obtain written informed consent, provide inhalers, and collect (self-performed) nasopharyngeal swabs for SARS-CoV-2 RT-PCR testing (appendix p 2).

Each participant received a paper symptom diary, calibrated pulse oximeter, and thermometer for daily home monitoring. All participants were contacted by telephone daily to record oxygen saturation and temperature, and to be assessed for any adverse events by the study team. Participants allocated to budesonide were asked to stop taking the inhaler when they felt they had recovered (self-reported symptom recovery) or if they hit the primary outcome; all participants ceased daily monitoring (including daily telephone calls) when symptoms had resolved (self-reported symptom recovery) or if the primary outcome was achieved. At day 28, all study participants were seen in the trial centre and serum SARS-CoV-2 antibody testing was done.

Outcomes

The primary outcome was defined as COVID-19-related urgent care visits, including emergency department assessment or hospitalisation. During the pandemic, the public in the UK were encouraged to contact a government telephone advice line before attending the emergency department, and COVID-19-specific general practice hubs were created for patients who were deteriorating at home to receive medical treatment including transfer to hospital.

Secondary outcomes were clinical recovery, as defined by self-reported time to symptom resolution; viral symptoms measured by the Common Cold Questionnaire (CCQ)[12] and the InFLUenza Patient-Reported Outcome (FLUPro)[13] questionnaire; blood oxygen saturations and body temperature; and SARS-CoV-2 viral load.

Statistical analysis

Descriptive statistics were used for variables between the groups in the budesonide group and the usual care group. Appropriate parametric or non-parametric statistical tests were done. For continuous variables, the difference between treatments in the means or medians and the corresponding 95% CI were reported. For continuous variables, fixed-factor ANCOVA models (*t* tests) adjusted for treatment, age group (>40 years or ≤40 years), sex, number of comorbidities (≤1 or ≥2), and baseline or Wilcoxon rank-sum tests were applied to compare the budesonide group and usual care group. For categorical variables the number and percentage of patients in each category were reported for each treatment group and χ^2 tests were used for comparing treatment groups. CIs for the difference in proportion was by normal approximation (Wald). Time to self-reported clinical recovery and FLUPro symptom recovery were analysed using the Kaplan–Meier method and presented as the median time to event with 95% CIs. Comparisons between the two groups were done with the log-rank test; participants who did not have a primary outcome event at 28 days were censored. Sensitivity analysis for participants with confirmed SARS-CoV-2 infection was also done for the primary outcome. All tests were done at a 5% 2-sided significance level and all comparative outcomes are presented as summary statistics with 95% CIs and reported in accordance with the CONSORT statement. Missing data from study visits and daily monitoring were handled by last observation carried forward for temperature, oxygen saturations, and time to FLUPro symptom resolution. For FLUPro total score and individual domain time-series plots, missing data was handled by last observation carried forward or imputation of zero score for self-reported symptom resolution. Less than 1% of data was determined as missing. Post-hoc stochastic simulations of a virtual trial with the same study design, primary endpoint and duration, and community detection are presented in full in the appendix (pp 3–4). All p values are reported to a maximum of three decimal places. Further details are available in the appendix (pp 3–4).

See Online for appendix

At study inception in March, 2020, and using published data available at the time,[1,2] we assumed that 20% of all COVID-19 cases were severe and would require hospitalisation. Using 80% power at 0·05 level, we required 199 patients in each group to show a 50% reduction of urgent care visits or hospitalisations. The primary outcome was analysed for both the per-protocol and intention-to-treat (ITT) population. The per-protocol population was defined as the population who received the study treatment and had at least 1 day of study observations. The ITT population was defined as all participants who were randomised to a study group.

The study team requested an independent statistical monitoring committee review on Dec 9, 2020, due to reduced recruitment after the second national lockdown

