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REVIEW ARTICLE

Nitazoxanide in the Treatment of COVID-19: A paradigm for Antiviral Drugs Targeting Host-Infected Cells

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ABSTRACT

Despite significant breakthroughs in the discovery of direct-acting antivirals for several viruses, there is a need for improvement. Thus, drugs able to target host-infected cells may prove valuable in enhancing the efficacy of antivirals and avoiding resistance due to viral genetic changes.

In this context, we summarize in this review the current knowledge on nitazoxanide's potential for treating COVID-19. Our review highlights nitazoxanide's very specific mode of action, targeting cellular energy through inhibiting mitochondrial oxidative phosphorylation (OXPHOS) and stimulating the innate immune response. Thus, nitazoxanide lowers the cellular ATP content and this leads to impaired viral replication and assembly. However, since nitazoxanide only yields a mild OXPHOS inhibition, this does not affect cell viability. Preclinical results and some clinical studies have suggested that nitazoxanide might be helpful for treating COVID-19. Indeed, some clinical studies have shown a decrease in severe COVID19 evolution as well as in viral multiplication; yet the results are still debated. Overall, the available information suggests the potential of nitazoxanide in association with direct-acting antivirals. In fact, this may hold true for other viruses than SARS-CoV-2 in the future. The impact of nitazoxanide on COVID-19 should be viewed as a paradigm for antiviral drugs targeting host-infected cells, and nitazoxanide should be part of the therapeutic tools for future emerging virus-related pandemics.

Introduction

The increased frequency of viral pandemics over the 20th and 21st centuries, such as HIV and then Zika, Chikungunya, Ebola, and many others, and then COVID-19 as well as the ongoing Dengue epidemics, have emphasized the need for antiviral drugs[1].

Direct-acting antivirals (DAAs) have a major therapeutic impact by directly and specifically inhibiting viral multiplication. Tremendous progress has been made over the past decades in synthesizing potent and efficient antivirals against a variety of viral infections such as HIV, HBV, HCV, Dengue, and several others.

Yet, DAA's impact is frequently impaired by the development of resistance from the genetic evolution of the virus; also, their intrinsic efficacy is not always sufficient, and, finally, most of them do not target the immune response to the virus. In fact, there is increasing evidence that the innate immune response, the first non-specific barrier to viral infections, plays a key role in controlling viral infections[2].

The COVID-19 pandemic can be viewed as a paradigm for such discussion. The development of vaccines has been a breakthrough that has saved millions of lives. The novel SARS-CoV2 variants of the Omicron lineage, which have evolved from the original, so-called "Wuhan" strain, induce a much less severe infection. Yet these variants are extremely contagious and escape the immune response generated by the current vaccines. Thus, COVID-19 is still present and might, at least in theory, be again complicated by the occurrence of more dangerous novel variants. In addition, other viral pandemics are very likely to occur in the future, given the changes in the human ecosystem. In this context, the development of molnupiravir and Paxlovid have been major breakthroughs and are very useful for preventing and mitigating severe COVID-19. Yet their efficacy is incomplete, and their use in the general population has not been widely accepted. Finally, several studies have now demonstrated the importance of the control of COVID-19 of a "trained" immunity, i.e., a long-term increase in innate immune response triggered by some infections and vaccines[2].

Nitazoxanide might meet these needs and be part of the therapeutic arsenal against COVID-19 and other viral infections. Nitazoxanide or 2-acetyloxy-N-(5-nitro-2-thiazolyl) benzamide was first synthesized as an antiparasitic agent effective against intestinal protozoa, nematodes, cestodes, and trematodes[3]. It is the first and remains the only drug effective against the emerging protozoa, *Cryptosporidium parvum*[4]. In addition to their antiparasitic and antiviral activities, nitazoxanide and nitazoxanide are active in vitro against a broad range of anaerobic gram-positive and gram-negative bacteria, as well as replicating and non-replicating strains of *Mycobacterium tuberculosis* and *Clostridium difficile*. It was later discovered that nitazoxanide and tizoxanide, their active circulating metabolite, were potent antiviral drugs with a broad spectrum of antiviral activity against both DNA and RNA viruses, including rotavirus, norovirus and influenza viruses[5]. Interestingly, inhibition of OXPHOS may have other therapeutic implications, such as the treatment of cancer and neuropathic pain as well as neurodegenerative diseases.

