Drug Interactions: A Review of the Unseen Danger of Experimental COVID-19 Therapies

Running Title: Drug Interactions with Experimental COVID-19 Therapies

Catherine HODGE[1], Fiona MARRA[1,2], Catia MARZOLINI[1,3,4], Alison BOYLE[1,2], Sara GIBBONS[1], Marco SICCARDI[1], David BURGER[5], David BACK[1], Saye KHOO*[1,6].

[1]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK (Dr Catherine Hodge PhD, Ms Sara Gibbons MPhil, Dr Marco Siccardi PhD, Professor David Back PhD, Professor Saye Khoo FRCP).

[2]Department of Pharmacy, NHS Greater Glasgow and Clyde, Glasgow, UK. (Ms Fiona Marra MPharm, Ms Alison Boyle MPharm).

[3]Division of Infectious Diseases and Hospital Epidemiology, Departments of Medicine and Clinical Research, University Hospital of Basel, Basel, Switzerland (Professor Catia Marzolini, PharmD, PhD).

[4]University of Basel, Basel, Switzerland (Professor Catia Marzolini, PharmD, PhD).

[5]Radboud University Medical Centre, Nijmegen, the Netherlands (Professor David Burger, PharmD, PhD).

[6]Royal Liverpool University Hospital, Liverpool UK (Professor Saye Khoo FRCP).

Corresponding Author: Professor Saye Khoo khoo@liverpool.ac.uk

khoo@liverpool.ac.uk

Tel: 0151 794 5560

Fax: 0151 794 5656

Synopsis

As global health services respond to the coronavirus pandemic, many prescribers are turning to experimental drugs. This review aims to assess the risk of drug-drug interactions in the severely ill COVID-19 patient.

Experimental therapies were identified by searching Clinicaltrials.gov for COVID-19, 2019-nCoV, 2019 novel coronavirus, SARS-CoV-2. The last search was performed on 30th June 2020. Herbal medicines, blood-derived products, and *in vitro* studies were excluded. We identified comorbidities by searching PubMed for the MeSH terms “COVID-19”, “Comorbidity” and “Epidemiological Factors”. Potential drug-drug interactions were evaluated according to known pharmacokinetics, overlapping toxicities, and QT risk. Drug-drug interactions were graded GREEN and YELLOW: no clinically significant interaction; AMBER: caution; RED: serious risk.

A total of 2,378 records were retrieved from ClinicalTrials.gov, which yielded 249 drugs that met inclusion criteria. Thirteen primary compounds were screened against 512 comedications. A full database of these interactions is available at www.covid19-druginteractions.org.

Experimental therapies for COVID-19 present a risk of drug-drug interactions, with lopinavir/ritonavir (10% RED, 41% AMBER; mainly perpetrator of pharmacokinetic interactions but also risk of QT prolongation particularly when given with concomitant drugs that can prolong QT), chloroquine and hydroxychloroquine (both 7% RED and 27% AMBER, victim of some interactions due to metabolic profile but also perpetrator of QT prolongation) posing the greatest risk. With management, these risks can be mitigated. We have published a drug-drug interaction resource to facilitate medication review for the critically ill patient.

Synopsis 232 words

Text 2,233 words

Introduction

“Desperate times call for desperate remedies”. But what if experimental treatments for COVID-19 have a risk of causing harm in the very group of individuals most in need of such therapies? And what if the majority of these harms remain unrecognised? Drug-drug interactions involving two or more drugs have long been recognised as having the potential to cause harm. *In vitro* data, clinical studies in healthy volunteers, and patients (usually evaluating the magnitude of change in drug exposure in the blood stream), and expert interpretation are the main tools to point to the likelihood of a clinically significant drug-drug interaction. However, it is important to recognise that for patients with multiple morbidities who may have organ dysfunction there is a real risk of increased susceptibility to adverse effects and therefore the same drug-drug interaction may be more likely to result in harm. People requiring experimental COVID-19 therapies will often be clinically unstable, and the development of toxicities from drug-drug interactions may easily be misattributed.

Since 1998, the University of Liverpool has established a prescribing resource for managing drug-drug interactions in individuals receiving antiretroviral therapy to treat or prevent HIV.[1] The database contains a review of over 31,000 drug interactions,

synthesised from data systematically collected from medical and scientific literature, information from drug regulatory authorities or expert opinion. Mirroring the principles of GRADE,[2] drug interaction assessments are based on predetermined criteria, with critical evaluation of the quality of evidence. The Liverpool methodology is published[3] and has been used in the review process for national and international treatment guidelines [e.g. WHO[4], BHIVA[5]]. A similar drug-drug interaction resource was developed for hepatology[6] in 2011, and, together with Radboudumc, Nijmegen, the Netherlands, for cancer[7] in 2018. In March 2020, we published a drug-drug interaction (DDI) resource for experimental COVID therapies [www.covid19-druginteractions.org]. This review summarises the methodology and processes undertaken to establish the resource.

Why is this review needed?

Use of experimental COVID-19 therapies is rapidly evolving, and steadily increasing. Whilst initial use was in the sickest individuals (who are also most likely to have multiple comorbidities and polypharmacy), wider deployment as prophylaxis (e.g. to frontline health workers) is being considered.[8-10] Several of these experimental therapies have the propensity for drug-drug interactions which may cause clinical harms. A review of potential for interactions with drugs used for common comorbidities, or frequently used in the intensive care setting is urgently needed. Resulting knowledge will be collated, curated, and made readily available to support prescribers as an online resource on www.covid19-druginteractions.org.

Methods

Identifying Experimental Therapies

Experimental therapies for COVID-19 were identified by searching Clinicialtrials.gov using the following search terms: COVID-19, 2019-nCoV, 2019 novel coronavirus, and SARS-CoV-2. The last search was run on 30th June 2020. Experimental therapies were selected for inclusion as a primary drug for drug-drug interaction analysis on the following basis i) use for treatment or prevention of COVID-19, ii) use in randomised controlled trials which are multi-country, or multi-centre within one country, iii) widespread use outside of randomised trials if listed as options to consider from national bodies and specialist societies. Our evaluation panel comprising senior/principal pharmacists, academic pharmacologists, and an Infectious Diseases specialist (CM, FM, AB, DBa, DBu, SK) discussed potential inclusion for all candidates identified. We excluded compounds where only *in vitro* data were available, as well as blood-derived products such as serum from recovered patients, and herbal and traditional medicines.

Identifying comedications

We utilised a semi-systematic approach to selection of drug classes to include as comedications. Briefly, we first gathered evidence on the frequency and type of comorbidities reported in individuals with severe COVID-19 disease (using MeSH terms “COVID-19” [supplementary concept], “Comorbidity” and “Epidemiological Factors”). We then identified commonly used classes of compounds for these

comorbidities from UK treatment guidelines (e.g. NICE).[11] Within each therapeutic class, we then selected a list of drugs which were most frequently used across Europe and North America (we have previously made this selection based on country guidelines and the input of our International Editorial Board for HIV).

In addition to high-frequency comorbidities in severe COVID-19 patients, we also selected comedications likely to be used in disease management as well as those associated with high-consequence drug-drug interactions. These included drugs used in anaesthetics and intensive care, drugs used for treating symptoms or complications of COVID-19, and commonly used narrow therapeutic index drugs.

Evaluation of potential DDIs

Drug-drug interactions were identified as previously described by Seden *et al.*[3] Briefly, data on the clinical pharmacology of experimental therapies were extracted from approved product labels, published submissions to regulatory authorities in Europe, USA and Japan,[12-23] published case reports or studies and, where none of the above were available, from personal communication with the manufacturer. Propensity for a drug interaction was based on screening against known pathways for absorption, distribution, metabolism, and excretion of all drugs involved. This included potential for induction and inhibition of enzymes and transporters, interactions affecting bioavailability, protein binding and hepatic/renal excretion. Additional considerations included overlapping toxicities and potential interactions involving drugs with a narrow therapeutic index (e.g. anti-arrhythmics, anti-coagulants). A significantly increased risk in QT prolongation as a result of

combining two drugs with known risk of torsade de pointes,[24] or else a drug interaction leading to elevated concentrations of a drug with known risk of torsade or QT prolongation were separately coded.

Details of how drug interaction evaluations are made with regard to strength of recommendation and quality of evidence underpinning that recommendation have been previously published,[24] and were undertaken by our evaluation panel (see above).

For our COVID-19 recommendations we also took the following additional considerations into account when assessing drug interactions: i) the likely critical condition of any patient requiring these therapies, ii) the relatively short duration of coadministration, iii) the incremental risks to health workers from additional monitoring, iv) available, safer alternatives, and v) the option of pausing the comedication whilst COVID-19 therapy is administered.

Interactions were graded into four levels: GREEN: no clinical significant interaction expected; YELLOW: potential interaction likely of weak intensity, additional action/monitoring or dosage adjustment unlikely to be required; AMBER: potential interaction that may require close monitoring, alteration of drug dosage or timing of administration; RED: these drugs should not be coadministered. The decision to give or withhold drugs is always the responsibility of the prescriber. A pragmatic use of our drug-drug interaction recommendations is to regard GREEN and YELLOW flags as an indication that no clinically significant drug-drug interactions exist, while RED flags indicate significant cause for concern. An AMBER flag does not preclude coadministration (since drug-drug interactions can usually be managed or monitored)

but rather indicates the need to consider risks and benefits in that individual patient for whom treatment is considered.

The DDI grading of the antiretroviral drug lopinavir/ritonavir is mostly similar between the COVID-19 and the HIV websites with the exception of contraceptives or antidepressants devoid of QT risk. The DDI has been downgraded on the COVID-19 site given the short treatment course making monitoring or dose adjustment of these therapeutic agents unnecessary. Another DDI grading difference relates to strong enzyme inducers (e.g. carbamazepine, phenytoin, St John's Wort) which are contraindicated in the COVID-19 website with drugs metabolized by cytochrome P450, given the risk of treatment failure and difficulty to manage the DDI.

Results

Experimental COVID-19 Therapies

As a new and evolving pandemic, it is unsurprising that little consensus has been reached between national and international guidelines and specialist societies surrounding the use and choice of experimental therapies, and the number of potential therapeutic compounds is rapidly increasing.[25-33] Therefore, our range of experimental therapies will necessarily be expanded over the coming weeks and months.

As of 30th June 2020, a total of 2,378 clinical trials were retrieved from ClinicalTrials.gov. Two hundred and forty-nine drugs from ClinicalTrials.gov met our inclusion criteria. The drugs listed included 27 antivirals, 48 immunotherapy drugs,

five anti-malarial drugs, six glucocorticoids, and 163 miscellaneous compounds with different modes of action.

After selection for inclusion as a primary drug for drug-drug interaction analysis based on the criteria above, the following thirteen drugs were taken forward for analysis of drug-drug interactions: anakinra, baricitinib, chloroquine, favipiravir hydroxychloroquine, interferon β, lopinavir/ritonavir, nitazoxanide, remdesivir, ribavirin, ruxolitinib, sarilumab and tocilizumab. We did not include azithromycin in this review, as the reasons for giving this drug appeared to be in part for use in preventing bacterial superinfection rather than as a true adjuvant. Dexamethasone which has recently been shown in the RECOVERY trial to reduce 28-day mortality in patients hospitalised with COVID-19 receiving invasive mechanical ventilation or oxygen, will be added to the COVID drug interaction site soon.[34]

DDI Potential of COVID-19 Therapies

Table 1 summarises the key interaction information for each experimental therapy. A comprehensive breakdown of interaction potential and references are given in Supplemental Table 1.

One main source of risk is inhibition of CYP3A4 by lopinavir/ritonavir (perpetrator). Given that ritonavir inhibits irreversibly CYP3A4, the inhibitory effect may last up to five days after stopping/ritonavir.[35] On the other hand, lopinavir/ritonavir induces CYP1A2, CYP2C9, CYP2C19 and glucuronidation. Increase in CYP activity has been observed even after short course treatment with lopinavir/ritonavir.[36] The resolution of the inducing effect can take up to three weeks. Thus, monitoring of

narrow therapeutic index drugs is warranted during and after stopping treatment with lopinavir/ritonavir. COVID-19 drugs are also potential victims of a drug-drug interaction when coadministered with strong cytochrome P450 (CYP) inducers, as are chloroquine, hydroxychloroquine, and remdesivir. Drug-drug interactions with involvement of P-glycoprotein (P-gp) may also have clinical relevance as both chloroquine and hydroxychloroquine are moderate P-gp inhibitors.

In addition to drug-drug interactions that have a pharmacokinetic basis (i.e. a change in drug exposure), pharmacodynamic drug-drug interactions can also be relevant, in particular because chloroquine, hydroxychloroquine and lopinavir/ritonavir can cause QTc prolongation, and combined use with other drugs which prolong the QTc should be avoided.

The most frequent comorbidities in patients with severe COVID-19 are hypertension, cardiovascular, and cerebrovascular disease, diabetes, malignancy, gastrointestinal disease, and respiratory system disease.[37-40] By including the different classes of treatments for each of these morbidities, and selecting other medicines used to support critical care or manage symptoms of COVID-19 disease, we identified a total of 512 comedications to screen against experimental COVID-19 therapies.

A full database of our drug-drug interaction recommendations is posted on www.covid19-druginteractions.org. This website is continuously updated as more comedications and further therapies for COVID-19 are added. Interactions between experimental COVID-19 drugs and comedications, may be searched, but not interactions between comedications. The interaction checker focuses on PK

interactions, but also warns for overlapping toxicity. Possible physicochemical interactions occurring in an infusion or syringe have not been addressed. We have also published prescribing resources advising how to administer experimental therapies in the case of swallowing difficulties, and renal or hepatic insufficiency. Examples of recommendations with the anti-coagulant, anti-platelet, and fibrinolytic class; antidiabetic class; and antibiotic class can be seen in figure 1.

As of 30th June 2020, a total of 512 comedications were screened against the 13 primary compounds. The number (frequency) of RED and AMBER flags for experimental agents were as follows: anakinra 8 (2%) and 9 (2%), respectively, baricitinib 7 (1%) and 12 (2%), chloroquine 35 (7%) and 138 (27%), favipiravir 0 (0%) and 14 (3%), hydroxychloroquine 35 (7%) and 138 (27%), interferon beta 1 (0%) 13 (3%), lopinavir/ritonavir 52 (10%) and 209 (41%) nitazoxanide 0 (0%) and 4 (1%), remdesivir 9 (2%) and 0 (0%), ribavirin 2 (0%) and 16 (3%), ruxolitinib 7 (1%) and 66 (13%), sarilumab 7 (1%) and 9 (2%), and tocilizumab 7 (1%) and 9 (2%).

Discussion

Experimental COVID-19 therapies carry significant risk for drug-drug interactions. Amongst these treatments, drug interactions involving the HIV protease inhibitor lopinavir/ritonavir was most frequent, followed by chloroquine, hydroxychloroquine, and ruxolitinib, with anakinra, baricitinib, favipiravir, interferon β, nitazoxanide, ribavirin, remdesivir, sarilumab, and tocilizumab having low propensity for drug interactions.

Assessing the likelihood of a drug interaction is not always straightforward. Whilst the magnitude of change in exposure of either or both drugs can be quantified through a clinical study, the clinical relevance may vary according to the therapeutic index of the affected compound. Pharmacodynamic interactions (including overlapping toxicities) can be equally complex to judge, as in the case of drugs which cause QT prolongation, and which may also have exposures increased by a drug interaction. Regulatory authorities in the US and EU may consequently differ in evaluation of risk and recommendations, e.g. with HIV boosted protease inhibitors and quetiapine.[1]

A potential weakness in our evaluation process is that the majority of the drug-drug interactions have never been studied, resulting in judgements based on 'expert opinion'. We have therefore assigned the lowest quality of evidence to these evaluations. These evaluations will be continually reviewed as data emerge and will be updated on www.covid19-druginteractions.org. The rapidly evolving nature of the COVID-19 field makes keeping the list of drugs up-to-date more challenging than our HIV, hepatitis, and cancer websites. We run the ClinicalTrials.gov search regularly to

identify new experimental COVID-19 therapies and survey our users as to which drugs they would find useful. We constantly review evidence, refine our interactions, and remove medications that are no longer in use. We propose to further develop the accessibility of the database by developing an app which will allow interactions to be view offline.

Risk of drug interactions should not necessarily preclude use of experimental therapies for COVID-19 since they are often manageable. For example, in critically ill patients, consideration should be given to stopping all but essential medications. Often there will be a need to balance the risk of "theoretical" drug interactions against the benefit (often incompletely quantified) of new therapies. Safe management of drug interactions can only be carried out when prescribers are aware of their presence, underlining the importance of a full medicines reconciliation even for patients who present unwell and who are unable to give a detailed history. Our online resource is an attempt to increase recognition of harmful drug interactions and promote safe prescribing in critically unwell patients during the COVID-19 pandemic.

Sources of Funding

This work was supported by the University of Liverpool Centre of Excellence in Infectious Disease Research, British HIV Association, European AIDS Clinical Society, AbbVie, Gilead, Novartis, Merck Sharp & Dohme, and UKRI/NIHR.

Role of the Funding Sources

None of the sponsors had any input into any aspect of the writing of this manuscript.

Transparency Declaration

AB received grants and personal fees from Gilead and personal fees from AbbVie, outside the submitted work. CM received a research grant from Gilead and speaker honoraria from MSD and was also supported by the Adolf and Mary-Mil Foundation, outside the submitted work. DBa received grants from AbbVie, Novatis, BHIVA, and EACS during the conduct of the study and grants from Merck, Gilead and ViiV outside the submitted work. FM received grants and personal fees from AbbVie and Gilead and personal fees from Janssen, MSD, and ViiV, outside the submitted work. SK has received research grants and speakers' honoraria from ViiV Healthcare, Gilead Sciences and AbbVie outside the submitted work. All other authors: none to declare.

Authors' contributions

SK, DBa, FM, CM, AB, and DBu conceived of the study. CH and FM performed the literature review, FM, CM, AB, SK, and Dba interpreted the data, SG and CH complied figures, CH and SK wrote the manuscript, and all authors revised the manuscript.

References

1. Liverpool Drug Interactions. HIV Drug Interactions. 2020. https://www.hiv-druginteractions.org/

2. Guyatt G, Oxman AD, Akl EA *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64**: 383-94.

3. Seden K, Gibbons S, Marzolini C *et al*. Development of an evidence evaluation and synthesis system for drug-drug interactions, and its application to a systematic review of HIV and malaria co-infection. *PloS one* 2017; **12**: e0173509.

4. World Health Organisation. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. 2018. https://www.who.int/hiv/pub/guidelines/ARV2018update/en/

5. British HIV Association. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). 2016. https://www.bhiva.org/HIV-1-treatment-guidelines

6. Liverpool Drug Interactions. HEP Drug Interactions. 2020. https://www.hep-druginteractions.org/

7. Liverpool Drug Interactions. Cancer Drug Interactions. 2020. https://cancer-druginteractions.org/

8. Agrawal S, Goel AD, Gupta N. Emerging prophylaxis strategies against COVID-19. *Monaldi Arch Chest Dis* 2020; **90**. doi: 10.4081/monaldi.2020.1289.

9. Pre-Exposure Prophylaxis With Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic (PrEP_COVID). 2020. https://clinicaltrials.gov/ct2/show/NCT04331834

10. Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial) (PHYDRA). 2020. https://clinicaltrials.gov/ct2/show/NCT04318015
11. National Instittue for Health and Care Excellence. NICE guidelines. 2020. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines
12. AbbVie Ltd. Kaletra 200 mg/50 mg film-coated tablets Summary of Product Characteristics. 2019. https://www.medicines.org.uk/emc/product/221/smpc
13. AbbVie Ltd. Norvir 100 mg Film-coated Tablets Summary of Product Characteristics. 2019. https://www.medicines.org.uk/emc/product/510/smpc
14. Alliance Pharmaceuticals. Avloclor Tablets Summary of Product Characteristics. 2016. https://www.medicines.org.uk/emc/product/5490/smpc
15. Merck Sharp & Dohme Ltd. Rebetol 200 mg hard capsules Summary of Product Characteristics. 2019. https://www.medicines.org.uk/emc/product/3832/smpc
16. Concordia Pharmaceuticals Inc. Plaquenil Hydroxychloroquine Sulfate Tablets US Prescribing Information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf
17. Sanofi. Plaquenil 200 mg Film-coated Tablets Summary of Product Characteristics. 2014. https://www.medicines.org.uk/emc/product/1764
18. Roche. RoActemara 162 mg Solution for Injection in Pre-Filled Pen Summary of Product Characteristics. 2019. https://www.medicines.org.uk/emc/product/9086/smpc

19. Genentech Inc. Actemara, US Prescribing Information. 2019. https://www.gene.com/download/pdf/actemra_prescribing.pdf
20. Biogen Inc. Avonex US Prescribing Information. 2019. https://www.avonex.com/content/dam/commercial/avonex/pat/en_us/pdf/Avonex_US_Prescribing_Information.pdf
21. Biogen Idec Ltd. Avonex 30 µg/0.5 mL solution for injection Summary of Product Characteristics. 2019. https://www.medicines.org.uk/emc/product/886/smpc
22. Toyama Chemical Co. Ltd. Avigan, Japanese Product Label. 2014. https://www.pmda.go.jp/files/000210319.pdf
23. Gilead Sciences, Inc. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Remdesivir (GS-5734). 2020. https://www.fda.gov/media/137566/download
24. Woosley RL HC, Gallo T, Tate J, Woosley D and Romero KA,. QTdrugs List. 2020. https://www.crediblemeds.org/.
25. Darmon M, Bouadma L, Morawiec C *et al*. Recommandations d'experts portant sur la prise en charge en réanimation des patients en période d'épidémie à SARS-CoV2. 2020. https://www.srlf.org/wp-content/uploads/2020/03/Recommandations-dexperts-COVID-19-10-Mars-2020.pdf
26. China Law Translate. Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 7th Edition). 2020. https://www.chinalawtranslate.com/en/coronavirus-treatment-plan-7/
27. The National Institute for Health and the Environment of the Netherlands. Medicamenteuze behandelopties bij patiënten met COVID-19 (infecties met SARS-CoV-2). 2020. https://swab.nl/nl/covid-19.

418 28. The Spanish Ministry of Health. Tratamientos disponibles para el manejo de
419 la infección respiratoria por SARS-CoV-2. 2020. https://www.aemps.gob.es/la-
420 aemps/ultima-informacion-de-la-aemps-acerca-del-
421 covid%E2%80%9119/tratamientos-disponibles-para-el-manejo-de-la-infeccion-
422 respiratoria-por-sars-cov-2/?lang=en
423 29. World Health Organisation. WHO R&D Blueprint Informal consultation on
424 prioritization of candidate therapeutic agents for use in novel coronavirus 2019
425 infection. 2020. https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-
426 RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1
427 30. Michigan Medicine, University of Michigan. Inpatient Guidance for Treatment
428 of COVID-19 in Adults and Children. 2020.
429 http://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf
430 31. Farkas J. The Internet Book of Critical Care. 2020.
431 https://emcrit.org/ibcc/COVID19/#background_on_antiviral_therapy
432 32. World Health Organisation. Landscape analysis of therapeutics as 21st March
433 2020. 2020. https://www.who.int/blueprint/priority-diseases/key-
434 action/Table_of_therapeutics_Appendix_17022020.pdf (09/04/2020.
435 33. Cytel. Global Coronavirus COVID-19 Clinical Trial Tracker. 2020.
436 https://covid19-trials.com/
437 34. Horby P, Lim WS, Emberson J *et al*. Effect of Dexamethasone in Hospitalized
438 Patients with COVID-19: Preliminary Report. *medRxiv* 2020: 2020.06.22.20137273.
439 35. Stader F, Khoo S, Stoeckle M *et al*. Stopping lopinavir/ritonavir in COVID-19
440 patients: duration of the drug interacting effect. *J Antimicrob Chemother* 2020.
441 https://doi.org/10.1093/jac/dkaa253

36. Yeh RF, Gaver VE, Patterson KB *et al*. Lopinavir/ritonavir induces the hepatic activity of cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP1A2 but inhibits the hepatic and intestinal activity of CYP3A as measured by a phenotyping drug cocktail in healthy volunteers. *J Acquir Immune Defic Syndr* 2006; **42**: 52-60.

37. Chen N, Zhou M, Dong X *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-13.

38. Huang C, Wang Y, Li X *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506.

39. Yuan M, Yin W, Tao Z *et al*. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. *PloS one* 2020; **15**: e0230548.

40. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 382-6.

41. Swedish Orphan Biovitrum Ltd. Kineret 100 mg solution for injection in a pre-filled syringe Summary of Product Characteristics. 2020. https://www.medicines.org.uk/emc/product/559

42. Eli Lilly and Company Ltd. Olumiant 4 mg Film-coated Tablets Summary of Product Characteristics. 2019. https://www.medicines.org.uk/emc/product/7486

43. Du Y-X, Chen X-P. Favipiravir: pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. *Clin Pharmacol Ther* 2020. https://doi.org/10.1002/cpt.1844

44. Okuno H, Takasu M, Kano H *et al*. Depression of Drug-metabolizing Activity in the Human Liver by Interferon-β. *Hepatology* 1993; **17**: 65-9.

45. Romark. Alina US Prescribing Information. 2017. https://91012-559190-raikfcquaxqncofqfm.stackpathdns.com/wp-content/uploads/2017/08/prescribing-information.pdf

46. Fox LM, Saravolatz LD. Nitazoxanide: A New Thiazolide Antiparasitic Agent. *Clinical Infectious Diseases* 2005; **40**: 1173-80.

47. Novartis Pharmaceuticals UK Ltd. Jakavi 20 mg Tablets Summary of Product Characteristics. 2020. https://www.medicines.org.uk/emc/product/7784/smpc

48. Sanofi Genzyme. Kevzara 200 mg solution for injection in pre-filled syringe. 2020. https://www.medicines.org.uk/emc/product/8144

49. Llibre JM, Romeu J, Lopez E *et al*. Severe interaction between ritonavir and acenocoumarol. *Ann Pharmacother* 2002; **36**: 621-3.

50. Welzen ME, van den Berk GE, Hamers RL *et al*. Interaction between antiretroviral drugs and acenocoumarol. *Antivir Ther* 2011; **16**: 249-52.

51. Nisly SA, Stevens BN. Ritonavir- or cobicistat-boosted antiretroviral therapy and direct oral anticoagulants: A case for apixaban. *Int J STD AIDS* 2019; **30**: 718-22.

52. Marsousi N, Daali Y, Fontana P *et al*. Impact of Boosted Antiretroviral Therapy on the Pharmacokinetics and Efficacy of Clopidogrel and Prasugrel Active Metabolites. *Clin Pharmacokinet* 2018; **57**: 1347-54.

53. Itkonen MK, Tornio A, Lapatto-Reiniluoto O *et al*. Clopidogrel Increases Dasabuvir Exposure With or Without Ritonavir, and Ritonavir Inhibits the Bioactivation of Clopidogrel. *Clin Pharmacol Ther* 2019; **105**: 219-28.

54. Bravo I, Alvarez H, Marino A *et al*. Recurrent coronary disease in HIV-infected patients: role of drug-drug interactions. *British journal of clinical pharmacology* 2018; **84**: 1617-9.

55. Metzger NL, Momary KM. A patient with HIV and tuberculosis with diminished clopidogrel response. *Int J STD AIDS* 2014; **25**: 532-4.

56. Kumar P, Gordon LA, Brooks KM *et al*. Differential Influence of the Antiretroviral Pharmacokinetic Enhancers Ritonavir and Cobicistat on Intestinal P-Glycoprotein Transport and the Pharmacokinetic/Pharmacodynamic Disposition of Dabigatran. *Antimicrob Agents Chemother* 2017; **61**: e01201-17. doi: 10.1128/AAC.01201-17

57. Wire MB, McLean HB, Pendry C *et al*. Assessment of the pharmacokinetic interaction between eltrombopag and lopinavir-ritonavir in healthy adult subjects. *Antimicrob Agents Chemother* 2012; **56**: 2846-51.

58. Ancrenaz V, Deglon J, Samer C *et al*. Pharmacokinetic interaction between prasugrel and ritonavir in healthy volunteers. *Basic Clin Pharmacol Toxicol* 2013; **112**: 132-7.

59. Lakatos B, Stoeckle M, Elzi L *et al*. Gastrointestinal bleeding associated with rivaroxaban administration in a treated patient infected with human immunodeficiency virus. *Swiss Med Wkly* 2014; **144**: w13906.

60. Bonora S, Lanzafame M, D'Avolio A *et al*. Drug interactions between warfarin and efavirenz or lopinavir-ritonavir in clinical treatment. *Clin Infect Dis* 2008; **46**: 146-7.

61. Hughes CA, Freitas A, Miedzinski LJ. Interaction between lopinavir/ritonavir and warfarin. *Cmaj* 2007; **177**: 357-9.

62. Schulman S. Inhibition of warfarin activity by ribavirin. *Ann Pharmacother* 2002; **36**: 72-4.

63. Peterson D, Van Ermen A. Increased warfarin requirements in a patient with chronic hepatitis C infection receiving sofosbuvir and ribavirin. *Am J Health Syst Pharm* 2017; **74**: 888-92.

518 **Table 1. Drug Interaction Risk of Experimental COVID-19 Therapies.** BCRP
519 breast cancer resistance protein, CYP cytochrome P450, MATE multidrug and toxic
520 compound extrusion, OAT organic anion transporter, OATP organic anion
521 transporting polypeptide, P-gp P-glycoprotein, QTc corrected QT interval, TdP
522 torsades des pointes.
523

Experimental Therapy	Interaction Potential
Anakinra	No effect on CYP450 *per se* but anakinra reverses interleukin induced suppression of cytochromes (e.g. IL-1 elevation during inflammation). Currently no a priori adjustment of CYP substrates needed. No effect on QTc.[41]
Baricitinib	Partially metabolized by CYP3A4 and a substrate for OAT3, P-gp, BCRP, and MATE2-K. May inhibit OCT1. Strong inhibitors of inducers of CYP3A4 are unlikely to significantly alter baricitinib exposure. Transporters inhibitors, with the exception of OAT3 inhibitors, are unlikely to cause a significant effect on baricitinib exposure. No effect on QTc.[42]
Chloroquine	A moderate inhibitor of CYP2D6 and P-gp and caution may be required when coadministering comedications metabolized or transported by these pathways with a narrow therapeutic index. Shown to prolong QTc and is on the known risk of TdP list.[24]
Favipiravir	Metabolized mainly by aldehyde oxidase (AO). Based on metabolism and clearance, clinically significant drug interactions are minimal. It does inhibit CYP2C8 and caution is required in combination with comedications metabolized by this route and AO. The QT prolongation risk is considered to be low.[22, 43]
Hydroxychloroquine	A moderate inhibitor of CYP2D6 and P-gp and caution may be required when coadministering comedications metabolized or transported by these pathways with a narrow therapeutic index. Shown to prolong QTc and is on the known risk of TdP list.[24]
Interferon β	Drug interaction potential not fully evaluated. May reduce the activity of CYP enzymes but the clinical significance is likely to be small. No effect on QTc.[44]
Lopinavir/ritonavir	Inhibits CYP3A as well as some key transporters: P-gp, BCRP and OATP1B1. Many drug interactions of clinical importance due to **increased** exposure of comedications using these pathways. Also, potential to **decrease** exposure of some drugs metabolized by other CYP enzymes (CYP1A2, CYP2B6, CYP2C9, CYP2C19) and glucuronidation. Known to cause QT prolongation and is on the Possible Risk of TdP list.[24]
Nitazoxanide	Rapidly hydrolyzed to tizoxanide; *in vitro* studies indicate nitazoxanide is unlikely to inhibit cytochromes. Tizoxanide is highly protein-bound (>99%), so caution is indicated when give with other highly protein-bound drug with narrow therapeutic indices. No effect on QTc.[45, 46]

Remdesivir	A prodrug predominantly metabolized by hydrolase activity. Based on rapid distribution, metabolism and clearance after i.v. administration, the likelihood of clinically significant interactions is low. No effect on QTc.[23]
Ribavirin	There is minimal potential for CYP450 or transporter-based interactions. No effect on QTc.[15]
Ruxolitinib	Metabolized by CYP3A4 and CYP2C9, ruxolitinib has the potential to be a victim of drug-drug interactions perpetrated by inhibitors or inducers of these enzymes. Ruxolitinib may inhibit BCRP and P-gp and caution is indicating with coadministering with substrates of these transporters with narrow therapeutic indices.[47]
Sarilumab	No effect on CYP450 per se but sarilumab reverses interleukin induced suppression of cytochromes (e.g. IL-6 elevation during inflammation). Currently no a priori adjustment of CYP substrates needed. No effect on QTc.[48]
Tocilizumab	No effect on CYP450 per se but tocilizumab reverses interleukin induced suppression of cytochromes (e.g. IL-6 elevation during inflammation). Currently no a priori adjustment of CYP substrates needed. No effect on QTc.[18]

Figure 1. Predicted drug-drug interactions between anti-coagulant, anti-platelet, and fibrinolytic drug therapies and antiviral experimental COVID-19 drugs or anti-inflammatory experimental COVID-19 drugs. GREEN = no clinically relevant interaction, YELLOW = potential weak interaction, AMBER = potential interaction which may require dose modification or monitoring, RED = do not coadminister. Arrows indicate the potential for increased, decreased or unchanged exposure of the comedication (solid arrows) or experimental therapy (open arrows). ♥ = these drugs have been identified by www.CredibleMeds.org as having a risk of QT prolongation and/or torsades des pointes. The risk may be concentration- or dose-related and/or additive if two or more such drugs are combined. Note, please check product labels for any additional cardiac warnings. Quality of evidence for PK interactions were assessed according to the principles of GRADE. Grades are High (1), Moderate (2), Low (3) and Very Low (4) as previously described by Seden *et al*.[3]

CLQ chloroquine, FAVI favipiravir, HCLQ hydroxychloroquine, INF β interferon, LPV/r lopinavir/ritonavir, NTZ nitazoxanide, RDV remdesivir, RBV ribavirin, TCZ tocilizumab.

Anti-viral experimental COVID-19 drugs

	CLQ	FAVI	HCLQ	IFN-β	LPV/r	NTZ	RDV	RBV
Acenocoumarol	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↓ [4][49, 50]	↑ [4]	↔ [4]	↔ [4]
Apixaban	↑ [4]	↔ [4]	↑ [4]	↔ [4]	↑ [3][51]	↔ [4]	↔ [4]	↔ [4]
Argatroban	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Aspirin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Betrixaban	↑ ♥ [4]	↔ [4]	↑ ♥ [4]	↔ [4]	↑ ♥ [4]	↔ [4]	↔ [4]	↔ [4]
Clopidogrel	⇑ [4]	↔ [4]	⇑ [4]	↔ [4]	↓ [3][52-55]	↔ [4]	↔ [4]	↔ [4]
Dabigatran	↑ [4]	↔ [4]	↑ [4]	↔ [4]	↔ or ↓ [2][56]	↔ [4]	↔ [4]	↔ [4]
Dalteparin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Dipyridamole	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↓ [4]	↔ [4]	↔ [4]	↔ [4]
Edoxaban	↑ [4]	↔ [4]	↑ [4]	↔ [4]	↑ [4]	↔ [4]	↔ [4]	↔ [4]
Eltrombopag	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↓ 17% [3][57]	↔ [4]	↔ [4]	↔ [4]
Enoxaparin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Fondaparinux	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Heparin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Phenprocoumon	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↑↓ [4]	↑ [4]	↔ [4]	↔ [4]
Prasugrel	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4][54, 58]	↔ [4]	↔ [4]	↔ [4]
Rivaroxaban	↑ [4]	↔ [4]	↑ [4]	↔ [4]	↑ [4][59]	↔ [4]	↔ [4]	↔ [4]
Streptokinase	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Ticagrelor	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↑ [4]	↔ [4]	↔ [4]	↔ [4]
Tinzaparin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Warfarin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↓ [4][36, 60, 61]	↑ [4]	↔ [4]	↓ [4][62, 63]

Anti-inflammatory experimental COVID-19 drugs.

	Anakinra	Baricitinib	Ruxolitinib	Sarilumab	Tocilizumab
Acenocoumarol	↓ [4]	↔ [4]	↔ [4]	↓ [4]	↓ [4]
Apixaban	↓ [4]	↔ [4]	↔ [4]	↓ [4]	↓ [4]
Argatroban	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Aspirin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Betrixaban	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Clopidogrel	↓ [4]	↔ [4]	↔ [4]	↓ [4]	↓ [4]
Dabigatran	↔ [4]	↔ [4]	↑ [4]	↔ [4]	↔ [4]
Dalteparin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Dipyridamole	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Edoxaban	↔ [4]	↔ [4]	↑ [4]	↔ [4]	↔ [4]
Eltrombopag	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Enoxaparin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Fondaparinux	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Heparin	↔ [4]	↔ [4]	↔ [4]	↔ [4]	↔ [4]
Phenprocoumon	↓ [4]	↔ [4]	↔ [4]	↓ [4]	↓ [4]
Prasugrel	↓ [4]	↔ [4]	↔ [4]	↓ [4]	↓ [4]

Rivaroxaban	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4
Streptokinase	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Ticagrelor	↓ 4	↔ 4	⇑ 4	↓ 4	↓ 4
Tinzaparin	↔ 4	↔ 4	↔ 4	↔ 4	↔ 4
Warfarin	↓ 4	↔ 4	↔ 4	↓ 4	↓ 4

548

549