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Harnessing adenosine A2A receptors as a strategy for suppressing the lung inflammation and thrombotic complications of COVID-19: Potential of pentoxifylline and dipyridamole

A B S T R A C T

Counterproductive lung inflammation and dysregulated thrombosis contribute importantly to the lethality of advanced COVID-19. Adenosine A2A receptors (A2AR), expressed by a wide range of immune cells, as well as endothelial cells and platelets, exert cAMP-mediated anti-inflammatory and anti-thrombotic effects that potentially could be highly protective in this regard. The venerable drug pentoxifylline (PTX) exerts both anti-inflammatory and antithrombotic effects that reflect its ability to boost the responsiveness of A2AR to extracellular adenosine. The platelet-stabilizing drug dipyridamole (DIP) blocks intracellular uptake of extracellularly-generated adenosine, thereby up-regulating A2AR signaling in a way that should be functionally complementary to the impact of PTX in that regard. Moreover, DIP has recently been reported to slow the cellular replication of SARS-CoV-2 in clinically feasible concentrations. Both PTX and DIP are reasonably safe, well-tolerated, widely available, and inexpensive drugs. When COVID-19 patients can be treated within several days of symptom onset, using PTX + DIP in conjunction with hydroxychloroquine (HCQ) and an antibiotic – azithromycin (AZM) or doxycycline – might be warranted. HCQ and AZM can suppress SARS-CoV-2 proliferation in vitro and may slow the cell-to-cell spread of the virus; a large case series evaluating this combination in early-stage patients reported an impressively low mortality rate. However, whereas HCQ and AZM can promote QT interval lengthening and may be contraindicated in more advanced COVID-19 entailing cardiac damage, doxycycline has no such effect and exerts a potentially beneficial anti-inflammatory action. In contrast to HCQ, we propose that the combination of PTX + DIP can be used in both early and advanced stages of COVID-19. Concurrent use of certain nutraceuticals – yeast beta-glucan, zinc, vitamin D, spirulina, phase 2 inducers, N-acetylcysteine, glucosamine, quercetin, and magnesium – might also improve therapeutic outcomes in COVID-19.

Versatile anti-inflammatory effects of adenosine A2A receptors

The potential lethality of advanced COVID-19 stems not so much from the direct cytopathic effects of the virus, but from the florid lung inflammation and the endotheliopathy-induced thrombotic complications that it evokes [1–3]. Adenosine A2A receptors (A2AR) exert broad-spectrum anti-inflammatory and anti-thrombotic effects in a range of cells - including neutrophils, macrophages, lymphocytes, platelets, and endothelial cells – that have potential for providing protection in this regard [4–6]. A2AR is a 7-pass G-protein-coupled receptor that stimulates adenylate cyclase activity via $G\alpha_s$ [7]. The intracellular increase in cAMP that this evokes works in multiple complementary ways to suppress oxidant production, cytokine generation, expression of adhesion molecules, *trans*-endothelial migration of neutrophils, opening of the endothelial barrier, tissue factor generation, and platelet aggregation in A2AR-responsive cells [5]. Down-regulation of NF-kappaB activation and JAK-STAT signaling pathways contribute importantly to these effects of cAMP [5]. Importantly, neutrophils, whose activation and transit into lung interstitial tissue and alveolar space is a key mediator of the respiratory distress syndrome associated with COVID-19, are highly responsive to the functionally suppressive effects of A2AR, as are the endothelial cells whose activation attracts and enables transendothelial passage of activated neutrophils [8–11].

These considerations suggest that selective agonists of A2AR may have important potential for blunting the lethality of COVID-19.

As may be expected, such agents have shown protective effects in rodent models of inflammatory lung injury [12–15]. Unfortunately, these agents are not yet clinically available. However, at least two drugs are currently available – venerable, reasonably safe and well tolerated, and inexpensive – that can function to up-regulate A2AR signaling: pentoxifylline (PTX) and dipyridamole (DIP).

