



NSAIDs and Kelleni's protocol as potential early COVID-19 treatment game changer: could it be the final countdown?

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Received: 26 September 2021 / Accepted: 14 November 2021 / Published online: 25 November 2021
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Abstract

We have previously published several papers illustrating numerous immunomodulatory and anti-inflammatory potential benefits when we repurposed safe, generic non-steroidal anti-inflammatory drugs (NSAIDs)/nitazoxanide/azithromycin (Kelleni's protocol), to early manage our COVID-19 pediatric, adult, and pregnant patients. In this manuscript, we discuss some recently published meta-analysis and clinical studies supporting our practice and discuss a molecular study that might be interpreted as an academic proof that our protocol might also prevent SARS-CoV-2 replication. Moreover, after aspirin has been suggested to be independently associated with reduced risk of mechanical ventilation, ICU admission and in-hospital mortality of COVID-19, we claim that the molecular interpretation of the results that led to this suggestion was not scientifically accurate, and we provide our academic interpretation confirming that low-dose aspirin is least likely to improve COVID-19 mortality through anticoagulation as was suggested. Furthermore, we describe other potential benefits related to aspirin-triggered lipoxins and resolvins while illustrating how NSAIDs interfere with COX-1, COX-2, SARS-CoV-2/SARS-CoV-2 ORF protein-dependent activation of caspases and their subsequent mitochondrial dysfunction, endoplasmic reticulum stress, apoptosis and necroptosis which were associated with COVID-19 complications. Similarly, NSAIDs are known caspase inhibitors and thus they might independently inhibit other caspase-related COVID-19-associated downstream pathological signaling mechanisms. Finally, we postulated that CARD-14, a caspase recruitment domain-containing protein, polymorphisms might play a role in the development of severe and critical COVID-19 and confirmed our old call to early adopt NSAIDs, as an integral part of Kelleni's protocol, as of choice in its management aiming to end this pandemic.

Keywords COVID-19 · SARS-CoV-2 · NSAIDs · Nitazoxanide · Azithromycin · Kelleni's protocol · Aspirin · Caspases · Apoptosis · Endoplasmic reticulum stress

Introduction

With over five million global deaths, COVID-19 has suddenly and dramatically struck our life, not only as regards to its huge medical consequences, but in many other aspects including social, economic, and political unprecedented conflicts. Unfortunately, it is continuing to daily waste thousands of precious lives all over the world and thus, the quest for a safe pharmacotherapy that could end this pandemic is considered a top global priority. Our approach to manage COVID-19 started in March 2020, when we sent a correspondence to NEJM (20-06753) to refute the claims that

led the world to avoid using non-steroidal anti-inflammatory drugs (NSAIDs) to manage COVID-19 patients, calling these claims a scam that lacked any scientific evidence. It was rejected, without a single peer review opportunity, by NEJM and numerous other journals, yet evolved for 5 months until *InflammoPharmacology* decided to send it for peer review and was eventually published with a more appropriate title (Kelleni 2020a). Fortunately, another paper was fast tracked and was published in April 2020 as we advocated repurposing nitazoxanide/azithromycin to early manage COVID-19 and interestingly, we preferred nitazoxanide over ivermectin as regards to safety and efficacy (Kelleni 2020b).

Since that time, our full protocol repurposing NSAIDs/nitazoxanide/azithromycin, which we, for sake of simplification, will call it as Kelleni's protocol, used to early manage COVID-19 was clinically practiced and evolving while

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using a personalized medicine approach to manage pediatric, adult and pregnant COVID-19 patients with remarkable safety and efficacy. Notably, numerous researchers supported early management for COVID-19 though differences occurred about which drugs to repurpose and why. We have published several articles that advocated potent anti-inflammatory and immunomodulatory effects for our repurposed drugs with a potential to prevent or restore the immune dysregulation that is well described in COVID-19 (Kelleni 2021a, b, c, d). Interestingly, numerous clinical and academic studies agreed with and supported the safety and efficacy of COVID-19 Kelleni's protocol, though separately for its drugs, as was cited in our previous publications.