In this context, we summarize in this review the current knowledge on nitazoxanide's potential for treating COVID-19.

The mechanism of action of Nitazoxanide and its derivatives

NITAZOXANIDE SHOWS IMMUNOMODULATORY ACTIVITIES AND STIMULATES INNATE IMMUNE RESPONSE.

This has been analyzed through different and complementary approaches: 1. Daria Trabbattoni et al[6] have demonstrated inhibition by NTZ of HIV1 replication *in vitro* in Peripheral Blood Mononuclear Cells from healthy blood donors. Moving forward, they discovered that NTZ stimulated the expression of the innate immune response to the virus through activating type I Interferon pathways via TLR7 and TLR8 signaling and increasing the expression of several Interferon Stimulated Genes (ISGs). Interestingly, the stimulated ISGs included genes involved in the cholesterol pathway, such as the cholesterol-25 hydroxylase (CH25H). Moreover, NTZ led to increased levels of IFNɣ and IL-2 as well as CC chemokines such as MCP-1, MIP1-α, MIP1-β, and RANTES. 2. Jasenosky et al.[7] have demonstrated in vitro inhibition of Ebola Virus replication; they showed that NTZ interferes with several pathways used by the virus to evade the immune response, such as RIG-1 and PKR sensing of the virus. They also showed inhibition of vesicular stomatitis virus (VSV) replication, which correlated with increased type I interferon (IFN) signaling pathways and induction of the cell stress and antiviral 80 phosphatase GADD34[8] expression; and 3. NTZ inhibits IL6 production and inflammation in mice. *In vitro*, NTZ inhibits inflammation in a model of lipopolysaccharide (LPS)-stimulated RAW264.7 cells and suppresses the production of NO as well as pro-inflammatory cytokines, such as IL-1β, IL-6,

and TNF-α in a dose-dependent manner. Moreover, a clinical trial in Brazil based on a limited number of subjects has led to observe a decrease upon NTZ treatment in the levels of biomarkers such as TNF, IL6, US-CRP and D-Dimers (see section on clinical studies).

NITAZOXANIDE IMPACTS THE METABOLIC AND BIOENERGETICS STATUS OF THE HOST CELL AS AN INHIBITOR OF MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION (OXPHOS)

This effect on cell bioenergetic status is likely a main driver of NTZ's overall biological activity. The inhibition of mitochondrial oxidative phosphorylation has been well-established in different systems[9,10]. It has been recently investigated in more detail by Noureddine Hammad et al[9]. They analyzed the effect of NTZ and tizoxanide in a virus-releasing cell line. They confirmed the OXPHOS inhibition but showed that the impact on OXPHOS was modest (≤25%) and disappeared when a high concentration (25 mM) of glucose was used to enhance glycolytic generation of ATP; yet the antiviral effect was significant. The hydrolysis of ATP is responsible for the production of most of the cellular and viral energy requirements; ATP comes from the OXPHOS, which is the main consequence of mitochondrial respiration in the cell. Thus, the most likely explanation is that a moderate interference with mitochondrial OXPHOS moderately lowers the cellular ATP content and that viral particle synthesis and assembly are highly sensitive to these metabolic changes.

This effect on cellular ATP may account for several of the NTZ activities on viral proteins maturation and folding as well as the activation of AMPK and AMPK-dependent pathways, which has been established[10]. There is solid evidence for the impact of OXPHOS on cancer cell proliferation. Interestingly, there is also evidence for the impact of OXPHOS on cellular susceptibility to viral infections[11]. Further detailed analyses will be needed to clarify these points.

Importantly, these host cell-directed mechanisms of NTZ activity should not be affected by viral genetic changes[3,5].

Pre-clinical effects of Nitazoxanide on the SARS-CoV 2 virus.

STUDIES OF NITAZOXANIDE AND TIZOXANIDE IN CELL ASSAYS OF SARS-COV-2

Wang et al[12] reported the antiviral activity of nitazoxanide against SARS-CoV-2 (using the Wuhan 2019 strain) in Vero cells with an EC_{50} of 2.12 µM, compared to an EC_{50} of 0.77 µM with remdesivir, which was more effective. Two research teams carried out pre-clinical studies with nitazoxanide. Riccio et al.[13,14] studied the antiviral mechanism of action of nitazoxanide against SARS-CoV-2, showing that nitazoxanide was interfering with SARS-CoV-2 spike protein maturation, hampering its terminal glycosylation at an endoglycosidase H-sensitive stage. They engineered five variant-pseudo viruses of SARS-CoV-2 and utilizing quantitative cell-cell fusion assays; they showed that nitazoxanide-induced spike modifications hinder progeny virion infectivity as well as spike-driven pulmonary cell-cell fusion, a critical feature of Covid-19 pathology. The antiviral activity of nitazoxanide was not cell-dependent, and equal activity was recorded when the virus was grown in human lung cells (A549 & MRC-5) as well as in colon cells (HCT116).

