Submitted February 2021; Accepted February 2021

ORIGINAL ARTICLE

REMAP-CAP: delivering research in the pandemic

J.L.G. Haitsma Mulier[1,2], E.R. Rademaker[1,2], M.J.M. Bonten[2,3], L.P.G. Derde[1,2]

[1]Department of Intensive Care, [2]Julius Centre for Health Sciences and Primary Care, [3]Department of Medical Microbiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

Correspondence

J.L.G. Haitsma Mulier – j.l.g.haitsmamulier-2@umcutrecht.nl

Keywords - **REMAP-CAP, randomised, embedded, adaptive, platform, trial, research, pandemic**

Abstract

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic is an unprecedented global health crisis. For hospitalised patients with Coronavirus Disease 2019 (COVID-19) mortality and morbidity is high. A case fatality rate of 49% for critically ill patients was reported in early studies. We urgently need effective treatments for these patients. In past pandemics, the clinical research response has largely failed. During the Influenza A(H1N1) pandemic, no randomised trials delivered results. Traditional randomised trials are not well suited for research in pandemics. They are robust, but lack the flexibility to adapt to changing circumstances and only investigate a single treatment against a control arm. Additionally, sample size calculations are almost impossible in new diseases. Adaptive platform trials, specifically REMAP-CAP, help overcome the challenges of pandemic research. We describe the key design principles of adaptive platform trials, the design of REMAP-CAP, and how this trial has delivered important results that contribute to the treatment of hospitalised and critically ill patients with COVID-19.

Introduction

Since the start of the current pandemic, over 100 million cases of COVID-19 and over 2.2 million deaths globally have been reported.[1] The disease presents as severe pneumonia with typical imaging abnormalities, hypoxaemia, an exaggerated immune response and thromboembolic complications. Initially, with no treatment available, mortality rates for critically ill patients were around 49%.[2] Although vaccination is commonly seen as the largest contributing factor to tackling this global crisis, rapid identification of effective treatments is crucial as morbidity and mortality from COVID-19 is significant, with a large proportion of hospital and intensive care unit (ICU) beds occupied by these patients. We describe how adaptive platform trials, specifically REMAP-CAP, can help overcome challenges and find effective treatments for patients.

Research during pandemics

In past pandemics, the clinical research response has largely failed.[3] The influenza A(H1N1) ('swine flu') pandemic of 2009 is the most recent example. In response to that pandemic, 15 clinical trials were registered with anticipated enrolment of approximately 7000 patients. To date, only three trials, including 153 patients in total, have published results. None delivered results during the pandemic.[4]

Delivering research in a pandemic is challenging for several reasons. High-quality data are needed in the shortest time possible, and once a conclusion has been reached, that information should become publicly available immediately to let patients benefit from it. Secondly, most studies are designed to investigate the effect of a single treatment, but patients may receive multiple therapies. For COVID-19 this implies treatment with antiviral drugs, immune-modulators and anticoagulation, which may interact and may differ in subsequent disease states. A third challenge is that randomised controlled trials (RCTs) depend on assumptions about effect size to calculate a required sample size. Yet, effect sizes are notoriously difficult to estimate and this often leads to retrofitting the effect size to match the predicted recruitment.[5] Lastly, there is a need to immediately investigate newly available therapies, and the standard of care may change rapidly if effective treatments are found. In summary, pandemics call for a different approach in study design.

A novel approach

Adaptive platform trials (APTs) deliver answers in the shortest possible timeframe, investigate the best treatment regimen instead of comparing single treatments, and can adapt to the dynamic changes during a pandemic.[6]

There are three key design features of APTs. First, as with all RCTs, an APT is a prospective randomised experiment — a trial — of different treatment strategies. Second, APTs are a platform, allowing testing of multiple hypotheses at the same time under a core (or master) protocol. Because APTs focus on the underlying disease, rather than individual interventions, the overarching design can be created before any specific experimental arm is defined. The third element, distinguishing APTs, is that they are adaptive. They use information generated during the trial conduct to alter subsequent operations of the trial in a pre-specified way. New treatments can be added to the trial during its lifetime. Both elements (master protocol and adaptive design features) add complexity to the trial, but with the intent of making it more efficient.

REMAP-CAP

A Randomised, Embedded, Multifactorial, Adaptive Platform (REMAP) trial adds two important features to the APT design elements. First, it is embedded in clinical care, facilitating recruitment. This is especially relevant in a pandemic where time for research activities is limited. Second, it is multifactorial, allowing testing of multiple hypotheses and multiple interventions at the same time. Randomisation occurs to multiple aspects of the treatment regimen at the same time. This enables ever-increasing knowledge generation about the best treatment regimen for a disease or condition.

