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EDITORIAL

A brief note on randomized controlled trials and compassionate/off-label use of drugs in the early phases of the COVID-19 pandemic

Matteo Bassetti MD, PhD[1,2], Paolo Pelosi MD, FERS[3,4], Chiara Robba MD, PhD[4], Antonio Vena MD, PhD[1,2], Daniele Roberto Giacobbe MD, PhD[1,2]

[1]Infectious Diseases Unit, Ospedale Policlinico San Martino – IRCCS, Genoa, Italy; [2]Department of Health Sciences, University of Genoa, Genoa, Italy; [3]Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy; [4]Anaesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS, Genoa, Italy

Abstract

Randomized controlled trials (RCTs) are the best way to find effective and acceptable safe treatments for COVID-19 and any possible future outbreak. However, caution is needed when comparing the number of participants in RCTs with that of patients with COVID-19 treated with compassionate and/or off-label drugs to support the hypothesis that the latter are preferred by clinicians as an alternative to the former.

Keywords: compassionate, coronavirus, COVID-19, off-label, RCT, SARS-CoV-2

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Randomized controlled trials (RCTs) are the best way to find effective and acceptable safe treatments for COVID-19 and any possible future outbreak.[1] In this regard, the present pandemic is an unprecedented opportunity to improve our ability to guarantee participation in RCTs to as many patients as possible, in order to rapidly provide high-level evidence that can firmly improve our therapeutic approach to COVID-19 patients. Furthermore, administering unapproved/off-label drugs instead of offering participation in RCTs carries the risk of perpetuating cognitive and availability biases, which may increase the risk of violating the principle of 'first, do not harm'.[2]

However, all of this should not give the wrong impression that, in real life, many COVID-19 patients were offered (or are being offered) off-label or compassionate drugs as an alternative to participation in RCTs. Indeed, based on our clinical experience during these first weeks at the bedside of COVID-19 patients, this is not true for different reasons:

- The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has unfortunately been very fast, and participation in RCTs was not feasible when most hospitals received the first hundreds of patients.
- Local approval of RCTs correctly requires time even during an emergency to guarantee ethical standards; thus, participation in RCTs was (and is) precluded to most of the first COVID-19 patients.
- Many patients may also be precluded from participation in RCTs because of the strict exclusion criteria, even after their implementation.[3]
- Temporary shortages of some investigational drugs may also become of concern when dealing with rapid exponential increases in the number of potential enrollments.

Against this backdrop, we think that compassionate and/or off-label use of drugs, provided their activity against SARS-CoV-2 is supported by reliable preclinical data, still represent an ethically justifiable option for those critically ill patients excluded from RCTs who are not improving while receiving only supportive care. It is nonetheless important to note that compassionate and/or off-label drug use should not interfere with enrollment in RCTs – that is, they are not an alternative but rather an option in those situations in which participation in RCTs is impossible, which unfortunately are not uncommon. This is in line with what some of us recently reported in a narrative review detailing the current position of the Italian Society of Anti-Infective Therapy and the Italian Society of Pulmonology, in which we also highlighted that data from compassionate/off-label experiences, although being not solid enough for guiding treatment, may remain very useful for hypothesis-generating purposes that may help in fine-tuning the design of future RCTs.[4]

In conclusion, participation in RCTs should always be the first option whenever feasible. However, we advocate caution in comparing the number of participants in RCTs with that of patients treated with compassionate and/or off-label drugs to support the hypothesis that the latter are preferred by clinicians as an alternative to the former, as there are several factors hampering a firm interpretation of the meaning of the ratio. This is especially true in the first phases of rapidly evolving pandemics like COVID-19, when RCTs are not immediately available even when rapidly implemented. Certainly, we need to increase the absolute number of participants in RCTs, independent of the denominator.

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Correspondence: Matteo Bassetti, Clinica Malattie Infettive, Ospedale Policlinico San Martino – IRCCS, L.go R. Benzi 10, 16132 – Genoa, Italy. matteo.bassetti@unige.it

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