These results were confirmed by Miorin et al.[15] showing that nitazoxanide and tizoxanide were effective in cell culture assays against several strains of the SARS-CoV-2 virus in Vero E6 cells when applied to the culture 4 hours before infection. Tested in a BSL-3 laboratory against isolate USA-WA1/2020, IC_{50s} of 4.04 and 3.62 µM were recorded for nitazoxanide and tizoxanide respectively without exhibiting cytotoxicity. The antiviral activity of both compounds was then evaluated using the same isolate USA-WA1/2020, but in the human cell line A549. The two drugs were applied 4 hours before infection. IC_{50s} 48 hours post-infections of 1.695 and 1.322 µM were recorded for nitazoxanide and tizoxanide, respectively, which showed a different sensitivity of the virus for nitazoxanide depending on the cell line used.

SARS-CoV-2 targets and infects ciliated airway epithelial cells and type 2 pneumocytes in alveolar regions of the lung. To evaluate the ability of nitazoxanide to restrict SARS- CoV-2 replication in a physiologically relevant cell type, Lisa Miorin et al have used two independently derived human pneumocyte *in vitro* models that were generated by the directed differentiation of human pluripotent stem cells (PSCs), the H9 embryonic stem cell line and SPC2-ST-B2 induced pluripotent stem cells (iPSCs). Strikingly, pre-treatment of H9-pneumocytes or iAT2 cells with nitazoxanide for 4 hours prior to infection with SARS-CoV-2 (isolate USA-WA1/2020) resulted in a significant dose-dependent inhibition of virus replication without significant cytotoxicity. In addition, nitazoxanide's antiviral activity against SARS-CoV-2 in iAT2 cells was also validated using the NG-SARS-CoV-2 recombinant virus and the Image Stream platform. It was found that nitazoxanide significantly

inhibited NG-SARS-CoV-2 fluorescence and the number of NG-SARS-CoV-2 infected cells in the culture. Furthermore, NTZ synergized with remdesivir.

NTZ INHIBITS VIRUS REPLICATION OF SARS-COV-2 VARIANTS OF CONCERN.

Different SARS-CoV-2 variants have contributed to successive waves of the COVID-19 epidemic due to their increased transmissibility, as well as the waning of vaccine-mediated immunity. To determine nitazoxanide's activity against three of the recently emerged variants of concern, Vero E6 cells were treated with nitazoxanide for 4 hours and then infected with SARS-CoV-2 Beta (B.1.351), Gamma (P.1), or Delta (B.1617.2)[13,14]. As a control, cells were also infected with the original SARS-CoV-2 WA1 strain. Nitazoxanide strongly inhibited the replication of each variant tested with an efficacy similar to that against SARS-CoV-2 WA1. Thus, nitazoxanide can inhibit different viral variants with divergent spike proteins that are associated with increased virulence and transmissibility. To test the hypothesis that nitazoxanide restricts SARS-CoV-2 dissemination by directly inhibiting spike-mediated fusion, they overexpressed spike protein from SARS-CoV-2 (USA-WA1/2020) and SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1617.2) in Vero-TMPRSS2 cells. Four hours after transfection, 15 µ Mol of nitazoxanide or vehicle (DMSO) was added to the cultures and 24 hours later cells were fixed to evaluate syncytia formation. Nitazoxanide broadly and significantly inhibited syncytia formation induced by overexpression of spike from the USA-WA1/2020 strain and from each variant tested in this assay. These data indicate that nitazoxanide targets a cellular process mediating spike-induced cell-cell fusion that is not significantly affected by the spike mutations in the variants tested. Finally, nitazoxanide was also effective against the seasonal strains of coronavirus, HCoV-OC43, HCoV-229E and HCoV-NL63[16]. Previous studies have shown that nitazoxanide was also effective against SARS-CoV1 and MERS-CoV viruses.[17]