A REMAP for Community Acquired Pneumonia (REMAP-CAP) was set up after the swine flu pandemic with the explicit goal to deliver research in pandemics. Initially an ICU trial, it focused on CAP, as this was considered to have the highest likelihood of resembling a future pandemic disease relevant to ICUs. It was set up across multiple regions, acknowledging the global nature of pandemics. Seed funding was obtained from the European Union in 2014 (FP7-HEALTH-2013-INNOVATION-1 #602525), extending to Australia, New-Zealand, Canada and the United States afterwards. Recently, India, Nepal and Pakistan joined REMAP-CAP through the Critical Care Asia network.

Analysis of REMAP-CAP

APTs often use Bayesian statistical inference models, as these are well suited for handling the adaptive and multifactorial design aspects. In REMAP-CAP, the primary analysis is generated from one overarching Bayesian cumulative logistic model, which calculates posterior probability distributions for the primary outcome based on evidence accumulated in the trial and assumed prior knowledge in the form of a prior distribution. The primary model adjusts for location (site, nested within country), age, sex, and time period (two-week periods). The model contains treatment effects for each intervention within each domain and pre-specifies relevant treatment-by-treatment interactions across domains. The model is fit using a Markov Chain Monte Carlo algorithm that draws iteratively (10,000 draws) from the joint posterior distribution, allowing calculation of odds ratios with their 95% credible intervals (CrI) and the probability that each intervention (including control) is optimal in the domain, that an intervention is superior to control, that two non-control interventions are equivalent, or that an intervention is futile.

The model for the primary analysis includes all patients enrolled in the trial, providing the most robust estimation of the coefficients of all covariates. Importantly, not all patients are eligible for all domains or interventions. Therefore, the model includes covariate terms reflecting each patient's domain eligibility. The estimate of an intervention's effectiveness, relative to any other intervention within that domain, is thus generated from those patients that might have been eligible to be randomised to those interventions within the domain.

From theory to practice

The first REMAP-CAP patient was randomised at the University Medical Center Utrecht in April 2018. At the start of the pandemic, in March 2020, 56 centres globally participated

Box 1. Key concepts of REMAP-CAP

Key concept: multifactorial

To allow investigation of multiple aspects of treatment, REMAP-CAP organises treatments into domains, each covering one common therapeutic area (e.g., antiviral therapy) and containing at least two interventions (including a control arm). Patients eligible for the platform are assessed for eligibility and potentially randomised to multiple interventions across multiple domains (but to only one intervention in each domain for which they are eligible). Thus, they are randomised to a regimen of treatments rather than a single treatment. Participating sites can choose the domains and interventions they offer locally.

Key concept: adaptive

The adaptive design allows interventions to be added or altered over the course of the trial. Accumulating evidence in the trial is used to update the statistical model that is then used to decide about termination for graduation (e.g. superiority or futility of one part of the trial) and for updating randomisation probabilities (response adaptive randomisation, RAR). With RAR, patients are more likely to receive more promising interventions. The weights of the randomisation probabilities are updated at each interim. The interim analyses for assessing if pre-specified platform triggers that lead to termination (graduation or futility) have been reached are pre-planned. Accumulating evidence is also used to re-estimate the optimal sample size and an experimental arm can leave the trial as soon as the data permit.