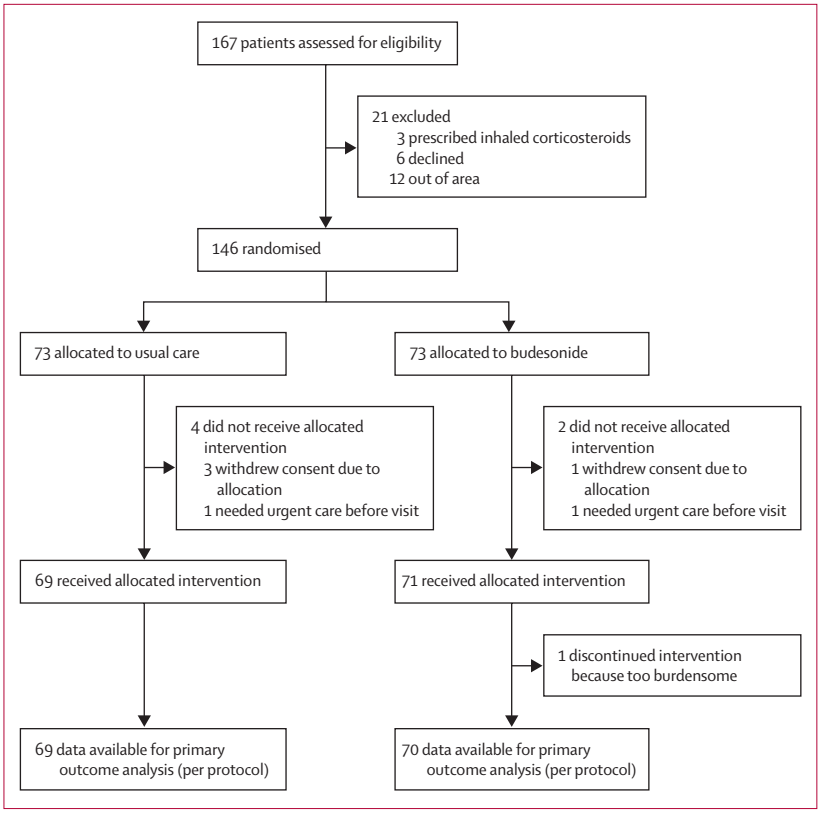

Figure 1: **Trial profile**

	Budesonide (n=70)	Usual care (n=69)
Age, years*	44 (19–71)	46 (19–79)
Sex		
Female	39 (56%)	41 (59%)
Male	31 (44%)	28 (41%)
Race or ethnicity		
White	65 (93%)	64 (93%)
Non-White	5 (7%)	5 (7%)
Body-mass index, kg/m^2	27 (4·9)	26 (4·6)
Number of comorbidities†	1 (0–2)	1 (0–1)
Cardiovascular disease	6 (9%)	6 (9%)
Diabetes	3 (4%)	4 (6%)
Past or current history of asthma	11 (16%)	10 (14%)
Duration of symptoms, days†	3 (2–5)	3 (2–4)
Evidence of COVID-19-positive status	66 (94%)	65 (94%)
Presence of symptoms at baseline		
Cough	55 (79%)	48 (70%)
Fever	49 (70%)	44 (64%)
Headache	40 (57%)	38 (55%)
Fatigue	32 (46%)	23 (33%)
Loss of sense of smell or taste	25 (36%)	30 (43%)
Gastrointestinal symptoms	11 (16%)	12 (17%)
Breathlessness	11 (16%)	11 (16%)
Myalgia	6 (9%)	10 (14%)
Nasal symptoms	3 (4%)	5 (7%)
Sore throat	0 (0%)	2 (3%)
Chest pain or tightness	4 (6%)	1 (1%)
Other	7 (10%)	8 (12%)
Highest temperature recorded, °C†‡	36·6 (36·2–37·1)	36·6 (35·5–38·3)
Lowest oxygenation recorded, percent saturation†‡	96% (95–97)	96% (95–97)
SARS-CoV-2 viral cycle threshold‡	32·6 (22·4–39·4)	31·8 (15·6–40·0)

Data are mean (SD) or n (%), unless stated otherwise. *Mean (range). †Median (IQR). ‡At randomisation.

Table: **Characteristics of study participants in the per-protocol population at study enrolment**

in England, implementation of the COVID-19 vaccine, and ethical consideration of the primary outcome. A priori stop criteria were used to determine futility of further recruitment (appendix p 20). The statistical packages R version 4, Gauss version 21, and SAS version 9.4 were used.

The trial is registered with ClinicalTrials.gov, NCT04416399.

Role of the funding source

The study was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre and AstraZeneca (Gothenburg, Sweden). The funders had no role in study design, data collection, data analysis, data interpretation, writing of the Article, or the decision to publish the study.

