Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Glucocorticoid treatment improves COVID-19 survival: the REMAP-CAP trial

Period when the underpinning research was undertaken: 2017 - present

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Anthony Gordon	Chair in Anaesthesia and Critical Care	2010 - present

Period when the claimed impact occurred: Sept 20 - present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

The REMAP-CAP is a novel adaptive platform trial created specifically to evaluate treatments in critically ill patients in intensive care during a pandemic. In COVID-19, REMAP-CAP recruited 614 patients to evaluate the use of intravenous hydrocortisone. The trial demonstrated that there was a 93% probability that hydrocortisone was superior to no hydrocortisone use in reducing mortality and the time receiving organ support in intensive care. These results were rapidly incorporated into treatment recommendations by the World Health Organisation (WHO) and the National Institute for Health and Care Excellence (NICE). Use of corticosteroids have become the standard of care around the world, improving survival in the sickest patients with COVID-19 and saving hundreds of lives.

2. Underpinning research (indicative maximum 500 words)

REMAP-CAP (Randomised Embedded Multifactorial Adaptive Platform for Community Acquired Pneumonia) is an international adaptive platform trial that was designed specifically for pandemic preparedness. Since 2017 Professor Gordon has been the UK Chief Investigator for the trial and a member of the international trial steering committee. The trial has grown considerably since its initial European funding in 2014 and there are now over 300 participating sites across 21 countries including the UK, Australia, New Zealand, Canada, India, Saudi Arabia and the US.

The trial was set-up to evaluate treatments for community-acquired pneumonia in critically ill patients. The protocol was designed to be modular and adaptive, so that if and when a pandemic occurred the existing protocol, regulatory approvals and trial infrastructure could be adapted to evaluate treatments for the pandemic infection rapidly. This was implemented in 2020 with the COVID-19 outbreak (1).

Corticosteroids, specifically intravenous hydrocortisone, was one of the first interventions that the trial studied. The first patient was recruited on 9 March 2020, two days before the global pandemic was declared. At that time the UK had 13 Intensive Care Units (ICU) as potential recruiting sites. On 1 April the trial was categorised by the UK Chief Medical Officer as one of the UK's national prioritised platform trials. Additional grant support was obtained from the NIHR. The central team were able to open recruitment to more than 100 UK ICUs within one month.

The corticosteroid intervention finished recruitment on 17 June 2020 when RECOVERY reported their dexamethasone result. RECOVERY is a platform study that examined dexamethasone as a treatment for hospitalised COVID-19 patients outside of the ICU setting. After the RECOVERY report, the blinded international trial steering committee for REMAP-CAP decided to stop

enrolment of patients due to a loss of equipoise, without reference to the REMAP-CAP data. By this time REMAP-CAP had recruited 614 patients with COVID-19 in ICUs from 8 countries (70% of patients were from the UK); 403 patients were included in the corticosteroid analysis.

Although stopped early, the Bayesian design of REMAP-CAP allowed a quantitative, easily interpreted, result to be reported. There was a 93% probability that giving hydrocortisone was superior to no hydrocortisone treatment, leading to more days alive and free of organ support in intensive care (the primary outcome). Additional pre-specified secondary analyses demonstrated that for less sick patients, not requiring mechanical ventilation at inclusion, there was a 99% probability that hydrocortisone was beneficial, leading to far fewer patients (30% reduction) deteriorating to need intubation, extra-corporeal membrane oxygenation or dying (2).

In view of the clinical imperative to share these important research results globally, REMAP-CAP joined the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. The data were shared with the other investigators in the working group before publication. Data from all clinical trials of corticosteroids in severe COVID-19 were combined. REMAP-CAP was the second largest steroid trial in the world and contributed 53% of the patients to the hydrocortisone analysis. The analysis demonstrated that corticosteroids (as a class of drug) led to an absolute mortality reduction of 8%, from 40% in the control group to 32% in the treated patients (3). The results were similar for dexamethasone and hydrocortisone, demonstrating this is a class effect, which is important in a global pandemic to ensure adequate drug supplies; significantly, hydrocortisone can be used during pregnancy where dexamethasone is contra-indicated. It demonstrated that the general anti-inflammatory mode of action is beneficial and that other similar anti-inflammatory strategies (e.g. interleukin-6 inhibition with tocilizumab and sarilumab) should be investigated. REMAP-CAP was subsequently the first trial to demonstrate this in November 2020 (https://www.imperial.ac.uk/news/209033/arthritis-drug-effective-treating-sickest-covid-19/)

3. References to the research (indicative maximum of six references)

(1) Angus, D.C., Berry, S., Lewis, R.J., Al-Beidh, F., Arabi, Y., van Bentum-Puijk, W., Bhimani, Z., Bonten, M., Broglio, K., Brunkhorst, F., Cheng, A.C., Chiche, J-D., De Jong, M., Detry, M., Goossens, H., Gordon, A., et al. (2020). The randomized embedded multifactorial adaptive platform for community-acquired pneumonia (REMAP-CAP) study: rationale and design. *Annals of the American Thoracic Society*; 17: 879-891. DOI.