Table 1. Currently active and paused domains of the REMAP-CAP study

Active domains	Method	CAP	COVID-19 severe§	COVID-19 moderate
Antibiotic	Comparing 5 different empiric antibiotic strategies			
Antiviral*	Comparing no influenza antiviral agent to 5 or 10 days of oseltamivir			
Corticosteroid†	Comparing administration of no corticosteroids to shock dependent or fixed dose hydrocortisone dosing regimens			
COVID-19 ACE2 RAS	Comparing 4 different RAS inhibition strategies (no RAS inhibition, ACE inhibition, angiotensin receptor blockers (ARB) and ARB+DMX-200, a chemokine receptor-2 inhibitor)			
COVID-19 Antiplatelet	Comparing 3 different antiplatelet interventions (no antiplatelet, aspirin and P2Y12 inhibitors)			
COVID-19 immune modulation	Comparing 5 different strategies targeting the immune response to COVID-19 (no immune modulation, interferon-beta, anakinra, tocilizumab and sarilumab)			
COVID-19 Statin therapy	Comparing no statin versus simvastatin for the treatment of ARDS caused by COVID-19			
Mechanical ventilation	Comparing guideline recommended mechanical ventilation strategies to clinician-preferred mechanical ventilation strategy			
Macrolide duration‡	Aimed at finding the most optimal treatment duration (3-5 vs 14 days) for macrolides.			
Vitamin C	Comparing no vitamin C to high dose vitamin C			
Paused domains				
COVID-19 Antiviral	Comparing 4 different COVID-19 specific antiviral treatment strategies (no antiviral agent, lopinavir/ritonavir, hydroxychloroquine and a combination of lopinavir/ritonavir and hydroxychloroquine			
COVID-19 Therapeutic Anticoagulation	Comparing therapeutic anticoagulation to local standard anticoagulation			
COVID-19 Immunoglobulin therapy	Comparing no immunoglobulin administration to convalescent plasma			

§patients on the ICU requiring organ support;*Influenza patients only;
†this domain is no longer open for COVID-19 patients;
‡only available for patients randomised into one of the beta-lactam plus macrolide interventions in the antibiotic domain;
ACE2 = angiotensin-converting enzyme 2; ARB = angiotensin receptor blocker; DMX = dexamethasone, RAS = renin-angiotensin system

active not active

in the study (including three Dutch centres). The pandemic stratum, facilitating inclusion of patients suspected or known to have COVID-19, was opened on 3 March 2020, and the first patient included six days later. Before the start of the pandemic, four domains were approved and open for recruitment. Nine domains containing 17 active interventions have been added so far (*table 1*). The number of participating sites increased rapidly during the pandemic, with now 296 active sites across the world. Of note, more than 130 sites from the United Kingdom, joined the trial after the chief medical officer had urged British hospitals to participate in REMAP-CAP.[7] Currently, 5312 patients with suspected or proven COVID-19 have been randomised for more than 10,000 treatment options, and six platform conclusions have been drawn during the pandemic, all guiding patient care.

After publication of the RECOVERY results, convincingly showing benefit of dexamethasone for patients admitted with COVID-19, the Corticosteroid Domain of REMAP-CAP was closed for these patients and available data were analysed.[8] In REMAP-CAP, treatment with a seven-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone resulted, compared with no hydrocortisone, in 93% and 80% probabilities of superiority for the primary outcome.[9] This treatment has now been incorporated in national and international treatment guidelines.[10,11] Despite not reaching the predefined statistical trigger (i.e., 99%), the 93% posterior probability of benefit from hydrocortisone contributes more information than the traditional frequentist result, where the only conclusion would have been that the null-hypothesis could not be refuted. The next two platform conclusions were that the interleukin 6 (IL-6) receptor antagonists sarilumab and tocilizumab are superior to no-immune modulation. These drugs reduce mortality for critically ill patients with COVID-19 by about 24%, and reduce time spent on organ support in the ICU, on top of treatment with corticosteroids.[12] A fourth result is that the antiviral drug lopinavir/ritonavir is futile in the treatment of critically ill patients with COVID-19. These results will be published soon. In the COVID-19 Antiviral Domain, two arms containing hydroxychloroquine were previously closed as equipoise for randomisation was lost as a result of external evidence. The results have been included in a meta-analysis, which yielded that treatment with hydroxychloroquine was associated with increased mortality in COVID-19 patients, and there was no benefit of chloroquine.[13] Lastly, two platform conclusions about anticoagulation were reached within six months of finalising the protocol. For this domain, REMAP-CAP collaborated with the ACTIV-4 and ATTACC trials in a multi-platform RCT (mpRCT). Therapeutic anticoagulation appeared to be futile, and possibly harmful, in critically ill patients receiving organ support, compared with local standard thromboprophylaxis, but superior in patients with less severity of illness.

Conclusion

In summary, adaptive platform trials are a 'new and improved' method for performing trials, in line with current practice. They combine a robust design with flexibility that makes them more efficient and safe for patients. They allow rapid identification of the best treatment regimen for a disease or condition, embedded in clinical practice. Thus, they facilitate 'learning while doing' and pave the way towards a more learning healthcare system.[3,14] REMAP-CAP is a fully Bayesian APT aimed at finding the best treatment for CAP and designed to adapt to pandemics. The results from this trial within a year of the start of the pandemic prove the practical value and the effectiveness of the design.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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