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Feature

Regulatory oversight on the use of experimental therapies during a pandemic: The case of early access to convalescent plasma therapy in three LMICs

Rosemarie Bernabe [a,b,*], Cristina Torres [c,d], Grace Wangge [e], Edlyn Jimenez [c], Juntra Karbwang [d]

Clinicians, especially in low- and middle-income countries (LMICs), contend with limited economic and healthcare resources in deciding appropriate and feasible care for their patients. Some of the LMICs affected by COVID-19 implemented convalescent plasma therapy without sufficient regulatory guidance. Based on this experience, there are several requirements going forward, including: the need for an immediately accessible data gathering and processing system; the necessity of establishing regulatory pathways for early access to experimental treatment during emergency situations; and the accompanying reporting and monitoring requirements must be set. The different stakeholders must also be properly incorporated in the system that such a pathway will create, without neglecting to properly inform the public of the patient rights especially during an emergency situation.

Keywords: Early access; COVID-19; Regulatory oversight; Experimental therapies; LMICs

Introduction

The global outbreak of COVID-19 has created an urgent demand for effective and safe interventions, in addition to supportive clinical care, to prevent its spread. Clinicians around the world are relying on limited knowledge of COVID-19 to improvise appropriate clinical care. However, clinicians, especially in low- and middle-income countries (LMICs), must additionally contend with limited economic and social resources in deciding appropriate and feasible care for their patients.

Especially during the early months of the pandemic, the use of convalescent plasma therapy (CPT) caught the interest of physicians, including those in LMICs, owing to its availability, although costs might not necessarily be minimal.[1] Calls for blood donations from COVID-19 patients started to circulate in social and mainstream media mixed with 'humanitarian and patriotic' appeals to help find solutions to the pandemic. Physicians also resorted to various regulatory pathways, such as off-label, compassionate use, and experimental therapy of available drugs and therapies. Here, we will provide an ethical reflection on the LMIC experience – specifically of the Philippines, Indonesia and Thailand – on the regulatory pathways available to healthcare workers for experi-

https://doi.org/10.1016/j.drudis.2021.12.002

mental therapies during the initial onset of the pandemic (i.e., prior to clinical trials), using the convalescent therapy experience as a springboard for discussion. Experimental therapies refer to medical therapies that are yet to be proven effective and safe for a specific medical condition. The experiences of these three countries provide valuable input because Indonesia and the Philippines, at the time of writing, are the most affected Southeast Asian countries in terms of COVID-19 incidence and death rates, with Thailand following closely behind in terms of number of cases.

CPT

There are examples of the use of CPT in the medical literature during previous outbreaks such as SARS, H1N1, Ebola and other viral infections.[2] Cheng et al. in 2005 reported favorable outcomes for 33 SARS patients who received CP within 14 days of symptom onset with no report of adverse events.[3] During the outbreak of Ebola in 2014, WHO issued a guidance on the use of CPT as an empirical treatment for Ebola.[4] However, there have not been any large trials to confirm the benefit over the risk of using CPT as the initial treatment against an emerging infection.

According to the Cochrane Report's living systematic review on CPT against COVID-19, there is high certainty "in the evidence that convalescent plasma for the treatment of individuals with moderate to severe disease does not reduce mortality and has little to no impact on measures of clinical improvement".[5] This agrees with the findings of an earlier systematic review by Janiaud et al.,[6] although another systematic review by Klassen et al. found that "the mortality rate of transfused patients with COVID-19 was lower than that of nontransfused patients".[7] It is noteworthy, especially during the first year of the pandemic, that some clinicians published results of preliminary studies, even if they were observational in nature. However, critics point out that the use of anecdotal evidence in simple observational studies does not determine the true clinical effect of the intervention. It does not conclusively answer the question whether CPT was responsible for patient recovery.[2]

Compassionate use and CPT

The USA and the EU facilitate or have facilitated CPT as a treatment for COVID-19 patients. In both cases, CPT was facilitated using compassionate use and emergency use authorization as the regulatory pathways.[8,9] Owing to the latest scientific findings, the USA and the EU limit the use and research on CPT to "early transfusion...with high neutralising antibody titres".[8,10]

In the USA and the EU, compassionate use refers to the access of patients with life-threatening or a seriously debilitating condition to access an unauthorized medicine.[11,12] However, there are noteworthy differences. In the USA, compassionate use (also called expanded access) includes the access of an individual patient, an intermediate-sized patient population or the wider population to unauthorized medicines in a normal or emergency setting, with or without clinical trials (although widespread compassionate use is possible only with a clinical trial),[9,13] whereas the EU restricts compassionate use to patient access to unauthorized medicines "undergoing clinical trials or [that] have entered the marketing-authorization application process".[12] For an elaboration of compassionate use and COVID-19, see, for example, Rizk et al.[9] Because our interest is on the early pathways at the onset of the pandemic (i.e., pathways that are almost immediately available to healthcare workers even before ethics and regulatory approvals for research are made available), US compassionate use is more relevant for our purpose.

