Off label, compassionate and irrational use of medicines in Covid-19 pandemic, health consequences and ethical issues

Uso off label, compassivo e irracional de medicamentos na pandemia de Covid-19, consequências para a saúde e questões éticas

Abstract When Covid-19 emerged in December last year, there was no vaccine nor was there specific effective treatment for this fast-spreading and life-threatening viral respiratory infection. Clinical trials were planned and are in progress to investigate whether drugs used for influenza, HIV and other viruses, and also anthelmintics (ivermectin, nitazoxanide, niclosamide), and antimalarials (chloroquine, hydroxychloroquine) showing antiviral activity in in vitro assays, are effective and safe for Covid-19. So far there is no convincing evidence that these antiviral and antiparasitic drugs are of any benefit for Covid-19. Notwithstanding the absence of evidence of clinical efficacy, these drugs are widely used outside of clinical trials (off label) for prophylaxis and treatment of this viral infection. The rationale behind the prescription of macrolide antibiotics (azithromycin) for Covid-19 is obscure as well. The widespread prescription and use of drugs of unproven efficacy and safety for Covid-19 is at odds with the rational use of medicines, a cornerstone principle of pharmacotherapy advanced by WHO in 1985. This irrational use of drugs is cause for concern because some of them are associated with serious heart disorders and deaths.

Key words SARS-CoV-2, Drug adverse events, Pharmacotherapy, Hydroxychloroquine, Antibiotics

Resumo Quando a Covid-19 surgiu em dezembro do ano passado, não havia vacina nem tratamento eficaz específico para esta infecção respiratória viral de rápida disseminação e risco de vida. Ensaios clínicos foram planejados e estão em andamento para investigar se os medicamentos usados para influenza, HIV e outros vírus e também anti-helmínticos (ivermectina, nitazoxanida, niclosamida) e antimaláricos (cloroquina, hidroxicloroquina) mostrando atividade antiviral em ensaios in vitro são eficazes e seguros para Covid-19. Até o momento, não há evidências convincentes de que esses medicamentos antivirais e antiparasítários sejam benéficos para a Covid-19. Não obstante a ausência de evidência de eficácia clínica, esses medicamentos são amplamente utilizados fora dos ensaios clínicos (off label) para profilaxia e tratamento dessa infecção viral. A lógica por trás da prescrição de antibióticos macrolídeos (azitromicina) para a Covid-19 também é obscura. A ampla prescrição e uso de medicamentos de eficácia e segurança não comprovados para a Covid-19 está em desacordo com o uso racional de medicamentos, um princípio fundamental da farmacoterapia promovido pela OMS em 1985. Esse uso irracional de medicamentos é motivo de preocupação, porque alguns deles estão associados a graves doenças cardíacas e mortes.

Palavras-chave SARS-CoV-2, Eventos adversos a medicamentos, Farmacoterapia, Hidroxicloroquina, Antibióticos


**Introduction**

There is nothing like a frightening pandemic for spreading unfounded beliefs in ‘miraculous’ medications. The Covid-19 pandemic is not an exception. Tackling such a life-threatening infection for which there is no vaccine nor are there specific effective therapies, not only lay people, but also physicians and public health practitioners may feel tempted to adopt healthcare practices that are not based on the best available scientific information. It is not surprising, therefore, a widespread prescription and use of medicines that were not approved, nor were demonstrated to be effective for Covid-19. This off-label use of drugs for primary treatment of Covid-19 is not compliant with WHO’s notion of rational use of medicines (RUM).

The concept of rational use of medicines (RUM), advanced by WHO in 1985, states that the use of medicines is rational when patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community. That is, the use of medicines is deemed irrational or non-rational, whenever it is not compliant with any of the foregoing requirements. From a slightly distinct perspective, the World Bank endorsed the WHO’s notion of RUM stressing that it integrates two key principles: use of drugs according to scientific data on efficacy, safety and compliance, and cost-effective use of drugs within the constraints of a given health system. Examples of irrational prescription and use of drugs are the use of too many medicines per patient (polypharmacy), the inappropriate use of antibiotics for non-bacterial infections, the failure to prescribe in accordance with the best evidence-based clinical guidelines, and inappropriate self-medication.

