

## Clinical trials during pandemics and beyond: time for a more efficient pharmacological strategy

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During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, clinical trials on antiviral or symptomatic drugs have been conducted very rapidly even for drugs with a poor pharmacological rationale for efficacy on SARS-CoV-2. Despite lacking basic pharmacological information, most of these clinical trials were also extremely redundant. Applying simple rules, (such as identifying a mechanistic rationale, confirming the ability to reach exposure targets at therapeutic dosage and ensuring tests show drug efficacy in appropriate *in vitro* and animal models before entering clinical trials) might have saved considerable amounts of time and money, and might have avoided useless research. Moreover, combining these simple rules with the implementation of a relevant policy at both an international and a national level, by limiting studies with a poor methodological/scientific approach and aggregating studies with similar design into single clinical trials, is potentially a far more-efficient strategy.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic hit the world at the beginning of 2020. This unprecedented worldwide epidemic led the World Health Organization to declare a Public Health Emergency of International Concern on 30 January 2020. Based on 175 seroprevalence studies, the crude infection fatality rate (IFR) is reported to be 0.33% to 2.3% in developing countries.<sup>1</sup> This important uncertainty surrounding the somewhat high IFR, as well as the explosive dynamics of the outbreak and the fear that hospital admissions for COVID-19 would outstrip healthcare capacity prompted efforts to find either a prophylactic/pre-emptive treatment or a treatment to reduce the severe symptoms of the illness.

When faced with such urgency, drug repurposing—defined as finding new indications for existing drugs—provides an opportunity to speed up the identification of drugs of interest. It is an advantage that many development steps, such as toxicology studies or formulation development, have already been carried out and the pharmacokinetic and safety profiles of the repurposed drug candidate are likely to have already been described in preclinical models and in early-stage trials. However, before considering clinical trials, it is essential to reassess the pharmacological rationale specifically for this new indication.

One example of a drug repurposed for COVID-19 is the antiviral remdesivir. After biotransformation into an active metabolite, this adenosine analogue acts as a false substrate for viral RNA polymerase and has shown promising *in vitro* activity against SARS-CoV-2 in a Vero-E6 cell infection model, with a half-maximal

effective concentration (EC<sub>50</sub>) of 0.77 μM and an EC<sub>90</sub> of 1.76 μM, which are targets attainable with usual drug dosage.<sup>2</sup> Remdesivir also showed reductions in viral load in the lower respiratory tract (but not in the upper respiratory tract) as well as improving clinical and radiological outcomes in SARS-CoV-2-infected rhesus monkeys.<sup>3</sup> These results legitimated the implementation of clinical trials, the results of which were obtained in a very short timeframe (by mid-April 2020), demonstrating the feasibility of drug-repurposing even in an ongoing pandemic. Although a reduction in hospital stay duration was reported in a randomized controlled trial versus placebo, the drug did not demonstrate any impact on 28 day mortality.<sup>4,5</sup> This highlights the fact that despite ticking all the boxes required for a sound preclinical evaluation, clinical trials can still show negative results, meaning that while pre-clinical evaluation and preliminary clinical evidence are necessary, they do not ensure the clinical relevance that is warranted for decision making. Moreover, a lack of transparency in this regard has been detrimental, as the evidence of lack of effect on mortality was available to Gilead (but not the European Union) when the company secured an agreement to supply the European Union.<sup>6</sup>

Unfortunately, owing to the rapid evolution of the COVID-19 situation, basic elements of pharmacology were forgotten in the rush to perform efficacy trials. Hydroxychloroquine is undoubtedly the most striking example. Its use was fuelled by some evidence of effect in *in vitro* experiments: Yao *et al.*<sup>7</sup> published results with an EC<sub>50</sub> of 0.72 μM obtained in a Vero-E6 cell model. However, hydroxychloroquine had no clear direct antiviral mechanism and had a

clearly unfavourable pharmacokinetic/pharmacodynamic profile for the treatment of SARS-CoV-2 infections. Although the drug might accumulate in the lung, there are no data on epithelial fluid measurements. The relevance of EC<sub>50</sub> as an endpoint for targeting drug exposure is debatable. Moreover, there are tremendous differences in the EC<sub>50</sub> reported in *in vitro* studies with a 24-fold difference between the lowest and the highest reported value, 0.72 μM being the lowest published value.<sup>8</sup> This is before mentioning that for the objective concentration determination, the unbound fraction (i.e. the active part) of the drug, should be considered, which increases the target threshold. Hence, taking into account the most favourable EC<sub>50</sub> and a 60% unbound fraction, the threshold of 1.2 μM can barely be reached in patients' plasma with the commonly proposed dosages.<sup>7</sup> Lastly, greater reliance on animal models may also have prevented such a waste of effort, as Maisonnasse *et al.*<sup>9</sup> reported in a non-human primate model the inability of the drug to act on SARS-CoV-2 clearance when it was given before infection or early after infection, at either low or high dosage. Hydroxychloroquine is perhaps the tip of the iceberg, but many other drugs are now subject to clinical evaluation without any solid pharmacological rationale (e.g. ivermectin, nicotine, azithromycin).