In a compassionate use application, the sponsor or investigator is responsible for ensuring that the potential benefit to the patient justifies the risks, that compassionate use will not "interfere with the initiation, conduct, or completion of clinical investigations,[13] that an IRB review has been secured, that not only safety but preliminary evidence of effectiveness is available (for compassionate use of at least an intermediate-sized population), and that safety and annual reports are accomplished.[13] A medical doctor attending to a patient under this program is considered an investigator as well. This means that, from a regulatory perspective, compassionate use access triggers some procedures and protections that are similar to research. From April 2020, CPT was initially accessible to US patients via the compassionate use for single patients route, which eventually led to widespread compassionate use, Emergency Use Authorization and then to clinical-trial only access.[9]

CPT against COVID-19 in LMICs

Several LMICs are also badly affected by COVID-19. At the time of writing, Asia has a substantial number of confirmed cases of COVID-19,[14] with Indonesia overtaking India in terms of daily confirmed cases.[15] Within Southeast Asia, Indonesia, the Philippines, Malaysia and Thailand are the top four in terms of number of cases.[16] Indonesia, the Philippines and Thailand used CPT whereas Malaysia did not; hence, we shall look at the experiences of the three Southeast Asian countries that implemented CPT.

In Indonesia, initially, the use of CPP was promoted by an intensivist who claimed and promoted her 'breakthrough innovation' to the mass media, organized several webinars and printed a book on the CPT procedure. This finding was then endorsed by Indonesian national figures and was publicly hailed as the nation's pride. The therapy was then offered as a therapeutic option in several hospitals. The Indonesian Medical Regulatory Agency then tried to regulate this and officially issued a special regulation in May 2020, where the use of CPT was then only allowed in a clinical trial setting or in a well-monitored observational study.[17] A multicenter trial of CPT, involving 29 hospitals in Indonesia, was then established in September 2020, led by the Nation Health Research Agency. In January 2021, there was a nationwide call for plasma donors by the Indonesian Red Cross and the National COVID Task Force, three days after the result of an unsuccessful Recovery Trial was announced. The promotion disregarded the fact that the use of CPT should only be in a clinical trial setting or a duly registered observational study. In June 2021, a report published in the *Lancet* from a single-center study of ten patients that was sponsored by a state-owned pharmaceutical company.[18] In spite of these findings, CPT was used heavily by medical practitioners outside the clinical trial and expanded access setting without proper monitoring from the health authorities (The FDA does not have control over the medical practice in Indonesia). Patients are given CPT as their therapeutic of choice without being informed about the legal status of the ther-

apy. The scarcity of available drugs and insufficient supply of highly effective vaccines have also fueled the popularity of CPT. With the increasing number of positive cases and deaths, the requests for convalescent plasma donors increased and some people even started civil movements to help desperate patients and families.

The Philippines has a compassionate use program that enables access to medicines that are "not registered or are in the process of registration in the Philippines by patients who are terminally or seriously ill".[19] The permit can be applied for an individual patient or for institutional use by a qualified specialist who then will be required to submit to the Food and Drug Administration a "Clinical Study Report for every patient given the product describing the quantity administered/use, therapeutic/desired effect and any adverse reaction. . .at the end of each year".[19] Notice that, in the list of requirements, no ethics approval was mentioned. In the case of CPT, however, the common interpretation was there was no need for a compassionate use application because CPT is not considered an investigational new drug. This means that, for individual patients, attending physicians can prescribe CPT without any research or reporting requirements. Research ethics committees are not involved in clinical care ethics hence no ethical oversight was in place. At an institutional level, some medical centers requested compassionate use permits; however, because there was no requirement to do so, applications were on a voluntary basis. As in Indonesia, CPT was openly advertised through television and social media to recruit plasma donors. Major hospitals launched their own CPT programs and the participation of well-known personalities as donors further encouraged public support through the coverage of mainstream media.[20] A clinical trial meant to investigate CPT as an adjunctive therapy for hospitalized COVID-19 patients was launched by the University of the Philippines in September 2020.[21] This study found that there was "no significant difference in using CPT in terms of further emergency or in-hospital care, progression to severe disease, use of mechanical ventilation and length of stay, COVID-19 death, and all cause mortality".[22] Thus, in April 2021, the Department of Health issued a memorandum recommending the discontinuation of any other access to CPT aside from clinical trials.[22]