In this manuscript, we will discuss and analyze some molecular, clinical, and meta-analysis studies that further support our protocol while adding more insights towards novel molecular and immunomodulatory targets that could add to the mechanisms by which our safe and economic Kelleni's protocol exert its potential COVID-19 game-changer effects.

Kelleni's protocol is safe to manage COVID-19

Moore et al. have recently published a comprehensive systematic review and meta-analysis that confirmed the safety to use NSAIDs in COVID-19 (Moore et al. 2021). They have confirmed an earlier published one (Kow and Hasan 2021) and a third preprinted article with similar findings (Zhou et al. 2021). Interestingly, a large study by Drake et al. (2021) has urged policy-makers to review their advice regarding prescribing NSAIDs in COVID-19 and some colleagues have recently suggested that earliest COVID-19 home therapy with NSAIDs may greatly prevent hospitalizations (Consolaro et al. 2021; Pandolfi and Chirumbolo 2021). As early mentioned, all these observations and recommendations side with our old one that started since May 2020 when we started to recommend adopting NSAIDs as lifesaving and of choice in COVID-19 management, unless contraindicated due to other reasons or diseases.

Similarly, both the safety and efficacy of nitazoxanide and azithromycin when repurposed to manage COVID-19 are also currently well established and supported by numerous reputable authors who have been cited in our recently published articles (Kelleni 2021b, d) as well as in others (Blum et al., 2021; Cadejani et al. 2021; Lokhande and Devarajan 2021; Meneses Calderon et al. 2020; Patel et al. 2021).

Kelleni's protocol might inhibit SARS-CoV-2 replication

Interestingly, a recent research has revealed the vital role played by NF- κ B signaling in SARS-CoV-2 replication while insightfully reasoning for the concomitant diminished

type I interferon response (Nilsson-Payant Benjamin et al. 2021). In their research, the authors experimentally tested several compounds that disrupted NF- κ B signaling, yet they repeatedly stated that there are no specific FDA-approved drugs that inhibit NF- κ B (Nilsson-Payant Benjamin et al. 2021). We would like to confirm that some non-specific FDA-approved drugs augment our natural interferon response while inhibiting and disrupting NF- κ B signaling, including our repurposed Kelleni's immunomodulatory COVID-19 protocol that was shown to restore homeostasis of the SARS-CoV-2 inhibited and/or dysregulated interferon response (Kelleni, 2020b, 2021a, b, c) as well as to inhibit the concomitant SARS-CoV-2-induced robust activation of the IL-6 amplifier including NF- κ B signaling as an essential component (Smart et al. 2020; Kelleni 2021b) which was also showed by Nilsson-Payant and colleagues to play a fundamental role in SARS-CoV-2 replication (Nilsson-Payant Benjamin et al. 2021). Moreover, we suggest that azithromycin might also disrupt the NF- κ B and signal transducer and activator of transcription-1 synergistic induction of inflammatory genes expression that could also play a role in the dysregulated COVID-19 immune response (Hiroi and Ohmori 2005; Xing and Liu 2021).

Notably, safe nutraceuticals like resveratrol and quercetin are also known to counteract the inflammatory process partly through modulation of microRNAs which are involved in regulation of NF- κ B signaling (Cione et al. 2020) and were suggested to be of potential value in COVID-19 management (Kelleni 2021e; Manjunath and Thimmulappa 2021).

Low-dose aspirin is not the best NSAID to manage COVID-19

Interestingly, a retrospective cohort study demonstrated that low-dose aspirin, a prototype of NSAIDs, use was independently associated with reduced risk of mechanical ventilation, ICU admission and in-hospital mortality while there were no differences in major bleeding or overt thrombosis between aspirin and non-aspirin users (Chow et al. 2021). However, we suggest that this study has some major flaws in its interpretation and should be properly interpreted from a pathophysiologic and pharmacologic point of view for the best interests of the prospective medical research and more importantly for the welfare of our precious COVID-19 patients. Thus, we will discuss some novel insights about the role that low-dose aspirin, and more clinically importantly other NSAIDs, might play in management of COVID-19 which might include aspirin triggered lipoxins and resolvins, inhibition of cyclooxygenases, SARS-CoV-2 ORF proteins induced caspase activation, necroptosis and endoplasmic reticulum stress aiming at further exploration of COVID-19

pathophysiology that might guide us in our vigorous quest for a highly anticipated cure.