Results

From July 16 to Dec 9, 2020, 167 participants were recruited and assessed for eligibility. 21 did not meet eligibility criteria and were excluded. 146 participants were randomly assigned—73 to usual care and 73 to budesonide. 139 participants were included in the per-protocol analysis, with 70 participants in the budesonide group and 69 participants in the usual care group (figure 1). 146 participants were included in the ITT analysis, with 73 participants in the budesonide group and 73 participants in the usual care group Participant characteristics were similar between the study groups, as shown in the table (appendix p 6). SARS-CoV-2 infection, measured by RT-PCR, was detected in 137 (94%) participants. Serological conversion was detected in 67 (55%) of 122 samples. The median duration of symptoms before randomisation was 3 days (IQR 2–4). The median time to symptom resolution was 7 days (5–11). Budesonide was taken for a median duration of 7 days (4–10).

The trial was stopped early after independent statistical review concluded that study outcome would not change with further participant enrolment.

Simulations using bootstrap was done to determine the conditional power for an evaluation of an early stop,

using the a priori decisions described in the appendix (p 20). Estimated power was more than 99% using both the total population (n=124) and, at the time of the simulation, sensitivity analysis for the known subgroup of SARS-CoV-2-positive patients (n=78).

For the ITT population, the primary outcome occurred in 11 (15%) participants in the usual care 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 usual care group and one (1%) participant in budesonide group (difference in proportions 0·131, 95% CI 0·043–0·218; p=0·004), indicating a relative risk reduction of 91% for budesonide. The number needed to treat with inhaled budesonide to reduce COVID-19-related urgent care or hospitalisation was eight. Sensitivity analysis in participants with confirmed COVID-19 (eight [14%] in the usual care group *vs* one [2%] in the budesonide group), showed that the difference in proportions was 0·125 (95% CI 0·035–0·216; p=0·007). There was no difference in participants with a primary outcome event compared with participants without a primary outcome event (appendix p 7). For all primary outcome events in the per-protocol population, three participants were symptomatically breathless with oxygen saturations below 94%; one developed diabetic ketoacidosis; one developed acute kidney injury; one had suspected pulmonary embolism; one had suspected rib fractures; three were seen at least twice by an out of hours general practitioner (which included one participant in the budesonide group); and one was seen by a paramedic crew on day 6 and subsequently seen again by a general practitioner on day 8 and sent to the emergency department, where they were directly admitted to the respiratory high dependency unit, requiring continuous positive pressure ventilation for 8 days. All participants not admitted to hospital had daily telephone checks with the COVID hub general practitioner team.

In the per-protocol population, self-reported clinical recovery was 1 day quicker with budesonide compared with usual care (median 7 days [95% CI 6–9] *vs* 8 days [7–11]; log-rank test p=0·007; figure 2). The mean time to recovery was 8 days (SD 5) in the budesonide group and 12 days (SD 8) in the usual care group. Further sensitivity analysis for clinical recovery in participants with confirmed SARS-CoV-2 infection showed similar median times to recovery (7 days [95% CI 6–9] *vs* 8 days [7–10]; p=0·012; appendix p 10). At day 14, self-reported symptoms were present in seven (10%) participants randomly assigned to budesonide compared with 21 (30%) participants randomly assigned to usual care (difference in proportion 0·204, 95% CI 0·075–0·334; p=0·003).

In the per-protocol population, the mean proportion of days with a documented fever (≥37·5°C) during the first 14 days, was 2% (SD 6) in the budesonide and 8% (18) in the usual care groups (Wilcoxon test p=0·051; Hodge-Lehmann median 0%, 95% CI 0 to 0). Eight (11%) participants in the budesonide and 16 (23%) participants in the usual care group had at least 1 day of fever (difference in proportion 0·067, 95% CI –0·678 to 0·242; p=0·076). Violin plots showing the distribution of pooled highest temperatures are presented in figure 3, demonstrating a statistically higher mean in the usual care group (mean difference 0·49, 95% CI 0·32 to 0·66; p<0·001). Temperature plots relative to the day of randomisation showed that temperature fell quicker in