In Thailand, a TV advertisement for a convalescent plasma donation for a trial came before the submission of a protocol for ethics review. The research ethics committee requested for information on the quality of the convalescent plasma but the investigator did not provide sufficient information. The investigator eventually withdrew the application which resulted to no CPT clinical trial in Thailand. However, the campaign for convalescent plasma donation continued, and CPT was used by individual physicians as experimental therapy, a pathway that does not have any reporting mechanism.

In all three settings, it is easy to imagine how the presentation of CPT can lead to therapeutic misconception (i.e., the misunderstanding where an experimental treatment is confused with established clinical care). Plasma donors and recipients could perceive CPT as a real therapeutic option (as opposed to an experimental option) for life-saving therapy because the message of 'life-saving therapy' has already been widely disseminated.

We also noticed that although CPT was used to treat COVID-19 in these three LMICs, there was no requirement for swift data gathering, reporting and analysis of safety and efficacy data in place, a system that could have collected vital information that might be useful in clinical decision-making. CPT outside trials was justified as compassionate use or emergency therapy, or simply as another therapeutic option that does not require any justification or regulatory permits and oversight. The pandemic seems to have placed healthcare systems in several LMICs on autopilot mode where the default is individualized emergency care given the limited financial and healthcare resources, with the principles of research ethics and human subject protection (in the form of regulatory and ethics reviews and valid informed consent) taking a back seat; but, what do we learn from all of this?

Concluding remarks: Lessons and recommendations from the CPT experience

First, there is a need for an immediately accessible system and procedures on data gathering and processing of efficacy and safety data that immediately apply during a large-scale emergency. Considering that all three countries under discussion have some pharmacovigilance system in effect,[23] future studies should look at, for example, how a system could incorporate the data processing needs in emergency situations. In settings with comparably limited economic and healthcare resources to high-income nations, access to information that can inform and guide clinical decision making and the allocation of scarce economic and healthcare resources is crucial.

Second, regulatory pathways for early access to experimental treatment during emergency situations, and the accompanying reporting and monitoring requirements, must be set. The US compassionate use during emergency situations as a regulatory pathway can be considered as an example that LMICs can start with. Establishing this regulatory pathway should enable the much-needed data gathering and processing, also for regulatory oversight.

Third, using US compassionate use as an example of a regulatory pathway, preparation of the regulatory pathway for early access in LMICs entails making sure that the different stakeholders are properly incorporated in the system that such a pathway will create. This means, among several things, administrative preparedness and oversight procedures and mechanisms for the regulatory bodies, clear procedures for research ethics committees during emergency situations specifically to cater to the requirements of early access, a system in place for mandatory reporting and medical practitioners duly informed of the process.

Fourth, in this era of the infodemic and misinformation, it is important to educate the general population about their rights as patients during emergency situations, including being properly informed about therapeutic options and the nature of such options, experimental or not. This, after all, is a requirement of patient-centered healthcare and good clinical practice.

Although necessary, it is not sufficient, especially during emergency situations to simply provide care. Giving the necessary regulatory guidance to healthcare workers on the use of experimental therapies and gathering relevant scientific data in support of effective interventions are real and urgent needs, especially when doing so means directing and redirecting emergency care and the allocation of scarce economic and healthcare resources.

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Rosemarie Bernabe [a,b,*], Cristina Torres [c,d], Grace Wangge [e], Edlyn Jimenez [c], Juntra Karbwang [d]

[a] Faculty of Health and Social Sciences, University of South-Eastern Norway, Norway
[b] Centre for Medical Ethics, Institute of Health and Society, University of Oslo, Norway
[c] National Institutes of Health, UP Manila, Philippines
[d] SIDCER-FERCAP Foundation, Pathumthani, Thailand
[e] Southeast Asian Ministry of Education – Regional Center for Food and Nutrition (SEAMEO- RECFON), Indonesia

* *Corresponding author at: Faculty of Health and Social Sciences, University of South-Eastern Norway, Norway. Bernabe, R. (Rosemarie.Bernabe@usn.no)*