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Antiretroviral HIV drugs in COVID-19 research: promises and risks. An opinion piece.

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Abstract: The unprecedented global scale of COVID-19 globally has triggered a race to discover interventions to reduce associated morbidity and mortality and rapid release of research findings prior to any degree of critical review. As with previous novel infection outbreaks, antiretrovirals are just one drug class that has been held up as a potential strategy for prophylaxis and treatment with scant evidence and risk of harm. Here we summarise the evidence for antiretrovirals to treat COVID-19 and, as a drug that has also been studied in HIV, hydroxychloroquine, and flag some of the pitfalls of using therapies that have not been evaluated robustly.

Introduction

December 2019 in China saw the start of an outbreak of a novel coronavirus, SARS-CoV-2. The associated illness, COVID-19, emerged as a global pandemic with more almost6.5 million cases and exceeding380,000 deaths worldwide at the time of writing [1].

The speed at which COVID-19 has taken hold is mirrored by the speed at which related research has been undertaken, and published. Whilst the drivers for rapid assessment of possible interventions are obvious, we have seen widespread

promotion, and implementation, of poor quality findings and consequent harm that was potentially avoidable.

An outpouring of case reports and case series supporting the use of repurposed drugs for serious outbreaks is nothing new, as described for the Ebola epidemic in 2015/2016 [2].Drugs may yield benefit of course, though few have yet done so convincingly for COVID-19; they may also cause harm to individuals and to broader populations, for example, where surges in use create shortages for people with an evidence-based indication for the agent in question. Drug repurposing offers many advantages including bypassing earlier stages of drug development and opportunities to utilise off-patent medications [3]. Drug repurposing does not negate the need for some preclinical validation, yet despite this, phase 3 trials are underway for drugs that have not yet demonstrated any in vitro or animal model activity against SARS-CoV-2 [4-6].

The balance of research speed and research quality is delicate, and though rapid and open publication is laudable, we must include the impact of less rigorous, or even absent, peer review when appraising that evidence. Pre-publication access [7,8], rapid online and social media dissemination of conclusions (valid and otherwise), and the breakneck speed at which national and international bodies include new findings in their guidance, create an environment rife with myth propagation.

Here we highlight some of the proposed antiretroviral-based treatment and prevention strategies for COVID-19, where hysteria may have trumped objectivity.

Obviously, this is a rapidly evolving field so we direct readers to the 'living mapping and living systematic review' of COVID-19 studies accessible here: https://covid-nma.com/.

HIV Antiretrovirals for COVID-19 treatment

A recent systematic review summarised the efficacy of ARVs against three serious coronavirus-associated disease, COVID-19, severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [9]. The most studied ARV is the HIV protease inhibitor, ritonavir-boosted lopinavir (LPV/r) but, of the 10 published SARS and MERS 'trials', 6 were single case reports. The 14 COVID-19 trials comprised 3 single case reports, a case series (n=4), 8 retrospective cohorts (totalling 408 patients, many of whom received additional treatments including interferon, steroids, oseltamivir and ganciclovir);no clear benefits were reported.

To date there have been two published RCTs of LPV/r for COVID-19: one randomised 86 people with mild/moderate COVID-19 to LPV/r (n=34), umifenovir(n=35) or no antivirals (n=17) [10]. Numerically more individuals in the LPV/r arm experienced clinical deterioration and the authors concluded that neitherLPV/r nor umifenovir monotherapy provided clinical benefit over supportive care for hospitalised patients with mild/moderate COVID-19. A larger open-label RCT in 199 people hospitalised with severe COVID-19 demonstrated no benefit of LPV/r over standard of care [11] in terms of clinical improvement or viral clearance. However, a trend to better outcomes when LPV/r was started early (within 12 days of symptoms onset) was considered worthy of further study and there are many trials investigating LPV/r recruiting now or imminently. Of note, antivirals including LPV/r may offer more benefit when used in early [11] or less severe COVID-19 and immunomodulatory therapies, which we will not cover here, may be a better option for critically ill, hospitalized patients. Indeed, the lesson from the early reports and trials that have (understandably) focused on critically ill individuals may not necessarily be transferable to mild or moderate disease, nor to prevention strategies, and we will learn more about the best place for therapies over time.

