

Nitazoxanide/Azithromycin combination for COVID-19: A suggested new protocol for early management.

Mina T. Kelleni, MD, PhD

Pharmacology department, College of medicine, Minia University, Egypt.

Pharmacology department, College of pharmacy, Jouf University, KSA.

Mobile: +966560407874

E-mails: drthabetpharm@yahoo.com, mina.kelleni@mu.edu.eg, mtkelleni@ju.edu.sa

Abstract

Azithromycin has been shown to have a clinical efficacy against severe acute respiratory syndrome coronavirus 2; ivermectin has also demonstrated a remarkable experimental efficacy with a potential to be used for Coronavirus disease 2019. Further, BCG vaccination is being considered for clinical trials aiming to test its potential for lowering COVID-19 morbidity and mortality. This concept paper illustrates some structural and functional relationships that may gather these drugs. Further, the author, basing on a combined pathophysiological and pharmacological approach, recommends the FDA-approved antidiarrhea drug; nitazoxanide, which has been previously suggested but unfortunately very much ignored, to be tested in combination with azithromycin for their potential activity against SARS CoV-2; recommending their administration as early during the clinical course of COVID-19 as possible. Finally, relying on the same represented concept, the author suggests more trials for interferons to be tested against SARS CoV-2, especially in severe and critical COVID-19 cases.

Keywords: SARS CoV-2, COVID-19, Nitazoxanide, Azithromycin, Interferons.

Ivermectin (Fig. 1) is a broad spectrum macrolide endectocide macrocyclic lactone produced by *Streptomyces avermitilis* that is widely used for treatment of pediculosis, scabies, onchocerciasis and lymphatic filariasis¹⁻³. It's also been shown to possess an invitro antiviral activity against influenza A, dengue and Venezuelan equine encephalitis viruses. Importantly, Ivermectin has been recently proved, in an invitro experiment, to produce approximately 5000-fold reduction in the RNA of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) causing Coronavirus disease 2019 (COVID-19) at 48 h of its single addition⁴. Interestingly, ivermectin therapy has been shown to reverse onchocerciasis-associated immunosuppression through sustained production of IFN- γ in amicrofilaridermic individuals⁵, to be also noted that it was previously shown that recombinant human IFN- γ had a particular effect on the incidence of herpes simplex, and cytomegalovirus infections opportunistic infections in advanced HIV disease⁶. Similarly, another macrolide macrocyclic lactone antibiotic; azithromycin (Fig. 2) has been reported to have an invitro antiviral activity against Zika and Ebola viruses, it has also significantly decreased rhinovirus-16 viral load in bronchial epithelial cells inducing the expression of type I and III interferons in cells of donors suffering from chronic obstructive pulmonary disease, 24 h post infection^{7 8}. Noteworthy, only azithromycin which is a synthetic derivative of erythromycin; the prototype of macrolides antibiotics first isolated from the soil bacterium *Streptomyces erythraeus*, but not erythromycin or telithromycin, has been shown to significantly increase rhinovirus 1B- and rhinovirus 16-induced interferons and interferon-stimulated gene mRNA expression as well as protein production leading to a significant reduction of rhinovirus replication and release in bronchial epithelial cells⁹. This differential peculiarity associated with azithromycin should be properly investigated as regards to its structure activity relationship. Further, it's also been recently reported that when azithromycin was added to hydroxychloroquine, the efficiency of SARS CoV-2 elimination was significantly improved leading to a significant more rapid virologic cure as evident by a negative nasopharyngeal PCR, and healing in COVID-19 patients⁷. Surprisingly, a recent study has suggested an association of an increased overall mortality that was identified in patients treated with hydroxychloroquine without azithromycin as compared to the standard care alone¹⁰. The author wonders if the previously reported beneficial effects might be more appropriately attributed to azithromycin alone? Taken