Pentoxifylline and dipyridamole work in complementary ways to Up-regulate A2AR signaling

Although PTX is known to have broad anti-inflammatory activity, it is employed primarily in the treatment of intermittent claudication; by lessening neutrophil activation, PTX renders these cells more distensible, so that they can more readily pass through narrow capillaries in affected legs [16,17]. (Upstream stenotic obstructions decrease the transcapillary pressure gradient, rendering the passage of bulky neutrophils through narrow capillaries more difficult in this syndrome.) Although the clinical effects of PTX have usually been ascribed to the ability of this drug to inhibit cAMP phosphodiesterase – thereby boosting cAMP levels – this effect is only significant in vitro at millimolar concentrations that are orders of magnitude higher than the low micromolar concentrations of this drugs achieved clinically [16]. Ironically, however, it does appear that cAMP mediates PTX's clinical effects. Within the last decade, PTX's anti-inflammatory effects have been shown to be contingent on activation of A2AR [18–20]. Whether PTX can act as a direct agonist for A2AR is currently unclear, and some data argue against this [18]. What *is* clear is that PTX can potentiate the responsiveness of this receptor to adenosine. The latter is produced extracellularly from ATP released into the extracellular space, which is then converted to adenosine by the sequential activity of the CD39 and CD73 ecto-phosphatases expressed on the plasma membranes of A2AR-expressing cells [5,21].

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The signaling activity of extracellularly-generated adenosine is terminated by intracellular uptake of the adenosine. The platelet-stabilizing agent DIP is distinguished by its ability to block this re-uptake by platelets [22,23]. Hence, DIP up-regulates the adenosine-mediated activation of platelet A2AR, thereby boosting platelet levels of cAMP, which functions to suppress platelet aggregation. Moreover, DIP blocks adenosine uptake by a range of other A2AR-expressing cell types, including endothelial cells, neutrophils, and monocytes [23–25].

It is evident that PTX and DIP have the potential to work in a complementary fashion to boost A2AR signaling – DIP can be expected to boost the extracellular levels of adenosine whose signaling activity PTX potentiates. Surprisingly, only a handful of studies have evaluated this combination experimentally or clinically – with encouraging results – likely because the mechanism of action of PTX has been clarified only recently [26–28].

Anti-inflammatory and Anti-Thrombotic effects of pentoxifylline

Pre-administration of PTX is protective in rodent models of acute respiratory distress syndrome (ARDS) evoked by lipopolysaccharide (LPS) administration or severe haemorrhage [29–31]. Clinically, it was found to reduce mortality, lower plasma tumor necrosis factor, and achieve clinical and radiological improvements in ARDS associated with cancer [32]. A *meta*-analysis of clinical studies found that PTX therapy is associated with a decrease in plasma levels of both tumor necrosis factor and C-reactive protein [33]. In chimpanzees, it was shown to blunt LPS-induced activation of coagulation and fibrinolysis [34]. In isolated lungs, PTX pre-treatment reduces the tissue injury induced by neutrophil infusion [35]. In endothelial cells, PTX counteracts the ability of pro-inflammatory cytokines to stimulate expression of adhesion factors and chemokine production [36]. These findings are expectable in light of the known effects of A2AR signaling, and encourage the speculation that PTX could have potential for blunting the exuberant lung inflammation and pro-thrombotic effects of advanced COVID-19. Not surprisingly, the use of PTX for treatment of ARDS associated with SARS infection was suggested in 2003 [37]. (Presumably, this was not studied because the syndrome rapidly disappeared.)

In seeming contradiction, a large multi-center study of lisofylline therapy in ARDS patients failed to show benefit [38]. Lisofylline is the R-isomer of a reductive metabolite of PTX, notable for its protective impact in rodent models of type 1 diabetes [39]. Conceivably, the impact of this agent on A2AR signaling – which has not been reported – is different than that of PTX. Alternatively, this finding may reflect the fact that, for unclear reasons, A2AR agonism is more effective for controlling ARDS when implemented before the syndrome becomes florid. Konrad and colleagues, in interpreting this result, suggest that adenosine levels may be too low in the context of advanced sepsis [19]. If so, the concurrent use of DIP would make logical sense.