LPV/r at least demonstrates in vitro activity against SARS-COV-2 [12], unlike some of the other ARVs under investigation. The antiretroviral effect of LPV/r is through its inhibition of HIV's aspartase protease enzyme and activity against SARS-CoV-2 is mediated through inhibition of its cysteine protease. However, the concentration of LPV/r required to inhibit SARS-CoV-2 is 4,000-8,000-fold higher that that required to inhibit HIV [13] so it perhaps entirely unsurprising that the dose effective to treat HIV may be ineffective for COVID-19. The penetration of drug into target sites is also crucial; the protein-adjusted IC90 values of lopinavir required to inhibit SARS-CoV-2 replication in plasma, pulmonary epithelial lining fluid and cerebrospinal fluid, respectively, 200-fold, 20-fold and 2000-fold higher than the concentrations measured in vivo in COVID-19 patients [13] arguably the results of the LPV/r COVID-19 trials so far were predictable. LPV/r dose will be limited by toxicity and the higher concentrations of LPV described in COVID-19, compared to those observed in people on LPV/r for ART, are already significantly higher, likely due to the impact of coronavirus on liver function [14].

Since the protease binding of LPV/r is likely less selective than more novel HIV protease inhibitors, one cannot assume all will have activity against non-HIV viruses. Following anecdotal reports of the efficacy of darunavir, another HIV protease inhibitor, its manufacturer Janssen released a statement confirming no in vitro activity against SARV-CoV-2 and no evidence of benefit in a small, single-arm study [15]. Despite this, on the ClinicalTrials.gov website alone, there are two trials investigating darunavir as a therapeutic option for COVID-19 (one recruiting and one

pending) [5,6]. The HIVprotease inhibitor atazanavir, listed as an experimental COVID-19 therapy on the Liverpool drug interaction website [16], does demonstrate in vitro activity [17] yet there are no trials listed on ClinicalTrials.gov investigating its potential for treatment or prevention of COVID-19.

Antiretrovirals for COVID-19 prevention

Effective prophylaxis against SARS-CoV-2, particularly for health care workers who are at higher risk of exposure, is desirable.Anecdotal reports of fewer cases of severe COVID-19 in Spain in HIV positive people on ART has prompted a large, randomised trial in Spain investigating the use oftenofovir-disoproxilfumarate/emtricitabone (TDF/FTC) and low dose hydroxychloroquine in Spanish health-care workers [4]. A New York study suggesting lower than expected numbers of people with HIV amongst COVID-19 hospitalisation has been interpreted by some as indicative a some degree of protection but the difference was small and without adjustment for confounders such as age, socio-economic status and social distancing practices, firm conclusions cannot be drawn [18].

TodateTDF has shown no efficacy, in vitro [19] or in vivo, against SARS-CoV-2. Molecular docking work suggests that TDF might be active due to its tight union to SARS-CoV-2 RdRp [20]. However docking studies, though useful to pre-screen large numbers of compounds, are not a replacement for in vitro activity assessment [21].Indeed, in silico evidence, of which docking is an example, sits lowest in the hierarchy of evidence topped by clinical evidence in COVID-19.

TDF appears to have immune modulatory properties; one in vitro study found that tenofovir altered inflammatory cytokine production with reductions in IL-8, IL-10 y MCP-1 and increases in IL-12; while this may result in enhance pathogen-directed immune responses it may also be detrimental to patients with heightened COVID-19-induced inflammatory profiles [22]. The observation that there have been numerous COVID-19 infections in HIV-patients on TDF or TAF [23,24] at least speaks against a complete protection conferred by these agents. Clearly, the trial results must be awaited to shed light on the usefulness of this PrEP strategy.