IN VIVO STUDY OF NITAZOXANIDE IN SYRIAN HAMSTER

Lisa Miorin et al[15] selected a Syrian hamster model of SARS-CoV-2 infection, where animals develop severe pneumonia and clinical outcomes (i.e., peak weight loss around 5 days and complete resolution by 14 days post infection), which are predictable. They have evaluated in this model the effect of nitazoxanide (300 mg/kg/day) delivered BID for 5 days by oral gavage. The first nitazoxanide or vehicle dose was administered 6 hours prior to SARS-CoV-2 infection. This was a randomized study comparing treated and untreated animals, all of them infected by SARS-CoV2. They observed a significant protection from weight loss at 5 days post-infection in the nitazoxanide-treated animals as well as a strong trend for such protection at 4- and 6-day post-infection. In addition, Nitazoxanide-treated SARS-CoV-2-infected animals displayed lower viral titers in lung biopsies as compared to mock treated SARS-CoV-2-infected animals, as well as SARS-CoV-2 Spike protein expression in the lung. Moreover, in the nitazoxanide-treated group, almost all the SARS-CoV-2 Spike was in the proximal airways with a more localized and segmental distribution and was not detected in the interstitial compartment. Notably, epithelial cells syncytia formation was rarely observed in the nitazoxanide-treated group.

Clinical studies of Nitazoxanide as a treatment of COVID19.

Only a relatively small number of randomized clinical studies have evaluated the clinical benefit of nitazoxanide for the treatment of COVID-19. They have been mostly focused on patients with mild and moderate COVID-19. The overall interpretation of the results is still difficult due to the heterogeneity of the patients investigated; also, some of the studies have only tested a limited number of subjects. Finally, in some studies, nitazoxanide has been associated with other treatments, including hydroxychloroquine or ivermectin.

Yet, two meta-analyses of such clinical trials have been published, which yielded discrepant results. Paulo Ricardo Martins-Filho et al.[18] showed no evidence of a clinical benefit of nitazoxanide in patients with mild to moderate COVID-19; they only evidenced a modest reduction of D-dimers, which might reflect action on coagulation disorders. In contrast Mohamed Abuelazm et al[19] showed, also in patients with mild to moderate COVID19, that nitazoxanide accelerated the viral clearance and decreased oxygen requirement; yet they did not show an effect on the overall clinical evolution nor mortality and intensive care unit admission.

Given the discrepancies in the results of the meta-analyses and the difficulty of performing such meta-analyses for the reasons explained above, it is important to dissect in more detail some of the individual published studies and to distinguish the potential action of nitazoxanide on the several parameters of COVID19.

ACTIVITY ON THE VIRAL LOAD

Five investigators studied the antiviral activity of nitazoxanide against Covid-19. Blum et al[20]in

Brazil studied nitazoxanide versus placebo in a small pilot study in 50 patients with Covid-19. They showed a statistically significant difference between 600 mg of nitazoxanide twice a day for 7 consecutive days and its placebo with more patients yielding a negative RT-PCR test than in the placebo group. Silva et al.[21] from Argentina in a small study on 46 patients showed that seven days after initiating a 500 mg nitazoxanide treatment four times a day, a total of 2,000 mg per day, nitazoxanide was superior to its placebo in reducing Covid-19 viral loads. These data were consistent with those obtained by Rocco et al[22]in a larger study on 392 patients, based on a 5 days treatment with 500 mg of nitazoxanide three times a day, a total of 1,500 mg per day: negative viral loads were observed in 29.9% of the patients treated with nitazoxanide versus 18.2% treated with placebo. However, the same investigator showed in 2022, in a study of 367 hospitalized patients with viral pneumonia[23], that a treatment with nitazoxanide did not induce a statistically significant reduction of the viral load versus placebo in patients with a low viral load; in contrast, in patients with a higher viral load, nitazoxanide treatment was associated with a trend toward a greater reduction of the Covid-19 viral load. Finally, Rossignol et al.[24] carried out a study in the United States in 379 patients and failed to show an antiviral effect of nitazoxanide given as an extended-release 600 mg tablets twice a day for 5 consecutive days or 1,200 mg per day. Thus, four of the five studies showed an antiviral effect of nitazoxanide against Covid-19. It is important to indicate that qualitative or quantitative SARS-CoV-2 RNA in nasopharyngeal swabs have not been validated for use in clinical trials. They are not predictive at the patient- or trial-level of viral load, inflammation or symptoms in the lungs or of the clinical outcomes.[25] It is also unclear whether RT-PCR accurately measures infectious virus, since viral RNA may persist for some time, even in the absence of replication-competent virus.