Dipyridamole – an Anti-inflammatory agent which can suppress SARS-CoV-2 replication

Most studies with DIP have focused on its platelet-stabilizing effects – which presumably could provide some protection from SARS-CoV-2′s pro-thrombotic effects – but experimental studies also show that DIP can act on neutrophils to suppress superoxide production, adhesion to endothelial cells, and, in a mouse model of anti-phospholipid syndrome (a sometime feature of COVID-19), NETosis formation [40–43]. And DIP has been shown to suppress superoxide production and tissue factor expression in monocytes [44].

Of particular pertinence is this new discovery: Chinese researchers have reported that, in clinically relevant concentrations as low as 100 nM, DIP slows the replication of SARS-CoV-2 in Vero E6 cells; this effect may be mediated in part but not entirely by the binding to DIP to the SARS-CoV-2 protease Mpro [45]. In a controlled pilot study, 31 hospitalized COVID-19 patients with respiratory difficulties were treated with either DIP (50 mg 3 times daily) or placebo; of the 14 patients who received DIP, including 8 that were severely ill, all but one recovered, and the remaining patient was in remission at time of the report. Of 12 severely ill patients in the control group, 2 patients died and 2 were in remission [45]. The difference in therapeutic outcome just missed traditional statistical significance ($p = 0.06$). The response in D-dimer levels was significantly better in the treated than in the control patients.

An anti-viral effect of DIP is not unprecedented – cell culture studies have reported that this agent can slow the proliferation of various RNA viruses, and a Russian clinical report some decades ago concluded that DIP administered prophylactically was effective for reducing risk for influenza and upper respiratory infections [45–50].

These considerations suggest that a PTX/DIP regimen might have considerable potential for control of the progression and complications of COVID-19. Provisionally, we recommend dosage schedules for PTX and DIP typically used for their approved indications: PTX 400 mg 3 times daily, and DIP 50 mg 3 times daily.

Another venerable drug which has been suggested for use in COVID-19 management is the anti-parasitic agent ivermectin. Evidence that it can suppress proliferation of SARS-CoV-2 in cell culture is likely of little pertinence, as the IC50 concentration that achieves this – about 2 uM – is vastly higher than the plasma concentrations achievable by doses approved for clinical use [51,52]. Nonetheless, anecdotal claims of its apparent effectiveness in late-stage COVID-19 are encouraging clinical trials with this agent. Largely overlooked is the fact that, in oral doses that are roughly analogous to the standard clinical dose in humans, ivermectin pre-administration can protect mice from a lethal dose of LPS [53,54]. Hence, if ivermectin proves useful in COVID-19, an anti-inflammatory mechanism may underlie this benefit.

Concurrent nutraceutical support for antigen-specific immunity

However, it should be acknowledged that A2AR agonism also has potential for suppressing the dendritic cell activity that provides the antigen presentation necessary for developing an antiviral antibody response [4]. The authors have been unavailable to find any studies suggesting that PTX increases infection risk – in marked contrast to the well-known literature on anti-inflammatory corticosteroids – so perhaps this is a relatively minor consideration. Indeed, some studies fail to find an effect of A2AR agonists on dendritic cell antigen presentation [55]. And PTX has actually been suggested as an adjuvant to vaccination, as it boosts memory response to vaccination by increasing survival of activated T cells [56]. Nevertheless, it would seem prudent to complement PTX/DIP therapy with agents such as yeast beta-glucan that specifically boost dendritic cell activity, as a compensatory measure [57–59]. Curiously, beta-glucan administration has been found to be protective in rodent models of sepsis-induced ARDS [60,61]. Supplemental zinc could be another worthwhile adjuvant measure, as it has been found to decrease incidence of infection while lowering systemic markers of inflammation in elderly subjects [62].

