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Research on COVID-19 therapy: Putting the cart alongside the horse

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Assessing the efficacy of a new antiviral drug usually starts with in vitro studies, continues with in vivo animal studies, and ends with studies in humans. Each of these three levels has its own rules and logic, but the three together constitute a comprehensive and coherent step-by-step program which allows the most promising drugs to be prioritized for well-designed clinical trials, and eventually produces strong evidence of their efficacy and safety before their use is recommended on a large scale.

The method is consistent but it takes time, and in a dangerous outbreak time is crucial. Repurposing a drug used previously for other diseases in humans can save time because the efficacy of the drug can be targeted right from the start, its toxicity and pharmacokinetic (PK) parameters being already well known. The study can therefore move straight on from evidencing activity in cells to efficacy trials in humans, bypassing the intermediate phases of animal studies and human phase II studies centering on tolerance and PK.

In early 2020, hospitals in many regions were overwhelmed by the exponentially growing influx of patients with COVID-19. In this worrying context, repurposing drugs with *in vitro* activity against SARS-CoV2 seemed the quickest way to improve COVID-19 care [1]. Some countries included repurposed drugs in their standard of care from the outset, without waiting for further clinical evidence [2]. Many research teams decided to include repurposed drugs in efficacy trials without waiting for further preclinical evidence. In this issue of EBioMedicine, Liesenborghs *et al.* report how they put the cart alongside the horse and decided to study the efficacy of itraconazole (a long-known antifungal drug which they identified as having *in vitro* activity against SARS-CoV-2) in both SARS-CoV2-infected hamsters and humans with COVID-19 at the same time [3]. When they found that itraconazole had no *in vivo* efficacy in hamsters despite appropriate lung exposure, they stopped the trial in humans.

This approach was coherent at the time. The study was well-conducted and provided a clear answer to a clinical question. It also makes us wonder which method to adopt next time, when some other dangerous disease prompts a rapid assessment of the efficacy of promising drugs.

The history of infectious diseases teaches us that many drugs showing *in vitro* activity on non-specific cells eventually prove ineffective in treating the disease in humans [4,5]. Since the beginning of the COVID-19 pandemic, dozens of drugs have been upheld as showing *in vitro* activity against SARS-CoV-2 [6]. Running efficacy trials on all these drugs was not the solution, for two reasons.

First, large efficacy trials require time, money and effort. For drugs expected to have antiviral action, the effort required is even greater since outpatient trials have to be organized in order to start treatment as soon as possible after the onset of symptoms. Since the overall research system is more efficient at deploying hospital trials, the number of outpatient COVID-19 trials to date has remained low and cannot provide answers for all the drugs that show potential benefits *in vitro* [7,8].

Second, giving sick patients a drug that, with strong probability, is likely to prove ineffective raises ethical issues. Even if the drug is known to be well-tolerated, and even if the trial is as adaptive as possible and includes rules for stopping for futility, where do we draw the line between a risky gamble and the genuine ambivalence which justifies to conduct a randomized trial? Is it fair to expose people to a drug we know well, to assess its efficacy for treating a disease we do not know well, without first obtaining sufficient pre-clinical evidence for its activity?

The answer is likely to be "yes, but only if..." The conditions implied in this "if" include the existence of a high level of threat, a good tolerance profile and *in vitro* findings that suggest the drug may have significant antiviral activity at a dose that can be given to humans. Liesenborghs et al. suggest an additional condition: when an emergency trial is launched without all the preclinical prerequisites being available, a preclinical research program should be launched in parallel to ensure these prerequisites are made available as soon as possible.

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Declaration of Competing Interests

The authors have no conflicts of interest to disclose.

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