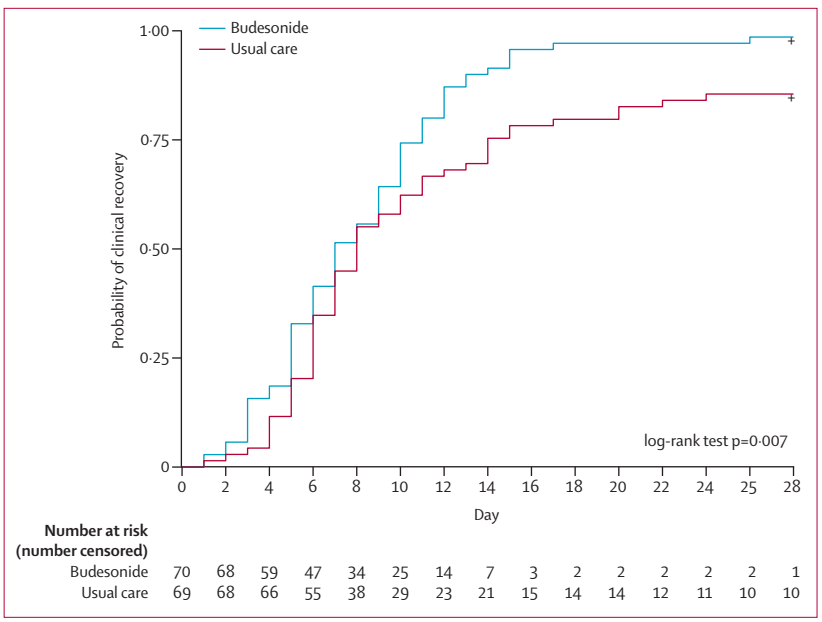

Figure 2: **Time to self-reported clinical recovery of per-protocol population using data censoring for primary outcome**

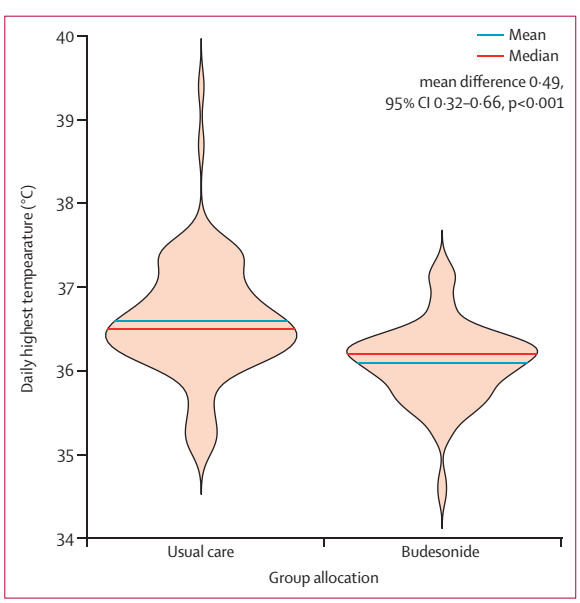

Figure 3: **Violin plots of pooled peak (maximum) temperatures in the budesonide and usual care group**