ACTIVITY ON SYMPTOMS RESOLUTION

Rocco et al.[22, 23] assessed in 392 patients with mild to moderate Covid-19, the effect of 500 mg of nitazoxanide three times a day, a total of 1,500 mg/day, for 5 consecutive days in recording dry cough, fever and/or fatigue. There was no difference between patients taking the drug and the placebo but there was a major deviation from the protocol since the patients began their treatment with a median time of 5 days instead of 3 in the protocol. It is well known that in respiratory viruses such as influenza, the treatment should be initiated no more than 3 days upon the onset of the first symptoms[26,27].Beyond that point, chemotherapy is ineffective. Two studies of nitazoxanide in the treatment of mild to moderate symptoms of Covid-19 carried out in 50 hospitalized patients in Brazil[20] and in outpatients in the US[24] showed that nitazoxanide was effective in reducing the duration and the severity of clinical symptoms of Covid-19. In Brazil there was a clear effect of the drug in the disease severity with a mean time for hospital discharge of 6.6 days in the nitazoxanide group versus 14 days in the placebo. In addition, two patients died in the nitazoxanide group versus 6 in the placebo group and despite these small numbers, it almost reached statistical significance. In the study from Rossignol et al in the US where 379 outpatients infected with mild to moderate Covid-19 were investigated, there was a reduction of 3.1 days in sustained clinical recovery versus placebo, but the methodology was complicated by the Flu-Pro questionnaire designed for influenza and not for Covid-19, which has very likely polluted the results. The pathology of Covid-19 has little to do with that of influenza in symptoms severity, evolution to viral pneumonia and severe respiratory distress and death. More interesting perhaps, and consistent with the study in Brazil, there was one patient of 184 treated with nitazoxanide progressing to severe illness compared to 7 of 195 patients treated with placebo; again, despite the small number of patients, these small numbers did approach statistical significance. In a study of hospitalized patients with Covid-19 and viral pneumonia (SpO_2 <93%) carried out in Brazil in 405 patients, 202 treated with 500 mg of nitazoxanide three times a day, a total of 1,500 mg/day, and 203 treated with a matching placebo for 5 consecutive days, there was no difference between the two groups on the progression of the disease and admission to intensive care unit or to death. However, nitazoxanide improved the clinical outcome, time to hospital discharge and reduced oxygen requirement.

Thus, these clinical studies suggest that nitazoxanide might be effective against the viral multiplication and, more importantly, might contribute to reduce the duration of the symptoms and the progression of the disease in patients with mild to moderate disease. In fact, combining the data of Blum et al.& Rossignol et al., a total of 14 patients progressed to ICU or death but only 3 were treated with nitazoxanide while 13 received a placebo.

CLINICAL AND BIOLOGICAL TOLERANCE OF NITAZOXANIDE IN THE TREATMENT OF COVID-19

Nitazoxanide (Alinia®, Daxon®, Dexidex®, Paramix®, Kidomax®, Annita®, Colufase®) has been initially developed and licensed in many countries in the world as an antiparasitic agent

effective against intestinal protozoa and helminths. More than 150 million people, mainly in the developing world, but also in North and South America were treated in the last 30 years with the drug for a few days or for prolonged periods of time and no serious adverse events were reported to the regulatory authorities including the United States Food & Drug Administration.

Regarding COVID19, the tolerance profile of nitazoxanide in the treatment of SARS-CoV-2 infection was studied in five well-controlled clinical studies carried out in a total of 1,272 patients, 638 received nitazoxanide tablets of 500, 600 mg immediate-release tablets of 300 mg extended-release tablets (NT300), 634 patients received a placebo and were kept as controls. As previously observed nitazoxanide was very well tolerated and only minimal, mostly gastrointestinal side effects were recorded.