In addition to a weak pharmacological rationale before starting clinical studies, the majority of drug trials that were launched during the COVID-19 pandemic lacked methodological rigour, with clear signals indicating a massive waste of resources, time and scientific efforts. Among the 689 trials planned over the first 100 days of the pandemic,<sup>10</sup> the median sample size was 120 patients. When the information was available, it was clear that the enrolment of trial participants was suboptimal among all these studies. There was a large overlap regarding interventions included in these studies. One hundred and eleven trials were planned to investigate the efficacy of hydroxychloroquine (in prevention or in treatment). One hundred and six of those planned to enrol fewer than 5000 participants and five were mega-trials enrolling more than 5000 patients (three in prevention and two in treatment). Eighty-six of these studies were registered after the first large trial with more than 5000 participants testing this drug. Cumulatively, the small trials studying hydroxychloroquine planned to enrol as many patients as the mega-trials. Two large trials were, however, sufficient to rule out any therapeutic effect for hydroxychloroquine.<sup>4,11</sup>

Although some excellent nationwide or cross-border initiatives, such as the OMS SOLIDARITY consortium, need to be acknowledged, many underpowered and poorly designed clinical trials based on scant prior evidence (i.e. with a poor pharmacological rationale) have been conducted during this period. This state of the affairs provides fertile ground for both non-reproducible research and wasted research.<sup>12</sup> Repurposing drugs might have been seen as a cost-effective approach but this should not lead to a decrease in the scientific standards for drug evaluation. These standards rely on there being a robust mechanistic rationale, a strong pharmacological background and solid methodology in building pre-clinical and clinical trials.

Such waste raises concerns. Reacting during a pandemic inevitably has unique features and some unavoidable waste will always be the price to pay for discoveries. Still, there is a subset of avoidable waste that is simply not acceptable, and options exist to reduce the number of patients being exposed to ineffective treatments, and optimize financial and human clinical resources.

Long before the pandemic, various calls to reduce waste in research have been issued.<sup>13</sup> Independent redundant clinical trials should be discouraged nationally and internationally, by a coordination of various stakeholders such as chief medical officers, health-care providers, funders and regulators as well as by institutional review boards. Any new trial must be authorized on strong prior evidence, including a mechanistic rationale, the ability to reach exposure targets at therapeutic dosage, *in vitro* tests showing drug efficacy in appropriate models and animal models confirming these results. Living mapping and living meta-analyses need to be used as a dashboard to monitor in real time the research agenda and setting priorities that are worth exploring.<sup>14</sup> While a difficult balance has to be found between freedom in academic research and stronger regulation of research programme authorization, regulatory agencies and/or ethics committees should benefit from extended competencies allowing them to require the above discussed prior evidence.

Implementing a relevant policy at both an international and a national level to limit studies with poor methodological/scientific approach and aggregating studies with similar design into unique clinical trials is potentially an efficient strategy. An example at a national level is an initiative aiming to prioritizing clinical trials for SARS-CoV-2 infections that has been proposed by France. The CAPNET (Comité Ad-hoc de Pilotage National des Essais Thérapeutiques et autres recherches sur la COVID-19) national agency has been created and offers a 'national research programme priority' label to a selected number of clinical trial projects allowing for a fast-track appraisal by ethics and regulatory organizations and facilities implementation. However, this cannot be called a strong policy as projects not labelled as 'national research programme priority', while not being fast tracked, can still be planned and approved by both ethics committees and the French regulator. It will therefore be important to monitor the exact output and impact of this initiative, to see if it meets its intended objectives and to propose any modifications necessary.

Finally, the present crisis highlighted the lack of research culture even in well-established teams. Clinical research certification programmes that include a strong background that insists on clinical pharmacology and reproducible research practices should be developed with certification promoted, if not required. That is the cost of the high-quality research we need.

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## Transparency declarations

None to declare.

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