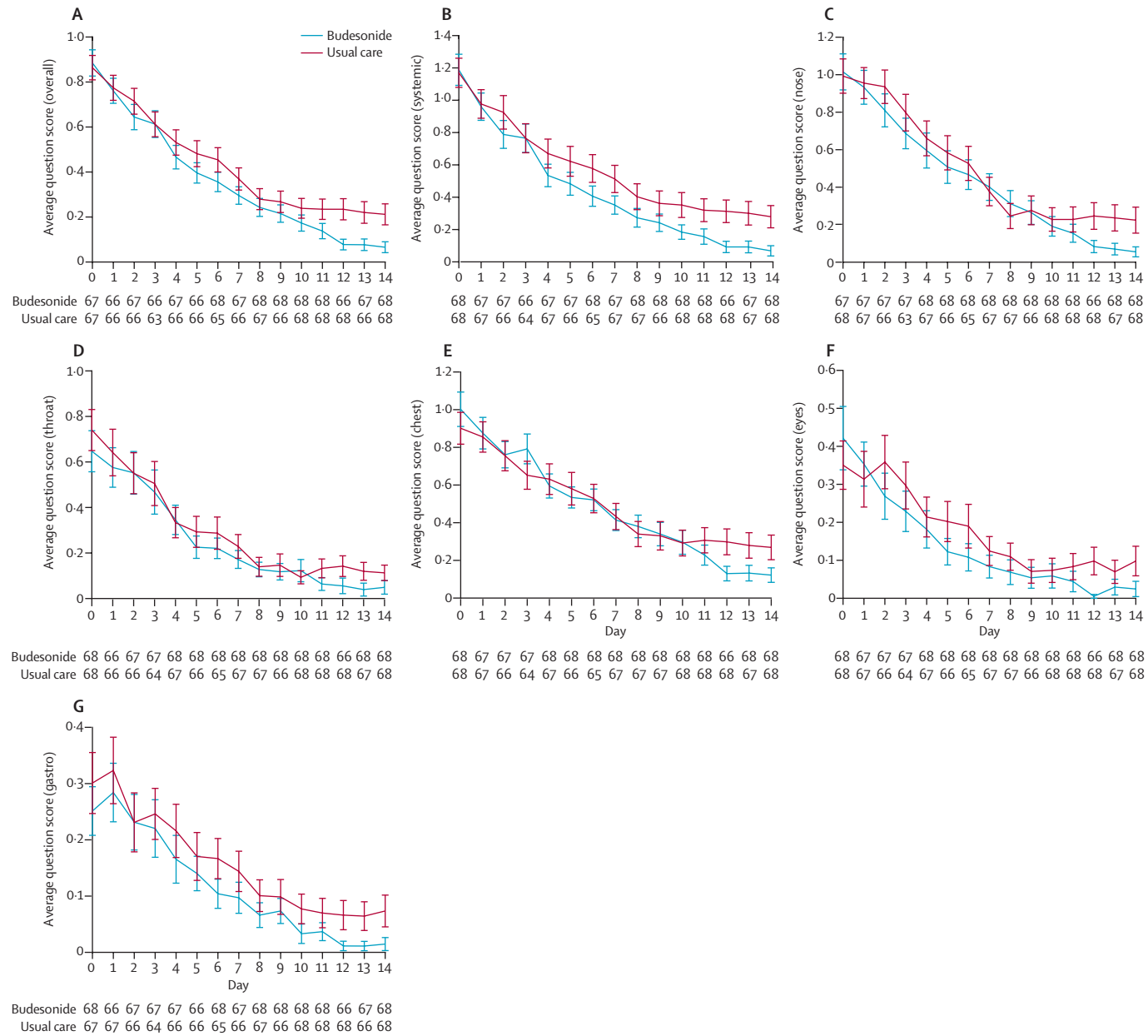

Figure 4: **Daily mean scores over 14 days using the FLUPro questionnaire**
(A) Total symptoms. (B) Systemic symptoms. (C) Nasal symptoms. (D) Throat. (E) Chest. (F) Eyes. (G) Gastrointestinal. Vertical bars indicate standard error.

the budesonide compared with the usual care group (appendix p 11). The median proportion of total days that participants required as-needed antipyretics (paracetamol, aspirin, or ibuprofen) in the budesonide groups was 27% (IQR 0–50) and in the usual care group was 50% (15–71; Wilcoxon test p=0·025).

Symptom resolution at day 14, as defined by the FLUPro user manual, occurred in 55 (82%) participants in the budesonide group and 49 (72%) participants in the usual care group (difference in proportions 0·100, 95% CI –0·040 to 0·241; p=0·166); whereas the 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 FLUPro total score between days 0 and 14 in the budesonide group was –0·65 (–0·80 to –0·50) and in the usual care group was –0·54 (–0·69 to –0·40; mean difference of –0·10, 95% CI –0·21 to –0·00; p=0·044). The mean daily FLUPro scores for the total symptom burden and individual domains are shown in figure 4. The mean change of the FLUPro domains showed that systemic

symptoms were significantly greater in budesonide compared with usual care (appendix p 8). 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). The CCQ symptom daily mean score is presented in the appendix (p 13).

The proportion of days with oxygen saturations of 94% or less, during the first 14 days, was 19% (SD 24) in the budesonide group and 22% (27) in the usual care group (Wilcoxon test p=0·627; Hodge-Lehmann median 0, 95% CI –0·07 to 0). During the first 14 days, 41 (59%) participants in the budesonide group and 40 (58%) participant in the usual care group had at least 1 day with oxygen saturations of 94% or less (difference in proportions 0·006, 95% CI –0·158 to 0·170; p=0·943).

The median cycle threshold nasopharyngeal SARS-CoV-2 viral load at day 0 was 32·1 (IQR 21·7–40·0), day 7 was 35·3 (32·4 to 40·0), and day 14 was 36·4 (34·2 to 40·0). Cycle threshold reduction was significantly different between visits 1 and 2 for both study groups (Wilcoxon matched pairs p=0·063 budesonide, p=0·004 usual care; appendix p 14); but not between groups (mean change between visits 1 and 2 in the budesonide was 3·20 [95% CI 0·46 to 5·94] and usual care was 3·75 [1·00 to 6·50]; mean difference –0·55, 95% CI –2·39 to 1·29; p=0·554).