together, ivermectin and azithromycin share a potential structural similarity and more importantly both drugs are potentiating the interferons' immune response which is essential to combat viral infections. Noteworthy, BCG vaccination which is currently being considered for clinical trials to test its potential against COVID-19, was previously shown when given once a month for 3 consecutive months to produce a significant reduction on the prevalence of adult upper respiratory tract infections in the elderly, at least partially through its induced significant increase of IFN- γ level as compared to the placebo group¹¹. Taken together, the author agrees that ivermectin deserves its enrollment for clinical trials to explore its potential for COVID-19 treatment and suggests that BCG vaccination might not be the proper fast response we need. On the other hand, more research for other macrolides to assess their potential antiviral effect might be fertile, not only for this COVID-19 pandemic but also afterwards. Similarly, the author recommends more COVID-19 clinical trials for recombinant human IFN- γ , interferon alfa-1, recombinant interferon beta and while a preliminary version of this manuscript was being submitted on the 8th of April, 2020 elsewhere; other colleagues have also been pointing out, both clinically and theoretically, the significance of interferons as potential drug candidates for COVID-19¹²⁻¹⁴. Further, it might also be beneficial to test the related possibility that SARS CoV-2 may produce interferon antagonist activities similar to the effect Middle East respiratory syndrome coronavirus (MERS-CoV) has previously exhibited^{15 16}.

Most importantly, the author basing on the same concept, would like to recommend the start of clinical trials for the widely available FDA-approved, for both adults and immunocompetent children, antidiarrhea drug; nitazoxanide,¹⁷ in combination with azithromycin¹⁸, soonest. Nitazoxanide (Fig. 3), is an orally active nitrothiazolyl-salicylamide broad-spectrum antiparasitic and antiviral prodrug that is converted rapidly to the active metabolites tizoxanide and tizoxanide conjugates and unlike metronidazole, these metabolites appear to be safer and free of mutagenic effects¹⁹. Similarly, nitazoxanide is also known to potentiate interferon alfa and interferon beta production and it has been previously shown to exhibit an in vitro activity against MERS-CoV and other coronaviruses²⁰. Moreover, when nitazoxanide was given as 600 mg twice daily for 5 days, it's proved to reduce of the duration of symptoms in patients with acute uncomplicated influenza with minor adverse effects²¹ and this dose regimen might be reasonably

considered to be used combined with azithromycin in a suggested new COVID-19 protocol aiming to test their integrated potential to decrease SARS CoV-2 morbidity and mortality. Noteworthy, the author would like to stress that on the 9th of March, 2020, nitazoxanide was previously suggested, among other drugs, by French colleagues to be evaluated for its potential against SARS CoV-2; unfortunately, their recommendation wasn't popular and it has been practically very much ignored²². Similarly, the author has recently found another research, though also unpopular and similarly ignored, that has been published on the 15th of March, 2020 to recommend nitazoxanide to be used with hydroxychloroquine for COVID-19 patients pointing to some links with the interferon immune system²³. To date, the 26th of April, 2020, only eight nitazoxanide clinical trials are undergoing worldwide with remarkable difficulties in recruitment of patients, who might have also doubted nitazoxanide potential, as only two of them are currently recruiting; one wishing to collect 50 participants with an estimated start date on the 12th of April, 2020 to compare nitazoxanide 600 mg, without any added drugs, against placebo for hospitalized patients with moderate COVID-19 condition and the author suggests that it's for the best interests of patients not to compare any drug against placebo in COVID-19. This might also come for the best interest for the researchers as it might help better enrollment and compliance of patients in their clinical trials. Similarly, the second currently recruiting nitazoxanide trial is wishing to enroll 86 participants with an actual start date on the 6th of April, 2020 to compare nitazoxanide alone to nitazoxanide/hydroxychloroquine combination in patients with COVID-19 risk factors for poor outcome, and the author wishes to suggest that their combination might be better considered for early cases not for late ones. Interestingly 4 out of the 8 nitazoxanide clinical trials for COVID-19 are undergoing in Egypt and 2 of them were posted on the same day the first version of this manuscript has been published at Preprints. However, none of the eight trials used an arm for nitazoxanide/azithromycin and the author wishes this should be changed soon²⁴. The author also recommends comparing the suggested nitazoxanide/azithromycin combination, against any other currently used protocol like hydroxychloroquine/azithromycin combination²⁵ which is still used in many countries all over the world. Unfortunately, if we may just compare the very small number with difficulties in recruitment, of nitazoxanide clinical trials that have been adopted only by Egypt, Mexico and Brazil as well as a single

pharmaceutical company which dared to test it, to the 133 COVID-19 registered and undergoing studies for hydroxychloroquine all over the world²⁶, we might eventually consider that this might not, after all, be scientifically justified especially after the recent report that showed no evidence for hydroxychloroquine to decrease the risk of mechanical ventilation in patients hospitalized with Covid-19¹⁰. The author recommends that regardless of the clinical outcomes of this suggested protocol, the reasons for this potentially unfortunate underestimation of nitazoxanide should be investigated, and to stress that all the all FDA approved drugs recommended by experts, should be properly explored for their potential against SARS CoV-2, and that for the safe drugs, including nitazoxanide, they deserve to be added to a standard protocol in an arm of an undergoing clinical trial even before a scientific justification appears to support their potential. The author also suggests that we should make this concept clear for any upcoming pandemics. Thus, and as discussed above, nitazoxanide/azithromycin combination for early management of COVID-19 is pharmacologically justified to be considered and popularized for clinical trials, soonest.