RUM is consistent with a healthcare practice known as Evidence-Based Medicine (EBM). As explained by David Sackett, one of the physicians who pioneered the concept in the 1990s, EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. Obviously, drugs appropriate to patient clinical needs are those of proven efficacy and safety to treat his/her medical condition, prescribed and used according to the best available empiric evidence on the effective and safe dose regimens, and that are the most cost-effective pharmacotherapy. Therefore, as far as therapeutic approaches are concerned, EBM-guided practices imply in selecting the most suitable pharmacological intervention based on the best available scientific evidence.

Five months or so of the emergence of the pandemic, in many cases, the primary pharmacotherapy of Covid-19 seems to be based on physicians’ guesses on what drug, or combination of drugs should work, rather than on the best empirical evidence from clinical trials. This conduct of practitioners is understandable, but not justifiable.

When mankind was struck by the pandemic, there was no antiviral drug of proven efficacy against SARS-CoV-2, nor were there evidence-based guidance and protocols of how to treat Covid-19 patients. There were on the market, however, a few drugs for other viral diseases such as inhibitors of viral neuraminidase (oseltamivir/zanamivir), RNA polymerase (favipiravir), and cell membrane fusion (umifenovir) for influenza A and B, protease inhibitors (lopinavir/ritonavir, darunavir) for HIV, and a guanosine (ribonucleic) analog inhibitor of virus RNA synthesis (ribavirin) for hepatitis C, respiratory syncytial virus (RSV) and other infections. Moreover, it was known that the antimalarial compounds chloroquine and hydroxychloroquine, and anthelminitics such as ivermectin, nitazoxanide and niclosamide strongly inhibited the replication of a variety of RNA (including SARS-CoV) and DNA viruses in cell-culture-based screening assays. These medicines began to be widely prescribed (off label) while clinical trials were still in progress to investigate whether they were in fact effective (and safe) for Covid-19 and thus could be repurposed for the treatment of this viral infection.

A major problem with off label prescription and use of medicines is that whereas their health risks (based on the use for approved indications) are generally predictable, their effectiveness for a new indication (Covid-19) is still underdemonstrated and cannot be taken for granted.

In the case of medicines approved for other viral infections, the antiviral mode of action may not work for SARS-CoV-2. For instance, since SARS-CoV-2 and other coronaviruses are enveloped positive sense single-stranded RNA viruses, they do not synthesize a complementary DNA and, thus, inhibitors of reverse transcriptase (like AZT or azidothymidine, active against HIV) do not block their replication.

Moreover, differences among viruses regarding the structure of the viral protein targeted by the drug, the mode by which viruses replicate (cell entry, multiplication and release), and the progression of infection in humans may eventually...
result in distinct clinical responses of viruses to antiviral agents. In summary, drugs that proved to work against influenza, hepatitis C or HIV, are not necessarily effective for Covid-19 and effectiveness against SARS-CoV-2 has to be confirmed by specific clinical trials.

When SARS-CoV-1 outbreak emerged in 2002-2003, oseltamivir and ribavirin were used (off label) and the clinical response of a small group of patients was followed up. A study of this case-series did not bring to light any clear therapeutic benefit of the two drugs. It is of note that, owing to the small number of infected people and relatively short duration of the outbreak, it was not feasible to plan and conduct RCTs on drug therapies for SARS-CoV-17,9. Therefore, information on possibly effective (or proven ineffective) antivirals for a closely related infection (SARS-CoV-1) was not available for tracking the SARS-CoV-2 (Covid-19) pandemic.

In the early 2000s, it was proposed that the antimalarials chloroquine (CQ), hydroxychloroquine (HCQ) and artemisinin10-11, the anthelmintics ivermectin, nitazoxanide and niclosamide, and indomethacin (anti-inflammatory) could be useful compounds to treat a diversity of viral infections including the then emerging virus SARS-CoV-112-16. This hypothesis was based on results from cell culture-based assays showing that all these antiparasitic drugs exhibited potent antiviral activity against a variety of viruses. In the case of the antimalarial 4-aminoquinolines (CQ and HCQ) and indomethacin (anti-inflammatory) could be useful in treating a diversity of viral infections including the then emerging virus SARS-CoV-1. This hypothesis was based on results from cell culture-based assays showing that all these antiparasitic drugs exhibited potent antiviral activity against a variety of viruses. In the case of the antimalarial 4-aminoquinolines (CQ and HCQ) and indomethacin (anti-inflammatory) could be useful in treating a diversity of viral infections including the then emerging virus SARS-CoV-1.