The safety profile of budesonide was as expected, with an adverse event reported in five participants (four had sore throat; one had dizziness). Each of these were all self-limiting and fully resolved on cessation of budesonide.

Stochastic simulations, in a virtual twin post-hoc study design, showed that the daily odds ratio of reaching the primary outcome, with budesonide reduced by a significant factor of 30-times (figure 5).

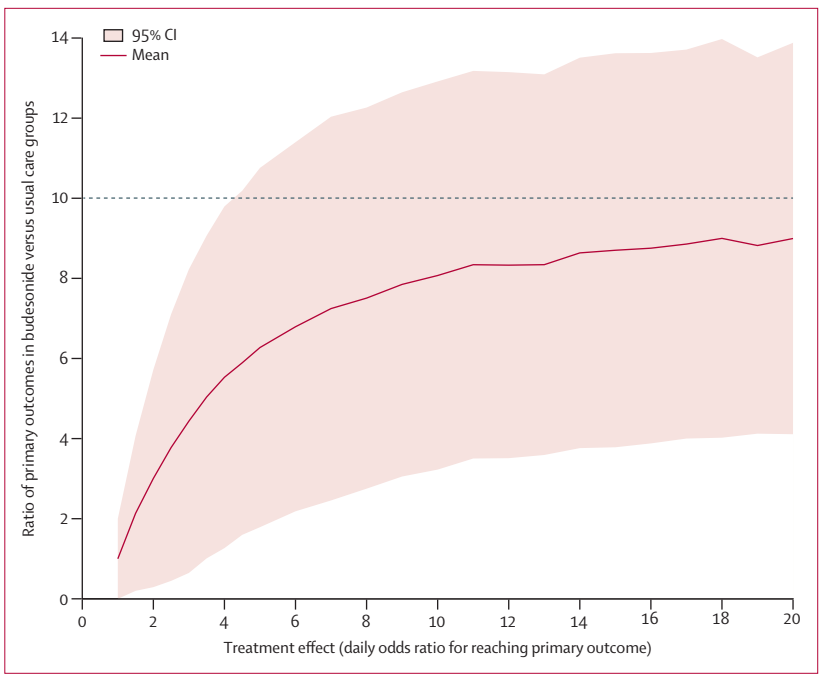

Figure 5: **Post-hoc stochastic simulation of daily odds ratio of reaching the primary outcome**
Relationship between treatment effect, here defined as the daily ratio of the odds of reaching primary outcome, in the usual care versus budesonide groups (horizontal axis) and the ratio of primary event outcomes in the usual care versus budesonide groups at trial completion (vertical axis). Plots derived from numerical simulations of the stochastic virtual twin trial. These indicate that to observe our findings (dotted line), then the daily treatment effect needed represents approximately 3000% (30x) reduction in the daily odds of reaching primary outcome (mean solid line; 95% CI shaded area).

Discussion

We have shown that the inhaled glucocorticoid budesonide, given for a short duration, might be an effective treatment of early COVID-19 in adults. This effect, with a relative reduction of 91% of clinical deterioration is equivalent to the efficacy seen after the use of COVID-19 vaccines[14] and greater than that reported in any treatments used in hospitalised patients and patients with severe COVID-19.[15] Our study showed a 14% incidence of urgent health-care need and is consistent with other community-based studies.[16] Our findings indicate that the primary outcome events were not mild events, despite occurring in participants with a mean age of 45 years with a spectrum of COVID-19 complications from deterioration of a premorbid condition (diabetic ketoacidosis), to the need for prolonged respiratory support. Although there is an indication to target the population at risk of severe illness, such as older and frailer patients with SARS-CoV-2 infection, the real-world setting shows that the majority of the population that will get COVID-19 are not old, and only 9% of the global population are over the age of 65 years.[17] Moreover, it would be unethical to ignore symptoms and to omit treatment for a younger person who has a lower population risk of severe COVID-19. During the study, the local management approach of COVID-19 changed to directing patients to COVID-19 hubs as a substitute to emergency department attendance. Despite this, we could see that the majority of the primary outcome events required hospital assessment.