Chow et al. have cited numerous references that correlated with SARS-CoV-2-induced hypercoagulable state and subsequent development of platelet rich thrombi with severe COVID-19 and mortality and they have cited a study performed by Paranjpe et al. (2020) which has suggested that systemic treatment-dose anticoagulation may be associated with improved outcomes among hospitalized COVID-19 patients to suggest that their reported aspirin beneficial outcomes might be due to its well-known antithrombotic properties. However, Paranjpe et al. have clearly enumerated numerous limitations of their study, and the effect of the prophylactic low-dose aspirin tested by Chow et al. might differ from that of the systemic treatment dose anticoagulants studied by Paranjpe et al. To be also noted is that a large observational study has demonstrated no significant association between ongoing use of direct oral anticoagulants and severe COVID-19 and wisely suggested that therapies should be better directed against thrombogenic inflammation, the cause, rather than against hypercoagulability, the symptom (Flam et al. 2021). Similarly, a systematic review of literature supported a similar conclusion while criticizing a low scientific quality of the described studies (Tieleman et al. 2021). Importantly, Chow et al. have not found a difference in incidence of overt thrombosis between aspirin and non-aspirin users and thus, we suggest that sub-overt mechanisms, discussed in the following paragraphs, should be attributed to reason for the potential aspirin beneficial effects in COVID-19 as expressed by Chow et al.

Moreover, Chow et al. have stated that aspirin, as a cyclooxygenase-1 (COX-1) inhibitor, modifies both inflammatory and coagulation responses and they cited a review written by Warner et al. (2011). However, in that cited reference, no mention to a link between COX-1 inhibition and inflammation was found and it was clearly stated, at that reference as elsewhere, that COX-1 is the constitutive form of the enzyme which is also exclusively or dominantly expressed in the anucleated platelets and that COX-2 is the inducible one associated with inflammation. Similarly, Chow et al. have cited a resourceful review and meta-analysis written by Panka et al. (2017) to reason for the aspirin's anti-inflammatory mechanisms including lipoxin formation. However, in that reference, these mechanisms were evident in murine or in in vitro preclinical models and in some of which aspirin was applied by local administration and in all these models, aspirin was used, as also stated, in high doses in contrast to the low doses used in clinical studies including that of Chow et al. and thus the evidence cited from Panka et al. does not reason for Chow et al. aspirin's anti-inflammatory properties. Additionally, Panka et al. discussed some contradictory results found in sheep and murine models and Chow et al. have also wisely confirmed that aspirin showed

mixed results when tested for acute respiratory distress syndrome and cited few studies though only thoroughly discussed the positive ones.

Furthermore, Chow et al. have also cited a study performed by Ikonmidis et al. (1999) in which 300 mg daily aspirin was administered for 6 weeks and decreased IL-6 and CRP to reflect on their 81 mg aspirin dose and this reflection is also not scientifically justified as low-dose aspirin cannot inhibit the inflammatory COX-2, as stated by Chow et al., and inhibits COX-1 almost selectively. Moreover, Ikonmidis et al. have also mentioned that aspirin exhibits anti-inflammatory action in a dose-dependent manner and its greatest effects occur at doses as high as 2 g.

Potential benefits of low-dose aspirin in COVID-19

In our opinion, the results presented by Chow et al. should be interpreted and built upon by researching potential aspirin's non-COX-dependent anti-inflammatory effects through modulation of the immune and inflammatory function of platelets (Sonmez and Sonmez 2017; Kasirer-Friede et al. 2019) as well as its peculiar ability to trigger induction of the beneficial anti-inflammatory and immunomodulatory lipoxins and resolvins which are synthesized through acetylated COX-2 (Serhan et al. 2008).