Finally, The author humbly suggests the approach represented in this manuscript might be considered a first of its kind as regards to its combined pathophysiological as well as pharmacological COVID-19 displayed concept, just to raise an Afro-Egyptian voice that nitazoxanide/azithromycin should be considered as a safe and available regimen that has a potential that should be tested immediately for early stages of COVID-19. Further, based on the same concept and supported by the recent release of clinical data disputing hydroxychloroquine efficacy, the author suggests that nitazoxanide/azithromycin combination might eventually appear be a safer, more effective regimen that might replace hydroxychloroquine/azithromycin combination as a standard care for early COVID-19, especially if the preliminary data regarding the inefficacy of hydroxychloroquine has been confirmed or as soon as nitazoxanide/azithromycin combination proved clinically effective as wished. There're also multiple questions and suggestions presented in this manuscript which are waiting to be researched and answered.

If this concept presented in this manuscript proved right, many lives might be saved as wished, but if not, then the author wishes to finally declare that we, humans, will never lose hope, abandon courage, or stop researching and we can't afford to do so.

Fig. 1 Ivermectin

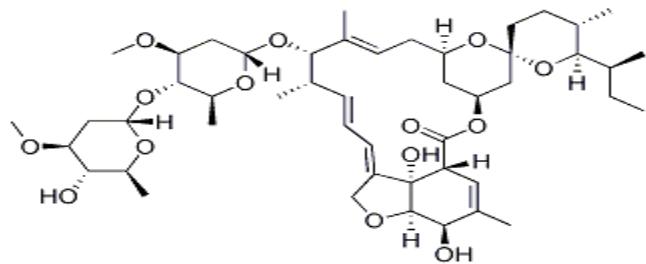


Fig. 2 Azithromycin

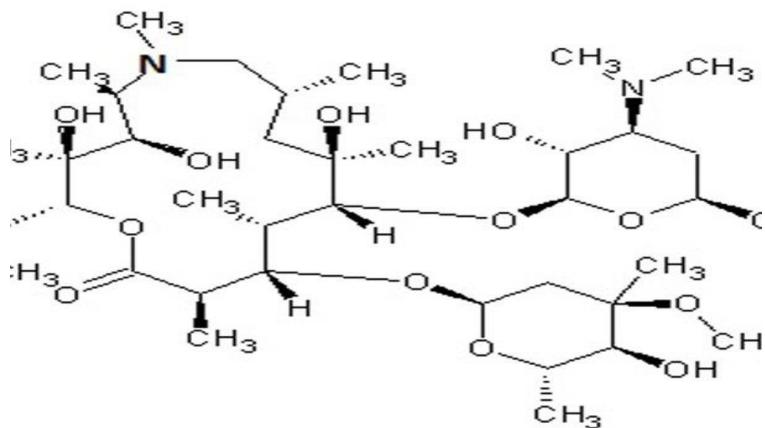
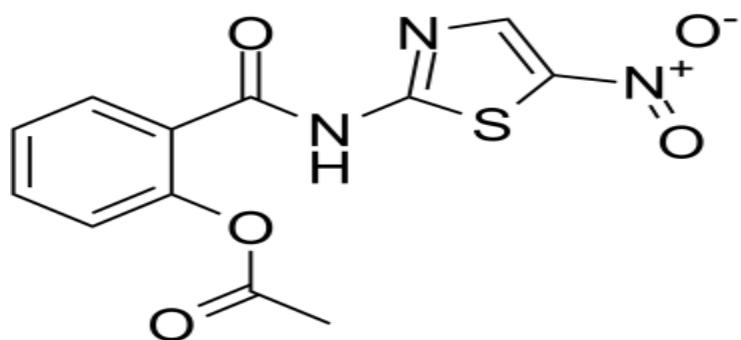


Fig. 3 Nitazoxanide



Conflict of interests

None

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