The broad inclusion criteria make this study intervention relevant to health-care systems worldwide. Inhaled budesonide is a simple, safe, well studied, inexpensive, and widely available treatment. The number of participants needed to treat to prevent increased health-care resource use is eight, and combined with the short treatment period required to achieve benefit, makes this potentially an affordable and scalable intervention for early COVID-19. This is especially significant in low-income and middle-income countries where the majority of currently approved COVID-19 treatments are unlikely to ever reach patients as a consequence of variable health-care systems.[18] For example, although dexamethasone is a widely available and low-cost medicine, with efficacy in reducing mortality in severe and intensive care-related COVID-19,[19] and there is potential for monoclonal antibody targets in early COVID-19,[5] this is unfortunately

irrelevant in countries with limited intensive care, hospital capacity, or functioning health-care systems.[20] Furthermore, in high-income countries, inhaled budesonide could work as an adjunct to reduce pressure on health-care systems until widespread SARS-CoV-2 vaccination can be achieved. Additionally, the efficacy of inhaled budesonide is unlikely to be affected by any emergent SARS-CoV-2 variant, which has been a source of concern with vaccine implementation.[21]

We selected this treatment intervention due to the unexpected observation of an under-representation of patients with asthma and COPD with severe COVID-19.[22] This finding from early hospitalised cohorts in Wuhan[1,2] was at odds with previous respiratory viral pandemics, such as H1N1 influenza.[23] The common therapy between these lung diseases is inhaled glucocorticoids, either as a mono, dual, or triple constituent. Furthermore, inhaled glucocorticoids are among the most prescribed medicines of any class around the world, listed by the WHO as essential medicines. Moreover, evidence of the utility of inhaled glucocorticoids in reducing viral exacerbations of asthma have been known for many decades,[24] while inhaled budesonide has shown effect at reducing rhinovirus replication in vitro.[25] Furthermore, single maintenance and reliever therapy has previously been shown to reduce asthma hospitalisations following influenza or the common cold (frequently a coronavirus);[9] while recent reports in asthmatics with SARS-CoV-2 infection have repeatedly shown protective effects.[26–28] In the RECOVERY trial,[19] the efficacy of dexamethasone for severe disease also supports our findings, while there is plausibility that the immune-modulatory effect of inhaled glucocorticoids might also apply to any future viral epidemics, but this requires further evaluation.

We found that inhaled budesonide also showed benefit in the secondary outcomes, with quicker symptom resolution in patients treated with budesonide either measured using a self-report of symptom recovery, or defined as normalisation of prospectively collected symptom scores measured using the FLUPro[13] or the CCQ.[12] There was a significantly greater population of participants randomly assigned to budesonide who were free of symptoms at 14 days compared with participants randomly assigned to usual care. Symptom resolution measured using either self-reported symptom recovery, FLUPro and CCQ showed ongoing symptoms at day 28 in participants in the usual care arm compared with budesonide. In the face of the evolving nature of chronicity of symptoms after COVID-19, our finding of an impact on both patient-reported and patient-measured symptoms are important.[29] In the UK, up to 20% of patients[30] report persistent symptoms 5 weeks after COVID-19. Our findings thus also suggest that intervention with an inhaled glucocorticoid might effect rate of the persistent long-term symptoms in COVID-19 (long COVID); and should be investigated further in view of the considerable long-term health and economic impact of long COVID. There are several open-label studies currently open to recruitment examining the role of inhaled budesonide in COVID-19 infection (ISRCTN86534580, NCT04355637, NCT04331054) and others investigating the role of inhaled ciclesonide (NCT04330586, NCT04377711, NCT04381364, NCT04356495); whether these studies also show an effect on long COVID will be of importance.

The positive effect on temperature when used to treat early COVID-19 is further evidence that inhaled budesonide is modifying the disease process. Fever has been repeatedly shown to be a poor prognostic marker in severe COVID-19[1,2] and our findings that budesonide significantly reduces this by clinical measurement and by anti-pyretic use as a surrogate is further supportive that this therapy is likely to be an effective treatment for COVID-19.

Our study examined the effect on viral titres as a secondary outcome and showed no difference between intervention groups. We were unable to demonstrate a mechanistic significant difference in reduction in viral load between budesonide and usual care, as per previous in-vitro data.[10] Our study returned lower viral copies (as measured by cycle threshold) compared with other studies,[31] but this is expected in view of the fact that swabs were self-taken, where we expect the viral yield to be lower. Moreover, assay sensitivity for detection of SARS-CoV-2 is recognised to be variable[32] and further comparisons taking into consideration the natural decay of virus in the nasopharynx to compare against an intervention are warranted.