For the widespread use of CQ and its hydroxylated derivative HCQ for Covid-19 is perhaps the best example of off label drug use that is irrational and is likely to cause more harm than benefits. The hypothesis that CQ/HCQ could be useful to treat SARS-CoV-1 and other viral infections was advanced by Savarino et al in 20037. When SARS-CoV-2 outbreak emerged in Wuhan in December 2019 January 2020, CQ/HCQ was one of several drugs potentially repurposable for Covid-19 that were selected for testing in clinical trials18. In parallel to clinical research, CQ and HCQ often in association with the macrolide antibiotic azithromycin (AZM) started to be extensively used to treat Covid-19 outside clinical trials as well. The off label prescription of CQ and HCQ often in association with the macrolide antibiotic azithromycin (AZM) started to be extensively used to treat Covid-19 outside clinical trials as well.
HCQ was apparently boosted by early reports of open, non-randomized and definitely underpowered studies suggesting that these 4-aminoquinolines plus AZM could be of benefit for severely-ill Covid-19 patients\textsuperscript{19}, although other preliminary (pilot) studies also showed no apparent benefit\textsuperscript{20}. Both CQ and HCQ are narrow MOS medicines causing a number of severe adverse events including ophthalmologic sequelae (retinopathy and loss of vision) and life-threatening heart disorders, such as QT interval prolongation, arrhythmias and cardiac arrest\textsuperscript{4,11,21}. Along this line, the US FDA has issued a warning (April 24\textsuperscript{th}, 2020) about serious adverse events, such as QT interval prolongation, ventricular tachycardia and ventricular fibrillation, and deaths, in patients with Covid-19 who had made use of CQ/HCQ, either alone or combined with AZM\textsuperscript{22}. A recent analysis of WHO's pharmacovigilance database reported signals of potentially lethal proarrhythmic effects leading to ventricular arrhythmias with AZM, and also with HCQ, and that HCQ plus AZM combination yielded an even stronger signal\textsuperscript{23}. Recently-published results of an observational retrospective study of hospitalized Covid-19 patients (New York, US) treated (off label) with HCQ, AZM, or both, compared with neither treatment found no association of treatment with HCQ or AZM or both with higher or lower risk of intubation or death\textsuperscript{24}. Notwithstanding suggesting that HCQ was not effective for Covid-19, this study suffers from limitations inherent to observational designs\textsuperscript{4,24}. It is of note that, whereas clinical trials yielded no convincing evidence that CQ/HCQ (alone or with AZM) is of benefit for Covid-19, this possibility cannot be ruled out because most studies have a poor design and methodological limitations\textsuperscript{4,11,18,24}. Large RCT trials with masking and concealment of allocation, therefore, remain needed for reaching a definitive conclusion about effectiveness of CQ or HCQ for Covid-19. The available evidence, however, is sufficient to strongly recommend not to prescribe and use CQ or HCQ outside clinical trials (i.e., off label).

**Antibiotics in severe Covid-19, what is the rationale?**

The rationale behind the widespread prescription of macrolide antibiotics such as AZM, clarithromycin and caramycin (mostly in China) for severe Covid-19 is obscure. Antibiotics are not active against viral respiratory infections and their use for non-bacterial infections is one of the most common examples of irrational use of medicines.

A recent analysis by the University of Oxford’s Centre for Evidence-Based Medicine (Nuffield Department of Primary Care Health Sciences) has reached the conclusion (April 28\textsuperscript{th}, 2020) that “there is insufficient evidence to recommend treatment with macrolides, alone or combined with hydroxychloroquine, for Covid-19 outside of research”\textsuperscript{25}. This conclusion is in line with NICE (UK National Institute for Health and Care Excellence) guidelines that explicitly recommend: ”not to offer an antibiotic for treatment or prevention of pneumonia if Covid-19 is likely to be the cause and symptoms are mild”\textsuperscript{26}. Unless physicians are uncertain about the viral (SARS-CoV-2) etiology of pneumonia, and/or cannot exclude the co-existence of viral and bacterial infections there is no apparent reason for prescribing antibiotics\textsuperscript{4,25,26}. Moreover, prescribers should take into account that AZM has been associated with QT interval prolongation and that it should be avoided, or used very cautiously, in patients with severe renal or liver failure\textsuperscript{25}.