Notably, while COX-2 acetylation, and the subsequent formation of lipoxins and resolvins, is not achievable by low-dose aspirin, induction of COX-1 upregulation in COVID-19 might be considered for further research as it has been previously described, with potential benefits of its inhibition under certain conditions, in some neuroinflammatory and neurodegenerative diseases. Additionally, COX-1 and/or COX-2 potential role in SARS-CoV-2 replication should be assessed and NSAIDs were also suggested, in a preprint, to directly affect SARS-CoV-2 replication (Chen et al. 2020).

NSAIDs potential modulation of SARS-CoV-2-induced activation of caspases, apoptosis, and necroptosis

Caspases are a family of enzymes associated with apoptosis, pyroptosis and their dysregulated activation was suggested to share in the pathogenesis of tumors, autoimmune, auto-inflammatory, inflammatory cytokine secretion including IL-1 β from viable monocytes as well as infectious disorders (Van Opdenbosch and Lamkanfi 2019). SARS-CoV-2 infection was reported to activate caspase-8-triggering pro-inflammatory cytokines, including IL-1 β , TNF- α , IL-7, IL-8, apoptosis, necroptosis and activation of the NF κ B pathway in lung epithelial cells which were suggested to

share in COVID-19-induced downstream immune pathogenesis causing lung damage (Li et al. 2020). Moreover, open reading frames (ORF) 3a protein of SARS-CoV-2 was shown to significantly induce cellular apoptosis which was shown experimentally to be significantly inhibited by either a caspase 8 or caspase 9 inhibitor (Ren et al. 2020) to be noted that several ORF SARS-CoV proteins were previously shown to induce apoptosis and ORF-6 protein overexpression was shown to induce caspase-3 mediated c-Jun N-terminal kinase (JNK)-dependent apoptosis that was blocked by a specific caspase 3 inhibitor or JNK inhibitor (Ye et al. 2008). Similarly, caspase-mediated apoptosis was suggested to play a significant role in COVID-19 complications (Fakhri et al. 2021), and blocking caspase activity was shown to in vitro rescue T cells by inhibiting their apoptosis and thus, inhibiting caspases could play a role in severe COVID-19 which is characterized by dysfunctional immune response (Thompson et al. 2021). Interestingly, several caspases were reported to modulate B and T cell proliferation and altered transcriptome levels of caspase genes were reported in natural killer cells and neutrophils. Moreover, uncontrolled caspase response in COVID-19 was suggested to share the immune pathological processes as well as in the inflammatory microvascular thrombi found in multiple organs leading to severe outcomes. Interestingly, caspase-1 in CD4+ T cells was shown to be upregulated in hospitalized COVID-19 patients and caspase-3 levels were reported to be significantly upregulated, compared to controls, in circulating red blood cells from COVID-19 patients as well as in tissue macrophages in postmortem analysis and were also demonstrated to be suppressed ex vivo by a pan caspase inhibitor (Plassmeyer et al. 2020). Thus, unsurprisingly, suppression of apoptosis was suggested to prevent viral pathogenesis in some diseases including SARS and targeting virus-induced apoptosis was implied as a promising strategy in COVID-19 management (Donia & Bokhari, 2021, though sometimes drugs with unbalanced risk:benefit ratio were suggested (Fakhri et al. 2021). Similarly, inhibition of the necroptosis signaling pathway, a subsequent outcome of caspase-8 activation, was suggested to possess a potential to protect against COVID-19 complications (Cao and Mu 2021).