Our study design involved randomisation at home, with home visits for study assessments, and a daily contact until symptom resolution by the study team, which limited participant drop-outs and enhanced the completion of symptom diaries. However, there are limitations to our study. First, this was an open-label study, done out of expediency, where a placebo-controlled group was not practical at the time of study inception. In comparison to the awaited randomised clinical trials investigating the efficacy of inhaled glucocorticoids (described above), all are open-label and not placebo controlled, with the exception of one (NCT04377711), and thus consistent with our study design. Although there is concern with respect to introducing bias, the expected degree of real bias in an open-label study for a new disease is unknown. Second, the study was stopped early due to the impact of the national pandemic control measures, with a second national lockdown, and national prioritisation rules for clinical research trials in the UK, which prevented recruitment from outside the local region. Third, our study did not reach the sample size. Our power calculations were made from the best available predictions in early 2020. Therapeutic randomised clinical trial design and sample size calculations are often dictated by statistical assumptions with treatment effect estimations based on the evidence

of best available care. However, in trial design for a new disease, with no known effective treatment, statistical assumptions are thus arbitrary. We found that the budesonide treatment effect size was larger than predicted; and independent statistical simulations concluded that the final sample size and treatment effect had a 99% power to reject the null hypothesis. In addition to this conclusion, the post-hoc stochastic simulations also provided estimations that the effect size could be construed as real; while the positive concordance of temperature and symptoms as secondary outcomes gives us confidence in our results. These aspects were crucial aspects to assess the validity of the study. Our inclusion criteria were very general and our study population is young, with fewer comorbidities than patient groups known to have increased mortality.[2] However, as discussed earlier, our population reflects the general global population, in whom we found a one in seven risk of harm from COVID-19, but with minor self-limiting side-effects of inhaled budesonide. Finally, stopping a study early is unusual and is a decision that is not taken without due diligence.[33] However, we ensured that a priori stop decision analysis was done by an independent statistical team for statistical rigor.

In conclusion, budesonide, an inhaled glucocorticoid, appears to be an effective treatment for early COVID-19 infection, which could be applicable to global health-care systems. Our findings require urgent validation and dissemination, especially in the setting of a treatment given early that is widely available and relatively safe.

Contributors

MB, SR, PJB, DVN, and REKR contributed to the literature search, study design, data interpretation, and critical revision of the work. SR, DVN, BL, MM, HJ, CM, KK, RF, IB, VG, SB, CB, REKR, and MB contributed to the recruitment of participants. SR, BL, HJ, CM, KK, and MM did all study assessments, study visits, and completed data entry. MM, PCM, LED, JLS, PJB, JLC, and JRB supported the laboratory assessments and RT-PCR. AH did the block randomisation. TB and SP were the independent statisticians and analysed all data. DVN and NTF provided additional statistical support. TB, SP, DBN, NF, SR, and MB accessed and verified the data. All authors contributed to the writing of the Article and approved its submission. MB was responsible for the decision to submit the Article.

Declaration of interests

SR reports grants and non-financial support from the NIHR Biomedical Research Centre, during the conduct of the study; and non-financial support from AstraZeneca, personal fees from Australian Government Research Training Program, outside the submitted work. HJ reports personal fees from AstraZeneca, outside of the submitted work. CB reports grants from NIHR, Roche Molecular Diagnostics, Janssen Pharmaceuticals, and the NIHR for research related to diagnostics and infections. CB has received personal fees from Pfizer, Roche Diagnostics, and Janssen Pharmaceuticals, outside of the submitted work. LED reports grants from AstraZeneca, and Boehringer Ingelheim, outside of the submitted work. SP reports personal fees from AstraZeneca, outside of the submitted work. TB reports personal fees from AstraZeneca, outside of the submitted work. PJB reports grants and personal fees from AstraZeneca and Boehringer Ingelheim, and personal fees from Teva and Covis, during the conduct of the study. REKR reports grants from AstraZeneca, and personal fees from Boehringer Ingelheim, Chiesi UK, and GlaxoSmithKline, during the conduct of the study. MB reports grants from AstraZeneca, personal fees from AstraZeneca, Chiesi, GlaxoSmithKline, and scientific adviser to Albus Health and ProAxsis outside of the submitted work. DVNJr, BL, MM, CM, KK, RF, IB, VG, SB, JLC, AH, PCM, JLS, JRB, and NTF declare no competing interests.

Data sharing

De-identified individual participant data and a data dictionary defining each field in the set can be made available to others on approval of a written request to the corresponding author. The request will be evaluated by a committee formed by a subset of co-authors to determine the research value. A data sharing agreement will be needed.

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