Pharmacokinetics profile of nitazoxanide

Antiviral agent efficacy is related to their pharmacokinetics. The concept of "peaks and valleys" is not acceptable against viruses where the replication should be suppressed all the time to finally kill the virus. It is with the treatment of AIDS that the "trough concept" was discovered and it was considered essential for a complete efficacy of an antiviral agent. In medicine and pharmacology. A trough level or trough concentration (C_{trough}) is the concentration reached by a drug immediately before the next dose is administered and is used in therapeutic drug monitoring. It determines the frequency of the administration and, with compounds with a short half-life, keeping a trough level at a level higher than the minimum inhibitory concentration of the drug against a given virus may require three or even four times a day administration. If not, it was observed with AIDS that the viral multiplication was reappearing at sub minimum inhibitory concentration and getting stronger when exposed to the appropriate antiviral concentration. Finally, lacking an appropriate trough is unfortunately a perfect way to rapidly select viral resistance to an antiviral agent.

Nitazoxanide has an extremely short half-life and after administration of a single 500 mg dose in six healthy volunteers with food, the maximum peak concentration of tizoxanide, the desacetyl metabolite of tizoxanide, reached maximum concentrations of 1.1 to 2.5 µg/ml (mean 1.8 µg/ml SD 0,5) with a half-life in the blood of 3.5 hours (SD 1,5)[28]. The trough for the antiviral activity against SARS-CoV-2 virus is approximately 2 µg/ml and a 500 mg tablets even given 3 or 4 times a day will never achieve this blood level for a significant length of time. Thus, the use of immediate-release tablets of nitazoxanide at low doses is not appropriate. Theoretically, the use of nitazoxanide immediate release tablets is possible with higher dose such as 1,500 or 2,000 mg and should demonstrate the efficacy of the drug against the virus. However, none of these dose regimens are producing a 2 µg/ml trough level, which will guaranty an optimal efficacy of the drug and prevent resistance to nitazoxanide. This lack of appropriate trough level should prevent regulatory authorities around the world approving such a formulation for treating viral infections. In fact, only extended-release tablets (NT300) can meet significant trough for the antiviral activity against viruses [5, 28].

Conclusion

Nitazoxanide use for COVID19 well illustrates the potential and limitations of repurposing a drug previously used for treating infections due to parasites, bacteria and other viruses.

Nitazoxanide yields an extremely interesting mechanism of action. Indeed, it shows a direct effect on cell metabolism and energy with a subtle balance in the magnitude of its effects on mitochondrial OXPHOS which allows it to interfere with viral multiplication without causing cell toxicity. In addition, it stimulates innate immunity and counteracts inflammation which are key drivers of susceptibility to viral infections and severity of their evolution.

Importantly, by targeting host cell mechanisms, NTZ activity should not be affected by viral genetic changes. Finally, although this is not the topic of this review, it is noteworthy that there is now solid evidence to suggest its usefulness for the treatment of cancer.

Regarding COVID19, the preclinical studies obtained in several *in vitro* and *in vivo* models by several independent research groups are convincing. Several clinical studies are also consistent with an impact of nitazoxanide on the clinical course of the viral infection and the viral load. Yet, when considering the overall clinical results, nitazoxanide alone is very unlikely to significantly and sufficiently modify the course of COVID19. However, nitazoxanide might prove extremely useful in combination with other treatments; indeed, one might consider associating nitazoxanide to drugs which directly inhibit viral multiplication, so as to enhance their efficacy, stimulate the immune response to the virus and

prevent resistance to the directly acting antivirals. Along those lines, Rocco et al[23] reported that there was a clear synergy of nitazoxanide with corticosteroid, significantly reducing the likelihood for the patients to enter ICU. It is not the first time that a synergy between nitazoxanide and corticosteroids has been observed. A large study carried out at Harvard University by Xu Tan et al[29] studied 1,000 US Food & Drug Administration-approved or clinical tested drugs. They studied synergies in targeting HIV and suggested the efficacy of combining nitazoxanide with several glucocorticoids. Based on the efficacy and the remarkable safety profile of nitazoxanide against SARS-CoV-19 virus, combinations of treatment using other anti-Covid-19 agents are mandatory to improve efficacy and avoid drug-resistance to the virus.

These studies would be very difficult to conduct in the present context of the significantly decreased impact of COVID19. However, it is unfortunately possible to witness in the future a rebound of COVID19 with the appearance of novel, more pathogenic, variants. Also, we believe that the results on COVID10 should prove useful when considering other potentially emerging viral threats.

Disclosure

Christian Brechot has been an employee of Romark LLC from 2018 to 2021.

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