Randomized trials are the real hope for Covid-19 treatment

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Facing the frightening Covid-19 pandemic, temptation to use unproven medications is great. Nevertheless, whatever the emergency, it is critical to develop relevant scientific approaches, namely through randomized trials. Surprisingly and unusually, the *New England Journal of Medicine* published data from a compassionate use of remdesivir for patients with severe Covid-19.[1] From a medical point of view, it is understandable to attempt to provide a possibly effective treatment in severely ill individuals but organizing the systematic dispensation of experimental treatment outside a well-designed protocol is more disputable.

The scientific and medical relevance of single-arm studies are limited and we will not list here all methodological limitations that the interpretation of such studies is faced. In the "study" cited above, it seems that the inclusion process was in part managed by the drug provider with unclear criteria. Given the world-wide distribution of patients, not considering the heterogeneity of medical practices is also an important bias. Highlighting the reduction of mortality on the basis of a debatable external comparison also raises question while the right choice of such comparator is probably the only way to provide results' credibility.[2] While present data are important to consider when developing new hypotheses, their wide dissemination may contribute to confusion among the general public, as was recently the case from similar studies with hydroxychloroquine. Thus, the present data mainly provide a signal for a hypothetic remdesivir repurposing rather than to demonstrate its benefit for the treatment of Covid-19 patients.

The real hope for Covid-19 treatment is elsewhere. Despite the epidemic situation, a real control group remains crucial. One concern, is whether it is ethical or not to give patients a placebo. Because the disease is not 100% lethal, it remains ethical to conduct randomized studies using placebo arm.[3] From the beginning of January 2020, an exponential number of clinical trials have been developed mainly randomized-trials exploring a large variety of drugs or treatment procedures (Figure 1A). Among the top ten drugs or procedures evaluated, an impressive number of studies concern hydroxychloroquine in various populations. Several trials are also testing a multiplicity of antivirals including remdesivir but more original approaches such as cell therapies are also developed (Figure 1B). Because some of these trials have an adaptive design that may help to early detect a beneficial or deleterious effect of drugs, it is urgent to wait their results before to disseminate data on possible inappropriate use of treatments.

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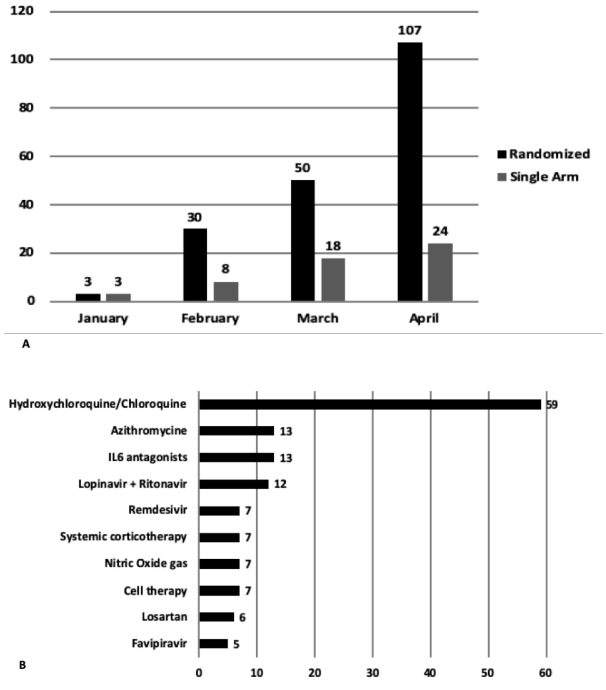

Figure 1. Interventional studies to fight Covid-19 since January 2020

In the Figure 1A, are represented the interventional studies (randomized or not) declared on clinicaltrial.gov from the beginning of January to April 14th 2020. Figure 1B illustrates the number of randomized trials declared according to the Top 10 drugs used in the same period.