Summary of ICS trials: Rapid Review by Professor Dee Mangin and Assoc Professor Michelle Howard
Department of Family Medicine McMaster University.

**PRINCIPLE trial:** A non peer reviewed preprint of interim data analysis (the trial is not yet complete)
- Country UK
- Conflicts of interest: a number of authors received AstraZeneca funding (among other companies). Trial not pharma funded
- Non blinded (open label) non placebo controlled randomised trial (751 budesonide, 1028 usual care and 643 to other interventions [overlap in time where various antibiotics were being tested])
- Platform trial: allows multiple treatments to be tested with criteria for determining futility, declaring interventions superior, or adding new interventions.

**Outcome Measures:**
- The PRINCIPLE trial original principle outcome was hospitalization or death, however fewer than expected hospitalizations were occurring, so the outcome (at 28 days) was changed to co-primary outcomes of 1) time to first reported recovery (feeling recovered) and 2) hospitalization or death related to COVID-19
- The original primary endpoint was interchangeably referred to in the paper and the protocol as “hospitalisation” and “COVID related hospitalisation”. This is important as there were 2 non COVID hospitalisations in the budesonide arm (none in the usual care arm) with no reason for hospitalisation given.

**Analysis considerations:**
- The analysis in this paper was done when pre-specified criterion of superiority was met for ‘time to first recovery’ outcome, in both confirmed +ve population and overall study populations (93% of participants had contributed data by this time)
- Therefore, results on the hospitalization/death outcome was limited to those with complete 28 follow-up data at the time of analysis, meaning that the hospitalization analysis is interim.
- This paper reports only the budesonide versus usual care results (not the antibiotic interventions)

**Main Results:**
- There was a significant difference in “time to first recovery” (hazard ratio 1.208 [95% BCI 1.076 – 1.356], with an estimated benefit [95% BCI] of 3.011 [1.134 – 5.41] days, compared to usual care
- Probability that COVID-19 hospitalizations/deaths were lower in the budesonide (8.5%) versus usual care (10.3%) did not meet the predefined superiority threshold of 0.975.

Comment: The proportion of people with asthma COPD or lung disease was markedly different in each arm (8.4% in budesonide, 15% in control arm for the COVID-19 positive cohort, in the overall cohort (with or without positive COVID test) it was 8.5% in the budesonide arm and 23.5% in the control arm.
Time to first recovery is a soft outcome measure. It is a self-report measure and so very susceptible to bias from non-blinding and lack of placebo (inhalers are susceptible to placebo effect). It does not appear that a validated questionnaire was used to assess first reported recovery. An online symptom diary was used daily, and telephone calls were made weekly. It is not clear exactly how this outcome was assessed.
The full trial is not yet reported or peer reviewed and the strength of the evidence for serious objective indices would not support early recommendation for widespread use (e.g. hospitalisation or death). The PRINCIPLE trial doesn’t have complete data yet – this is an interim analysis published as a preprint (preprints are not peer reviewed and come with a warning that they “have not been evaluated and should not be used to guide clinical practice”). As with many other potential COVID therapies, a prominent press release about benefits has circulated prior to formal review and publication of the complete trial data. It is not clear what effect this is going to have on the self reporting from the patients still in the trial.

STOIC Trial
- A peer reviewed publication
- Non blinded (open label) non placebo controlled randomised trial.
- 73 usual care 73 budesonide, within 7 days of onset of mild symptoms
- Country UK
- Conflicts of interest Trial funding from AstraZeneca

Outcome Measures:
- Primary outcome measure was a composite measure of anyone having an urgent care need (eg on call GP) OR ED attendance OR hospital admission.
- Outcome assessment appears to be based on reporting of events through daily phone calls by nurse (no blinding reported), self-completed symptom diary and questionnaires

Results:
- 6% of participants did not have COVID illness confirmed on PCR.
- The trial was stopped early due to difficulties recruiting. Larger than expected effect size was found and simulations indicated the result was unlikely to change with further recruitment.
- There was a significant difference between arms in the composite primary outcome per intention-to-treat analysis. (11 in control arm 2 in budesonide arm). No data was provided on how many hospital admissions there were in each group (an outcome less likely subject to design biases described below), nor whether these were PCR positive.
- Confidence interval for 12% difference were wide (3% to 21%)
- Among primary outcome events (per-protocol, n=11) - 3 dyspnoiec with sats <94, 1 diabetic ketoacidosis, 1 suspected PE, 1 acute kidney injury, 1 fractured ribs, 3 were seen by the out of hours GP, 1 called paramedics and was subsequently hospitalised. Data appears missing on 3 in the category of primary outcome.
- Differences in self-reported symptom measures were varied (some significant, some not).
- Systemic symptoms (FLUPro score) were significantly greater with budesonide vs usual care.
- Days with oxygen saturation <=94% difference not statistically significant

Comment:
This was a non blinded trial that was not placebo controlled which creates potential bias. When outcomes are self report measures they are very susceptible to bias from non-blinding and lack of placebo (inhalers are susceptible to placebo effect) and the main outcomes had very wide confidence intervals. It is not clear whether the difference in some symptom severity scores or duration are clinically important.

OVERALL COMMENT
While there is a plausible mechanism for effect there is also reason to be cautious about ICS for two reasons: first because oral steroids result in better outcomes for hypoxic COVID, they result in worse outcomes for mild-moderate COVID, secondly while patients with COPD and asthma appear to have a lower incidence of COVID-19 infection, which was the reason to speculate whether ICS might be protective, for those who do get infected those with respiratory disease actually have worse outcomes. (see refs at bottom of page) and one trial suggests that patients with COPD taking ICS who do get infected have worse outcomes than those who do not: https://breathe.ersjournals.com/content/17/1/200275

Both trials had no placebos (inhalers in particular have a placebo effect) and were not blinded (either for outcome assessment or intervention) and used self reported outcomes (susceptible to bias from these design gaps).

The evidence from these trials is not strong enough to recommend routine use at the moment. The MHRA have reviewed in Europe and take a similar view. This is an unlicensed indication so clinicians should read the evidence and use their judgement. This review will be updated when complete trial results are available to reassess the strength of the evidence.

Other References:


