1 Brief Communication

2 Tocilizumab, Remdesivir, Favipiravir and Dexamethasone Repurposed for COVID-19:
3 The Risk Benefit Ratio at a Glance.

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9 Abstract:

10 In this manuscript, we discuss the expectations versus the real word results of four
11 repurposed COVID-19 drugs; tocilizumab, remdesivir, favipiravir and dexamethasone
12 from a pharmacovigilant point of view. We recommend considering a personalized risk
13 benefit ratio before a decision is made using any of these drugs. We suggest that though
14 the results of phase III clinical trials have been less than expected; tocilizumab might have
15 a potential to treat some critical cases of COVID-19. On the contrary, remdesivir, though
16 its FDA approval, together with favipiravir are least likely to benefit COVID-19 patients.
17 Finally, we recommend that the RECOVERY dexamethasone should only be further
18 investigated and to be considered only for critical cases of hospitalized COVID-19 patients
19 and we urge physicians in the developing countries to avoid and stop using it in mild-
20 moderate COVID-19 cases.

21 Keywords: COVID-19, Tocilizumab, Remdesivir, Favipiravir, Dexamethasone

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Introduction

Drug repurposing is considered as a rapid strategy for COVID-19 drug discovery [1] and many drugs have been tried and we would like to discuss the outcomes of four of them from a pharmacovigilant point of view.

Tocilizumab

Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody which is FDA approved to manage diseases other than COVID-19, was initially shown to shorten the median time to COVID-19 clinical improvement [2] and it also showed non-statistically significant lower mortality results in patients with severe to critical COVID-19[3]. Interestingly, though several studies have showed tocilizumab to significantly improve the clinical outcomes in severe cases of COVID-19 pneumonia [4-8], yet phase III double blind, placebo-controlled clinical trials have recently declared that tocilizumab did not improve the clinical status in patients with COVID-19 associated pneumonia, and didn't prevent intubation or death in moderately ill hospitalized patients with Covid-19; though potential benefit/harm could not be entirely excluded [9, 10].

Remdesivir

In comparison, some preliminary results anticipated the success of remdesivir, a nucleotide analogue prodrug, to treat COVID-19 [11, 12]. However, other studies have suggested that remdesivir is unexpected to possess significant clinical benefits based on its released results and safety profile [13-17]. Moreover, even an open label phase III trial showed no significant difference between a 10-day remdesivir course (median length of treatment, 6 days) compared with standard care while claiming a benefit for the 5-day course[18], yet remdesivir continues to be marketed globally and priced at 3,120 USD for the typical patient with private insurance in USA. Moreover, a black market has developed in India [19] and perhaps other developing countries. Notably, the WHO Solidarity Trial Consortium has recently announced the results of randomized trials performed in 405 hospitals located in 30 countries where 2750 patients received remdesivir and it was shown to have little or no effect on hospitalized COVID-19 patients, as indicated by overall mortality, initiation of ventilation and duration of hospital stay[20]. However, despite all

criticism and warnings, the FDA has approved remdesivir to be used for COVID-19[21] after an unprecedented consultation of a diverse group of experts outside the FDA [22]. Fortunately, the WHO has subsequently recommended against its use in COVID-19 regardless of disease severity[23]. Unfortunately, many countries all over the world continue to use it, including the author's; Egypt.

Favipiravir

Similarly, favipiravir (T-705); a nucleoside analogue that acts as a mutagen with a distinct bias to induce transitions in influenza virus RNAs by incorporating into both positive and negative stranded RNA inducing lethal mutagenesis of influenza virus that might reason for the difficulty in isolating favipiravir-resistant influenza viruses in laboratories or to evolve resistance against clinically[24, 25]. Favipriavir was approved in Japan in 2014 as a treatment for novel or re-emerging influenza viruses, yet its local approval was heavily restricted as its clinical use needed governmental authorization, which was only permitted for potentially lethal diseases and a similar cautious attitude was also adopted in China[25]. Furthermore, the Japanese drug safety bureau, possibly due to limited safety data, recommended favipiravir to be avoided where alternative drugs could be used and adverse effects such as hyperuricemia and teratogenicity/embryotoxicity were reported from favipiravir human and four different animal species studies, respectively and QTc prolongation potential was recommended to be further investigated [25, 26]. Hepatitis was also reported in 4 out of 63 COVID-19 patients who received favipiravir[27]. Notably, >85% of favipiravir completed clinical trials in registries or in published papers are unavailable which led to failure of conducting meta-analysis to generate conclusive evidence to support recommendation of favipiravir use in COVID-19 or know about its safety and efficacy profile [28], and a Japanese study showed no significant efficacy of favipiravir in SARS CoV-2 elimination and might has also revealed a cautious attitude of a Japanese health authority, Fujita Health University, which conducted the study as out of 47 facilities across Japan that took part; only 88 patients were enrolled and completed the study[29].

Dexamethasone

On the other side, the randomized open-label evaluation of COVID-19 therapy (RECOVERY) collaborative group showed a small mortality benefit to dexamethasone therapy among patients who were receiving invasive mechanical ventilation; 482/2104 patients (22.9%) in the dexamethasone group and 1110/4321 patients (25.7%) in the usual care group [30], yet several concerns regarding the study design, the data and its interpretation were raised[31, 32]. Moreover, the RECOVERY results showing a potential benefit of dexamethasone in SRAS CoV-2 complicated patients contradicts the conclusive outcomes of several previous studies showing evidence of a possible harmful effect when corticosteroids were used to manage SARS, MERS and influenza pneumonia patients [33-35]. On the same day the results of the RECOVERY study were published; July 17, 2020, we have submitted a letter to New England Journal of Medicine (NEJM, ID 20-25534) representing some concerns about this study. Four emails were sent to NEJM, once every month wondering about the unprecedented delay in publishing a short letter and the response was that the editor has been contacted on multiple occasions but he/she is busy because of the large number of COVID-19 related submissions and eventually it was withdrawn on the next day we have requested; November 30, 2020. Our concerns were a wonder about the reason that the RECOVERY group chose 2:1 randomization though dexamethasone is a cheap drug and a 1:1 randomization maximizes the statistical power to detect the same difference[36, 37]. Further, in Table 2, the death ratio included in secondary outcomes was similar in both groups; 21.7% in dexamethasone group and 22.7% in the usual care group, and we encouraged the authors to explain the potential reasons and to provide a more clarification to the included numbers e.g. the number of living patients who have not been discharged from hospital within 28 days doesn't match the subsequent subgroups. Furthermore, a second randomization of 4.5% of patients, complaining of hypoxia and inflammation, performed in the dexamethasone arm to compare the addition of tocilizumab on top of dexamethasone has not been excluded in interpretation of the small mortality benefit assumed to be attributed only to dexamethasone. Unfortunately, We have encountered many Egyptian physicians who have not read the RECOVERY results or the clinical guidelines to use dexamethasone in severe-critical hospitalized COVID-19 patients and prescribed it to mild-moderate COVID-19 private patients leading sometimes to

catastrophic complications and we suggest that this medical malpractice might have also occurred in other developing countries.

Importantly, we would like to restate our previous agreement with the clinical recommendation against the routine use of glucocorticoids in the management of COVID-19 especially after important concerns were raised regarding the interpretation of data as well as the limitations of several studies showing potential benefit of glucocorticoids in COVID-19[38]. Moreover, a potential benefit from the RECOVERY dexamethasone as well as to assess its optimal dose and duration of administration in selected COVID-19 critical cases should be confirmed, or denied, by other well designed and interpreted large randomized and controlled clinical trials [39-41].

Conclusion

In conclusion, we would like to join the WHO in its recommendation against the use of remdesivir for COVID-19. Furthermore, a teratogenic, embryotoxic favipiravir should undergo extensive studies to assess its potential gene mutation and/or chromosomal damage effects as well as to evaluate its long-term potential human carcinogenicity before allowing wide scale global trialing. On the other hand, we would like to recommend considering tocilizumab and dexamethasone for selected critical cases of COVID-19 until the results of other much needed large clinical trials fill some important missing gaps as regards to their COVID-19 efficacy/inefficacy.

Conflict of interests:

None

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References:

- [1] Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK. Drug repurposing approach to fight COVID-19. Pharmacological Reports 2020.
- [2] Kewan T, Covut F, Al-Jaghbeer MJ, Rose L, Gopalakrishna KV, Akbik B. Tocilizumab for treatment of patients with severe COVID-19: A retrospective cohort study. EClinicalMedicine 2020;24:100418.

- 146 [3] Rojas-Marte G, Khalid M, Mukhtar O, Hashmi AT, Waheed MA, Ehrlich S, et al. Outcomes
147 in patients with severe COVID-19 disease treated with tocilizumab: a case-controlled
148 study. QJM 2020;113(8):546-50.
- 149 [4] Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the
150 treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute
151 respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmunity
152 Reviews 2020;19(7):102568.
- 153 [5] Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for
154 the treatment of severe coronavirus disease 2019. Journal of medical virology
155 2020;10.1002/jmv.25964.
- 156 [6] Klopfenstein T, Zayet S, Lohse A, Selles P, Zahra H, Kadiane-Oussou NdJ, et al. Impact of
157 tocilizumab on mortality and/or invasive mechanical ventilation requirement in a cohort
158 of 206 COVID-19 patients. International Journal of Infectious Diseases 2020;99:491-5.
- 159 [7] Samaee H, Mohsenzadegan M, Ala S, Maroufi SS, Moradimajid P. Tocilizumab for
160 treatment patients with COVID-19: Recommended medication for novel disease.
161 International Immunopharmacology 2020;89:107018.
- 162 [8] Keske Ş, Tekin S, Sait B, İrkören P, Kapmaz M, Çimen C, et al. Appropriate use of
163 tocilizumab in COVID-19 infection. International Journal of Infectious Diseases
164 2020;99:338-43.
- 165 [9] Roche. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra
166 in hospitalised patients with severe COVID-19 associated pneumonia,
167 <https://www.roche.com/investors/updates/inv-update-2020-07-29.htm>; 2020, July 29.
- 168 [10] Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al.
169 Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. New England Journal of
170 Medicine 2020.
- 171 [11] Ko W-C, Rolain J-M, Lee N-Y, Chen P-L, Huang C-T, Lee P-I, et al. Arguments in favour of
172 remdesivir for treating SARS-CoV-2 infections. International journal of antimicrobial
173 agents 2020;55(4):105933-.
- 174 [12] Lamb YN. Remdesivir: First Approval. Drugs 2020;80(13):1355-63.
- 175 [13] Marcolino VA, Pimentel TC, Barão CE. What to expect from different drugs used in the
176 treatment of COVID-19: A study on applications and in vivo and in vitro results.
177 European Journal of Pharmacology 2020;887:173467.
- 178 [14] Kelleni M. Rapid Response: Remdesivir is least likely to be effective for safe treatment of
179 COVID-19: A pharmacovigilant point of view. BMJ 2020, May 29;369:m2097rr.
- 180 [15] Kelleni MT. Remdesivir-Gate for COVID-19. Acta Scientific Gastrointestinal Disorders
181 2020, July 01;3(8):01.
- 182 [16] Carothers C, Birrer K, Vo M. Acetylcysteine for the Treatment of Suspected Remdesivir-
183 Associated Acute Liver Failure in COVID-19: A Case Series. Pharmacotherapy: The
184 Journal of Human Pharmacology and Drug Therapy 2020;n/a(n/a).
- 185 [17] Remdesivir-related acute kidney injury in patients with COVID-19. Reactions Weekly
186 2020;1826(1):5-.
- 187 [18] Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A,
188 et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With
189 Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020;324(11):1048-57.
- 190 [19] The Economic Times (Krishna Kumar). Remdesivir sold at high prices in Mumbai black
191 market; some doctors suggest cheaper alternatives

- https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/remdesivir-sold-at-high-prices-in-mumbai-black-market-some-doctors-suggest-cheaper-alternatives/articleshow/76861773.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst; 2020, July 08.
- [20] Pan H, Peto R, Abdool Karim Q, Alejandria M, Henao Restrepo AM, Hernandez Garcia C, et al. Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results. medRxiv 2020:2020.10.15.20209817.
- [21] FDA. FDA Approves First Treatment for COVID-19, <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19>; 2020, October 22.
- [22] Jon Cohen KK. The ‘very, very bad look’ of remdesivir, the first FDA-approved COVID-19 drug. *Science*. 2020, October 28.
- [23] WHO. WHO recommends against the use of remdesivir in COVID-19 patients. 2020, November 20.
- [24] Goldhill DH, Langat P, Xie H, Galiano M, Miah S, Kellam P, et al. Determining the Mutation Bias of Favipiravir in Influenza Virus Using Next-Generation Sequencing. *Journal of virology* 2019;93(2):e01217-18.
- [25] Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacology & Therapeutics* 2020;209:107512.
- [26] Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir - a potential treatment in the COVID-19 pandemic? *J Virus Erad* 2020;6(2):45-51.
- [27] Rattanaumpawan P, Jirajariyavej S, Lerdlamyong K, Palavutitotai N, Saiyarin J. Real-world Experience with Favipiravir for Treatment of COVID-19 in Thailand: Results from a Multi-center Observational Study. medRxiv 2020:2020.06.24.20133249.
- [28] Khambholja K, Asudani D. Potential repurposing of Favipiravir in COVID-19 outbreak based on current evidence. *Travel medicine and infectious disease* 2020;35:101710-.
- [29] The Mainichi. Avigan study fails to demonstrate benefit in COVID-19 treatment, <https://mainichi.jp/english/articles/20200710/p2g/00m/0fe/107000c>; 2020, July 10.
- [30] Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *New England Journal of Medicine* 2020.
- [31] Waterer GW, Rello J. Steroids and COVID-19: We Need a Precision Approach, Not One Size Fits All. *Infect Dis Ther* 2020;9(4):701-5.
- [32] Lanthier L, Mayette M, Huard G, Plourde ME, Cauchon M. [In patients hospitalized for COVID-19, does dexamethasone reduce 28-days mortality compared to standard treatment?]. *Rev Med Interne* 2020;41(11):790-1.
- [33] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet* 2020;395(10223):473-5.
- [34] Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *American Journal of Respiratory and Critical Care Medicine* 2017;197(6):757-67.
- [35] Ni Y-N, Chen G, Sun J, Liang B-M, Liang Z-A. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care* 2019;23(1):99-.
- [36] Torgerson D, Campbell M. Unequal randomisation can improve the economic efficiency of clinical trials. *J Health Serv Res Policy* 1997;2(2):81-5.
- [37] Hey SP, Kimmelman J. The questionable use of unequal allocation in confirmatory trials. *Neurology* 2014;82(1):77-9.

239 [38] Kelleni MT. Early use of non-steroidal anti-inflammatory drugs in COVID-19 might
240 reverse pathogenesis, prevent complications and improve clinical outcomes.
241 Biomedicine & Pharmacotherapy 2021;133:110982-.

242 [39] Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV
243 pneumonia. The Lancet 2020;395(10225):683-4.

244 [40] Singh AK, Majumdar S, Singh R, Misra A. Role of corticosteroid in the management of
245 COVID-19: A systemic review and a Clinician's perspective. Diabetes & metabolic
246 syndrome 2020;14(5):971-8.

247 [41] Ahmed MH, Hassan A. Dexamethasone for the Treatment of Coronavirus Disease
248 (COVID-19): a Review. SN Compr Clin Med 2020:1-10.

249