Hydroxychloroquine for COVID-19 treatment

Although chloroquine (CQ) and hydroxychloroquine (HCQ) are not antiretrovirals, they too were mooted as potential treatments for HIV, thanks to their immunomodulatory actions, with ‘promising’ pilot results [25] but no benefit (indeed a degree of harm) in the only randomised trial of sufficient duration [26].The

mechanism of any specific antiviral action of HCQ is unclear, but it is known to decrease endosome acidity, which might prevent release of virus into the cytoplasm [27].HCQ has also been trialed for other viral diseases after favourable in vitro results, but never shown to be efficacious, and even deleterious in the case ofChikungunya[28]. Unfortunately, a small,poorly designed study with non-clinical end-points [29], and media hysteria have led to HCQ, and azithromycin (the drug it was partnered with) to be the top two treatments used for COVID-19 in the 'COVID019 real time barometer' study of over 20,000 physicians in 30 countries, with 55% reporting HCQ use at the time of writing [30]. That HCQ and azithromycin were rapidly incorporated into some COVID-19 treatment guidelines [31] would be brave enough if this drug combination were harmless, but concerns of cardiovascular toxicity, including an increased risk of cardiovascular mortality in a preprint study [32], prompted the early termination of CQ + azithromycin trial in Brazil [33], and led the FDA to warn about conduction abnormalities associated with HCQ or CQ and advise that clinicians should prioritise clinical trials if considering the use of these agents to treat COVID-19 [34].Since then, a retrospective analysis of cardiovascular events associated with HCQ and azithromycin in the World Health OrganizationPharmacovigilance Database, undertaken prior to their use for COVID-19, described a significant association with prolonged QT interval and ventricular tachyarrythmia for each drug that was even greater when both were given in combination [35].

The potential for harm, both direct toxicity and indirect in terms of drug shortages for people with established indications for these drugs [36], combined with lack of evidence for benefit in large observational studies with *controls from the same population* [37] surely means CQ and HCQ should be used only within clinical trials? Of note the latest findings, in over 1000 people with predominantly mild COVID-19, from the same Marseilles group who first espoused the apparent benefits of HCQ + azithromycin [38] is single-arm with no comparator at all, even to historic outcomes.

At the time of writing a large retrospective multinational analysis concluding lack of benefit of CQ or HCQ, alone or with a macrolide, indeed decreased in-hospital survival and more ventricular arrhythmias [39]has been retracted due to serious methodological concerns [40].

HIV and COVID-19 may be very different conditions but the 'hypothesis>promising pilot>ineffective larger trial' cascade could have been anticipated and arguably, had better designed trials been implemented earlier and the results of a flawed study not promoted so widely by news outlets & political leaders, a potentially harmful treatment may not have gained such a firmfoothold in some guidelines [31]. HCQ was one of the interventions under study in the large Recovery trialtrial but,

following an interim data review,the independent Data Monitoring Committee recommended trial investigators review the unblinded data of the HCQ arm. Based on findings of no beneficial effect of HCQ in patients hospitalised with COVID-19 the HCQ arm was terminated immediately [41]. At the time of writing theSolidarity [42] andDiscoverytrials [43] trials, also investigating HCQ for COVID-19, were ongoing, the results of which are awaited eagerly.

Hydroxychloroquine for COVID-19 prevention

One published trial of HCQ post-exposure prophylaxis (PEP) showed no impact on subsequent SARS-CoV-2 acquisition in people reporting exposure, but more adverse events, compared to placebo [44] The excellent accompanying editorial flagged some important issues including the optimal timing of PEP (likely earlier than the average of 3 days post exposure in this trial) and the impact of these findings on the more than 200 trials investigating HCQ prophylaxis as of 1st June 2020 [56].

Conclusions

When dealing with a novel disease, we must not forget the hierarchy of evidence that should guide the interpretation of trials; in particular, drug modelling, as we have outlined, may be a poor predictor of clinical effectiveness.

Perhaps we should follow the advice from those websites that share pre-publication research: “preprints are preliminary reports of work that have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behavior and should not be reported in news media as established information” [7,8]. While the peer review process may be flawed [46], it offers a buffer that filters out some of the more ludicrous COVID-19 assertions, and, in our view, continues to play an important role.

Whilst a major pandemic understandably creates an urgent need for effective interventions, that does not mean the basic principles of clinical trials do not apply. Rapid assessment of in vitro drug activity, use of consistent consensus endpoints in case series and pilots, urgent modified peer review and prompt design of appropriately controlled trials will ultimately do a better service.

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