**Compassionate use and emergency approval of remdesivir for Covid-19**

Compassionate use, also known as expanded access, is a possible way through which patients with an immediately life-threatening or serious medical condition have access to investigational drugs outside of clinical trials. Compassionate-use status requires approval by the regulatory agency, and it is generally obtained when no comparable or satisfactory alternative therapy options are available. In the pharmaceutical jargon, therefore, compassionate-use status differs from using drugs available on the market for unapproved indications, or off label use.

On May 1\textsuperscript{st} 2020, the U.S. Food and Drug Administration issued an emergency use authorization for the investigational drug remdesivir (REM) for treatment of hospitalized patients with severe Covid-19\textsuperscript{27,28}. This antiviral drug had been previously available only for patients enrolled in clinical trials and for those cleared to get the drug under expanded use and compassionate use programs.

REM, a pro-drug, is an adenosine nucleoside triphosphate analog developed by US company Gilead Sciences. The REM active metabolite inhibits viral RNA-dependent RNA polymerase and, by doing so, it stops viral replication\textsuperscript{29}. It was
originally developed for hepatitis C but clinical trial results for hepatitis were frustrating. REM was then repurposed for Ebola virus infections and clinically tested during West Africa Ebola outbreak in 2013-2016. The initially promising results were not further confirmed and REM proved to less effective than monoclonal antibodies in the treatment of Ebola28,29.

Since in vitro assays indicated that REM strongly inhibited replication of SARS-CoV-1 and MERS-CoV viruses in several cell lines30,31, it was clinically tested for Covid-19. Data from a cohort of hospitalized patients with Covid-19, who had received REM on a compassionate-use basis, suggested that 36 (68 %) patients treated with this antiviral compound showed clinical improvement32. A recent Chinese RCT (double-blinded and placebo-controlled) multicenter study found no evidence of overall clinical benefit of REM for Covid-19 patients with ARDS. The Chinese study, however, suggested that REM might have reduced time to clinical improvement among those patients treated earlier33. Afterwards, preliminary results (29 April 2020) of an ongoing US NIH-sponsored large (> 1000 participants) placebo-controlled RCT indicated that REM cut recovery time for hospitalized Covid-19 patients by four days, or 31% (i.e., about 11 days in RDV-treated against 15 days in the placebo group)34,35. Death rate in REM-treated (8%) and controls (11%) did not differ statistically. Although suggesting a relatively modest therapeutic benefit, these preliminary results are encouraging because REM was the only tested antiviral drug that was somewhat effective for Covid-19 in clinical trials. It is not, however, a pharmacological “silver bullet” against Covid-19.

Conclusions
In conclusion, the widespread off label and irrational use of drugs for Covid-19 is cause for deep concern and might be contributing to the overall morbidity and mortality that has been attributed primarily to the infection. Of particular concern are the use of macrolide antibiotics for a viral infection, and the use of antimalarial drugs CQ and HCQ for prophylaxis and treatment of mild Covid-19. There is already enough evidence from observational and clinical studies to show that risks of serious adverse events clearly outweigh hypothetical (still undemonstrated) clinical benefits when these antimalarials are used for preventive interventions and treatment of mild to moderate Covid-19. Therefore, prescription of CQ/HCQ for non-infected people or patients with asymptomatic or mild disease, be it off label or in clinical trials, is deemed unethical until proof to the contrary. Finally, the putative clinical benefits of remdesivir (REM) for Covid-19, or drug-induced reduction of time to clinical improvement by 31%, are encouraging, but still need to be confirmed by additional clinical trials.

Collaborations
FJR Paumgartten and ACAX Oliveira jointly conceived the main ideas discussed in the article and are equally responsible for its conclusions. FJR Paumgartten elaborated a first version of the manuscript that was critically reviewed by ACAX Oliveira. Both authors approved the final version to be published.
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