(2) Angus, D.C., Derde, L., Al-Beidh, F., … Gordon, A.C. (2020). Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19. *JAMA;* 324 (13): 1317-1329. DOI.

(3) WHO Rapid Evidence Appraisal for COVID-19 Therapies REACT Working Group, Sterne, J.A.C., Murthy, S., Diaz, J.V., Slutsky, A.S., Villar, J., Angus, D.C., Annane, D., Azevedo, L.C.P., Berwanger, O., Cavalcanti, A.B., Dequin, P-F., Du, B., Emberson, J., Fisher, D., Giraudeau, B., Gordon, A.C., et al. (2020). Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*, 324 (13): 1330-1341. DOI.

4. Details of the impact (indicative maximum 750 words)

Since its known emergence in December 2019, there have been over 83,000,000 COVID-19 cases worldwide and over 1,800,000 deaths by the end of 2020, with over 120,000 deaths in the UK alone. From 1 September to end December 2020, during the second wave of COVID-19, there were 12,000 COVID-19 patient admissions to intensive care units in the UK.

Following publication of the REMAP-CAP trial results in September 2020, the WHO published updated treatment guidelines for corticosteroids in COVID-19 [**A**]. The number one recommendation was "*We recommend **systemic corticosteroids** rather than no corticosteroids*

for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence)". The REMAP-CAP trial (2, 3) findings provided critical evidence for the use of hydrocortisone [**A**].

NHS Chief Executive, Sir Simon Stevens said, in response to the trial data published in reference (2) above, "*One of the distinctive benefits of having our NHS is that we've been able to mobilise quickly and at scale to help researchers test and develop proven coronavirus treatments. Just as we did with dexamethasone, the NHS will now take immediate action to ensure that patients who could benefit from treatment with* ***hydrocortisone*** *do so, adding a further weapon in the armoury in the worldwide fight against Covid-19.*" [**B**].

A Chief Medical Officer (CMO) Central Alerting System (CAS) alert (Ref: CEM/CMO/2020/033) was issued by the Medicines and Healthcare products Regulatory Agency (MHRA) on 3 September 2020 [**C**] stating "*Corticosteroids, and in particular dexamethasone and* ***hydrocortisone****, have been demonstrated to have a place in the management of patients with COVID-19. Following recent publication of the* ***REMAP-CAP*** *trial for hydrocortisone and a meta-analysis of corticosteroids, the World Health Organization (WHO) has recently issued new interim guidance recommending the use of systemic corticosteroids in severe and critical COVID-19 disease.*"

NICE subsequently updated their COVID-19 prescribing briefing for corticosteroids in line with the WHO recommendations [**D**]. They recommend to "*Offer dexamethasone or* ***hydrocortisone*** *to people with severe or critical COVID-19*". This briefing directly refers to the MHRA CMO CAS alert quoted above.

Using the UK as an example, there have been 12,000 ICU admissions in England, Wales and Northern Ireland due to COVID-19 from 1 September to 31 December 2020 based on the Intensive Care National Audit & Research Centre (ICNARC) report at that time. In the meta-analysis described above mortality rates for this population were **reduced by 8%** with the treatment of steroids. This would equate to **approximately 960 lives saved in the last 4 months of 2020 in England, Wales and Northern Ireland alone** since this research was published. This improvement in survival is reflected in the latest outcome figures. In patients admitted to ICU for COVID-19 before 31 August 2020 survival rates were 61% (95%CI 60.1-61.9) at one month. For patients admitted from September to December 2020 **survival increased to 63.4%** (95%CI 62.4-64.4) – this excludes patients who are still being cared for in ICU and will therefore change over time.

[redacted]

Corticosteroids are now considered the standard of care for severely ill patients with COVID-19 who require oxygen or mechanical ventilation. These drugs are inexpensive and widely available, so that all countries around the world can provide them, saving tens of thousands of lives.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] Corticosteroids for COVID-19 (who.int) (evidence used in the recommendations in described on page 9. Ref 7 in the guidelines is underpinning research reference 3 above). Archived here.

[**B**]https://www.imperial.ac.uk/news/203273/steroid-found-improve-survival-critically-covid-19/ (Archived here).

[**C**] Chief Medical Officer Alert

https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103092 (Archived here)

[**D**] NICE COVID-19 prescribing briefing for the use of corticosteroids. https://www.nice.org.uk/guidance/ng191/resources/covid19-prescribing-briefing-corticosteroids-pdf-9071983117 (Archived here).

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