Incorporating pentoxifylline/dipyridamole into early-stage protocols

In early-stage ambulatory patients with COVID-19, it would be appropriate to consider using PTX + DIP in conjunction with hydroxychloroquine (HCQ). Currently, this agent is the most commonly used drug for treatment of early-stage COVID-19 [63]. HCQ decreases replication of SARS-CoV-2 in vitro in clinically relevant concentrations [64,65]. Studies examining the molecular biology of SARS-CoV-2 cell-to-cell spread have found that endosomal cathepsin L protease activity markedly expedites such spread, presumably because it enables SARS-CoV-2 virions taken up into cellular endosomes to fuse their membranes with that of the endosome, thereby allowing the virion to enter the

cytoplasm and begin replication [66]. It is well known that HCQ functions to alkalinize endosomes, and this would be expected to inhibit cathepsin L activity [67,68]. Moreover, HCQ has recently been shown to inhibit activation of NADPH oxidase complexes in endosomes; this would be expected to exert an anti-inflammatory effect that might complement the anti-viral activity of this agent [69]. This model makes evident the desirability of employing HCQ as early during the clinical course of COVID-19 as feasible, as the ability of this agent to slow cell-to-cell spread may be of less utility once the lung epithelium is already widely colonized by the virus. Pharmacokinetic modeling, combined with in vitro data, suggest a regimen for HCQ of 400 mg twice daily for one day, and 200 mg twice daily for a further 4 days; this is predicted to maintain antiviral plasma levels of HCQ for at least 10 days [64].

HCQ therapy often induces modest increases in QT interval, and concurrent administration of azithromycin can amplify this effect. Such increases can increase chances for dangerous torsade de pointes arrhythmias; studies examining ECGs in hospitalized COVID-19 patients treated with this combination reported 2 cases of torsade de pointes in 640 such patients [70–73]. Although it is very rare for these drugs to induce arrhythmias when used for their current indications, SARS-CoV-2 can directly attack the heart, and conceivably this could potentiate the pro-arrhythmic impact of HCQ [74,75]. Hence, monitoring of QT interval appears to be prudent when using HCQ in COVID-19. Fortunately, neither PTX nor DIP have been linked to QT prolongation or torsade de pointes arrhythmias.

Adding an antibiotic such as azithromycin or doxycycline to early-stage treatment of COVID-19 to prevent bacterial super-infection – as many doctors have done when employing HCQ in COVID-19 therapy – would also be a reasonable option [76]. In addition to their antibiotic activities, azithromycin exerts anti-viral effects in vitro against various viruses, and doxycycline has anti-inflammatory properties that likely would be beneficial in SARS-CoV-2-induced cytokine storm [77,78]. However, azithromycin might be inappropriate for late-stage therapy, as it has a greater tendency than HCQ to prolong QT intervals [75]; doxycycline does not have this effect.

Nutraceutical adjuvant measures

Nutraceutical adjuvant measures that support the antigen-specific immune response – such as yeast glucan and zinc – would also appear to be indicated. Nutraceuticals that might be expected to boost the interferon response evoked by SARS-CoV-2 while lessening the contribution of oxidants to lung inflammation have been proposed, including spirulina, phase 2 inducers, N-acetylcysteine [79]. Supplemental glucosamine may likewise up-regulate the type 1 interferon responses to viruses, while exerting anti-inflammatory effects that render it protective in rodent models of sepsis and lung inflammation induced by LPS or cigarette smoke [80–84]. This anti-inflammatory effect might reflect up-regulated activity of the de-ubiquitinase A20, which opposes TRAF6 signaling [85]. Up-regulation of type 1 interferon induction may also play a role in the anti-viral effects of quercetin [86,87].

Theoretical considerations as well as epidemiological findings suggest that good vitamin D status may also be protective [88–90]. In the context of inflammation, lung epithelium and alveolar macrophages can convert circulating 25-hydroxyvitamin D to the active hormone calcitriol; this in turn can boost expression of the antimicrobial protein cathelicidin, which is destructive to many enveloped viruses [91–95]. Intracellular magnesium supports effective function of the A2AR [96]. Lower serum magnesium has been associated with increased thrombotic risk and slowed fibrinolysis [97–101]. Hypomagnesemia predicts poor outcomes in ICU patients, and its correction may improve their prognosis [102,103]. Moreover, magnesium deficiency up-regulates NF-kappaB activation and HMBG1 secretion in LPS-treated macrophages – consistent with other evidence that it may up-regulate inflammation [104,105]. In light of the pro-thrombotic and pro-inflammatory diathesis associated with COVID-19, magnesium supplementation might be prudent.

Conflict of interest

Dr. DiNicolantonio is Director of Scientific affairs at AIDP.

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