Notably, we postulate that CARD 14, a caspase recruitment domain-containing protein of the membrane-associated guanylate kinases family <https://www.ncbi.nlm.nih.gov/gene/79092>, mutations might play a crucial role in COVID-19 pathogenesis and complications especially in severe and critical patients and we further suggest that the quest to design and develop novel caspase inhibitors and/or modulators might evolve to be corner stone in management of several immune-inflammatory diseases,

Importantly, we would like to pharmacologically confirm that NSAIDs are well known, at physiologic in vivo concentrations, caspase inhibitors (Smith et al. 2017) and we

suggest they are the safest drugs among all the suggested and investigated caspase inhibitors (Aranda et al. 2017).

NSAIDs potential modulation of SARS-CoV-2 induced endoplasmic reticulum stress

Furthermore, endoplasmic reticulum stress (ERS) was suggested to play an important role in the development of COVID-19 (Banerjee et al. 2020) and ERS markers were shown to be significantly increased in SARS-CoV-2 infection and COVID-19 pneumonia (KÖSeler et al. 2020). Interestingly, several NSAIDs including diclofenac, indomethacin, ibuprofen, aspirin, and ketoprofen were shown to suppress the ERS-induced human neuroblastoma SH-SY5Y cell death (Yamazaki et al. 2006). Similarly, oxicam-derived NSAIDs have been demonstrated to possess neuroprotective effects potentially through suppressed activation of caspase-3 and cell death as well as amelioration of ERS and/or mitochondrial dysfunction signaling pathways (Omura et al. 2018) and thus, NSAIDs potential direct and indirect positive immunomodulatory effects in COVID-19 are further amplified through their potential anti-ERS effects.

Potential therapeutic role of Kelleni's protocol in COVID-19

Taken together, we wish to highlight that overwhelming pieces of evidence should urge policy-makers to finally consider old recommendation to use NSAIDs as of choice in the management of COVID-19 and though we previously and relentlessly called for almost half past a year for large clinical trials to test Kelleni's protocol, we currently suggest that it might be more appropriate to adopt it soonest as proven safe and effective by numerous researchers who tested its used repurposed drugs, separately. Our call is aimed to save precious lives that have been and are being deprived safe, economic generic repurposed drugs especially as COVID-19 is re-surfing in the European countries to the extent that the WHO has recently described them again as the epicenter for the pandemic [<https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/statements/statement-update-on-covid-19-europe-and-central-asia-again-at-the-epicentre-of-the-pandemic/>] and we recommend adopting therapeutic doses of NSAIDs in the management of COVID-19 as explained in our published manuscripts if some authorities decided to simultaneously perform sufficiently powered randomized clinical trials against any standard protocol.

We have previously postulated that NSAIDs, as integral part of Kelleni's protocol, are potentially lifesaving intervention tools to prevent or reverse the evolution of the

well-described aggressive hyperinflammatory responses in COVID-19 (Kelleni, 2020a, 2021a) due to their immunomodulatory and anti-inflammatory properties (Kelleni 2021b) and in this regard, NSAIDs might possess a huge advantage as, unlike corticosteroids (Kelleni 2021f), they are not immunosuppressive. Moreover, we demonstrated our real-life personalized approach that adopts NSAIDs as an integral part of COVID-19 management (Kelleni 2021d). However, we recommend against the concomitant use of prophylactic low-dose aspirin and NSAIDs, or at least some of them (Gurbel et al. 2019), and we obviously opt for NSAIDs over low-dose aspirin.

Finally, we wish it might be the time for final countdown to return our world, our lives and our gatherings back to safety and we will never ask what if, it is not practical, but instead we will keep asking when will all policy-makers start to consider that a safe, economic, and highly effective potential COVID-19 curative protocol can end this pandemic?

Acknowledgements I wish to express my utmost gratitude and respect to *InflammoPharmacology*, its honorable editor in chief Prof. Dr. Kim D. Rainsford and editorial board for giving my manuscripts a very precious opportunity to be properly peer reviewed. I am also indebted to honorable anonymous peer reviewers whose highly constructive insightful remarks have significantly improved the quality of the presented manuscript.

Author contributions Sole author.

Funding None.

Declarations

Conflict of interest The author has no conflicts of interest to declare.

Statement of ethics Not applicable.

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