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Investigational treatment of COVID-19

LEDER

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What to do in the absence of drugs with proven effect?

In 2003, the world stood on the brink of a pandemic of a severe respiratory infection caused by the novel coronavirus SARS-CoV. The virus succeeded in spreading from China to 28 countries before it was defeated in only a few of months under the leadership of the World Health Organization (WHO). Nine years later, another deadly coronavirus, today known as MERS-CoV, was discovered in the Middle East. There it still causes outbreaks, with sporadic export of cases outside the region. A number of drugs have been tested in the treatment of both SARS and MERS, but this has not resulted in any drugs with sufficiently documented efficacy.

In January 2020, China and the metropolis of Wuhan again attracted world attention. A novel SARS virus, SARS-CoV-2, caused an outbreak of the severe respiratory infection today known as COVID-19. This was followed by a stream of reports on investigational drug therapy, including traditional Chinese medicine, glucocorticoids and plasma, and drugs against HIV and malaria (1). By using highly intrusive measures, China succeeded in bringing the disease under control. However, this could not prevent the virus from spreading beyond China's borders, where it has caused the worst pandemic since the Spanish flu more than a century ago. Western countries followed China in the widespread use of investigational treatment, emphasising quick publication of results. This has often been research of varying quality that has been published without peer review as so-called preprints.

Investigational treatment is defined as any treatment for which the efficacy, risk and adverse effects are insufficiently documented for inclusion in regular treatment programmes. In the absence of drugs with sufficient documentation we have three options: include the patient in clinical trials, administer 'something' based on uncertain assumptions and hope of effect, or refrain from treatment pending results of scientific studies.

Inclusion in a clinical trial is clearly preferable, as this may help document the efficacy and safety of a drug. Therefore, the Directorate of Health and the Norwegian Medicines Agency generally prefer that investigational treatment should be provided through clinical trials (2, 3). However, when inclusion in a trial is not an alternative, and in the face of a serious

disease, it can be difficult to refrain from more or less well-founded, and invariably well-intended, treatment attempts. During the pandemic we have seen numerous examples of investigational treatments outside of trials, but the disadvantage is that at worst this may exacerbate the disease, without providing any evidence for efficacy or safety of the treatment. These issues have been frequently debated in relation to COVID-19 during recent months. Two articles that are now being published in the Journal of the Norwegian Medical Association provide insight into this topic (4, 5).

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Eirik Hugaas Ofstad and colleagues administered both the antimalarial drug hydroxychloroquine and the immune-modulating drug methylprednisolone to a patient. They observed clinical improvement two days after start of the steroid treatment (4). The effect of hydroxychloroquine on COVID-19 has since been disproven by multiple studies (6). Dexamethasone on the other hand, which like methylprednisolone is a glucocorticoid, looks promising, and the Recovery Trial in the UK has shown reduced mortality after treatment with dexamethasone in COVID-19 patients who were treated on a ventilator or needed supplementary oxygen (7). Michael Hahn and colleagues present their experiences from the use of convalescent plasma in a patient and observe concurrence between the administration of plasma and recovery from the illness (5). The authors nevertheless conclude that these are insufficient grounds on which to assess the efficacy of this treatment.

Norway is a small country in the context of COVID-19, and it is therefore desirable that we participate in large-scale international randomised controlled trials. In this way, we can best help build evidence for the efficacy and safety of drugs. Norway was among the first countries to join the WHO's Solidarity Trial, and it is very gratifying to see that 29 Norwegian hospitals are taking part (6). Internationally, the trial has already helped reveal the lack of efficacy of hydroxychloroquine and the anti-HIV drug lopinavir/ritonavir (6). Preliminary results from the American-led ACTT-1 trial indicate that remdesivir, originally a failed anti-Ebola drug, reduces the time until recovery by a few days, but with no definitive effect on mortality (8). On this basis, the European Medicines Agency (EMA) has granted remdesivir conditional approval for treatment of COVID-19. The recommendation in Norway has so far been to show restraint in the use of remdesivir outside of the Solidarity Trial, until efficacy results from this trial are available.

This pandemic can be stopped by a vaccine, not by drugs. But pending an effective vaccine, effective drugs will at best be able to prevent and alleviate the disease, save lives and relieve the burden on strained health services. The warning lights have flashed during both the SARS and MERS epidemics without this resulting in adequate prioritisation of research on drugs against coronaviruses. There is no further time to waste!

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