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Virology & Mycology

Perspective

Histamine Antagonists to Temper the Cytokine Overproduction in Gastrointestinal Cells Infected by SARS-CoV-2

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ABSTRACT

The premise regarding COVID-19 disease is that it is a spectrum which begins with infection with viral SARS-CoV-2 exposure *via* airborne or oral virus particles. The individual response to it depends on many factors including co-morbid conditions. An important aspect of SARS-CoV-2 virus infection is the cytokine storm that develops after the infection. The immunochemical chaos created in this cytokine storm is to the benefit of the virus. In this meta-analysis the authors explore ways to let the cytokine storm die down by looking into the role of histamine. Histamine is a metabolic product of the essential amino acid histidine. Histamine has 4 known receptors: H1, H2, H3 and H4. The immuno globulines IgG and IgM are indicative for a COVID-19 infection. This immune response is related to inflammation. Inflammation, in turn, runs mainly *via* histamine after e.g. virus inoculation. The goal of the meta-study is to gather evidence to primarily block the H4 receptor (H4R) in gastrointestinal cells to diminish the cytokine overproduction in the problems caused by SARS-CoV-2. Our concept is as follows. If we can strike a careful balance between hampering the gastrointestinal spreading of the virus and histamine antagonists to tackle the cytokine storm, then the natural immunity can later on come on line again and attack the virus without being led astray by cytokine chaos. We will concentrate on H4R but also look at H1R and H2R related effects. The proposed substances in our systemic approach can be balanced for an effective early treatment. The nature of our work is by its method and results theoretical. In that respect we also may note the structural chemistry indol skeleton resemblance among a number of different medicinal substances.

Keywords: Cytokine storm; IL-1 and IL-6 production *via* SARS-CoV-2; Gastro-intestinal H4R receptor antagonists

INTRODUCTION

The illness COVID-19 is caused by the virus SARS-CoV-2. SARS-Cov-2 is a single-stranded RNA virus. Viruses are very tiny infectious agents that don't have metabolism or can replicate exclusively on their own. Following infection of a host (e.g., a cell), a virus can direct the cell machinery to produce viral proteins and produce more viruses. SARS-CoV-2 is, not only in name, closely related to a bat coronavirus SARS-CoV [1]. The spike S structure of SARS-Cov-2, i.e. the machinery with which the virus injects its RNA into the host, shows resemblance to RaTG13 bat virus [2]. There has been significant discussion about the origin of the SARS-CoV-2 (also referred to as HCoV-19), for example see [3]. SARS-CoV-2 and SARS-CoV likely do differ in drug sensitivity profile [4]. We note that our own scanning of the genome confirmed the presence of the gp120 elements and some gp41 (pubchem/16132114) small One of the elements. Latter is GARS from AVGIGALFLGFLGAAGSTMGARS on the nucleocapsid phosphor protein and represented as GGGGCGCGATCA in position 28375 of the genome. We have also found IGAL on the open reading frame 1ab. The results are preliminary but could support our study in one of the sections below. It is noted that there are theoretical reasons to believe that gp41 resides on SARS-CoV [5] and so we thought gp41 elements might also somehow be present on SARS-CoV-2.

In this paper we will focus on a treatment with antihistamines to let the cytokine overproduction, i.e. the storm [6] die down. It is remarkable that a systemic antihistamine route with supporting

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Received: June 08, 2020; **Accepted**: June 21, 2020; **Published**: June 26, 2020

Citation: Geurdes H (2020) Histamine Antagonists to Temper the Cytokine Overproduction in Gastrointestinal Cells Infected by SARS-CoV-2.Virol Mycol. 9:189. DOI: 10.35248/2161-0517.20.09.189.

substances to fight the virus appears to be largely ignored in the treatment of COVID-19. We believe that a systemic approach can exist next to direct attack approaches such as the use of anti-parasitic ivermectine [7] and [8], to eliminate the virus. In a previous study in Parasitology, [9], it was reported that pro-inflammatory interleukin IL-1 β was most likely increased in human material tested *in vitro* after treatment with ivermectin. The interleukins IL-1 and IL-6 are the cytokines that are generated *via* the virus to create cytokine chaos and to sneak through the immunity defenses. Moreover, IL-6 induces the overexpression of ACE2 receptors [10] on the host cell. So the ACE2 route of infection can be furthered by interleukin production. Histamine can influence the production of IL-1 in the lung tissue [11]. The mechanism of action of ivermectin is its resemblance to gamma-amino butiric acid (GABA) [12]. Additionally, there can be clinical toxicity problems associated with ivermectine, like e.g. ataxia and bradycardia[12]. It is used in HIV-1 treatment and can therefore, count as support substance to histamine in the attempt let the cytokine storm die down. The latter is the main pillar in our systematic theoretical treatment approach.

Highlights

With our approach we found e.g. JNJ-7777120 being capable to suppress cytokine overproduction *via* histamine. With indomethacine we are likely able to hamper the nonstructural protein nsp7 route of infection. In the gastrointestinal cells, the H4R antagonist JNJ7777120 repairs the damage by indomethacine.

INFLAMMATION

A major aspect of the SARS-CoV-2 infection is the occurrence of inflammation. Anti-inflammatory response is the coordinated activation of signaling pathways that regulate inflammatory-mediator levels in resident tissue cells and inflammatory cells recruited from the blood. The inflammation reactions can depend on local cellular environmental surroundings but they all share 1) cell surface pattern receptors recognize detrimental stimuli; 2) inflammatory pathways are activated; 3) inflammatory markers are released; and 4) inflammatory cells are recruited [13].

In [14], inflammation of tumor growth is described that shows epithelial cell growth and differentiation partly through histamine H1 and H4 engagement. The amount of natural IgE and of histamines are related. Let us first recapture the importance of histamine. Histamine has multiple effects on both the direct as well as the indirect immune response. To be more precise we recall [9]. The direct mechanism of immunomodulation involves interaction of an immune-modulator and/or its metabolite with a component of the immune cell itself. This can be investigated in vitro. The indirect mechanism of immune modulation involves interaction of the immune-modulator and/or its metabolite with a component of a non-immune cell. This depends on in vivo connections and is more difficult in vitro.

In the paper we will concentrate the attention on the role of histamine outside the central nervous system. This is the reason why we go very deep into the histamine 3 receptor. Obviously we are not excluding effects of antihistamines on the central nervous system microglia [15]. Moreover, histamine H3 receptors are also present in lung tissue and play an inhibitory role in the production of pro-inflammatory cytokine. There is increasing evidence suggesting that histamine is involved in the regulation of cytokine networks. More strongly: histamine can inhibit, next to IL-1, also inhibit the release of IL-2, IFN-g, and TNF (1115) and increase the release of IL-5, IL-6, and IL-8 [11].

Therefore, it depends which histamine receptor one targets in suppression and in which tissue it resides. Moreover, histamine H3 receptors are involved in gastric mucosal defense, inhibition of enteric neurotransmission and feedback regulation of histamine release [16]. A large body of evidence has unraveled the occurrence of histamine H4 receptors (H4R) in the gastrointestinal tract [16].

H1R

Concerning the role of the histamine H1 receptors (H1R) let us look e.g. at levocetirizine. This substance blocks the histamine H1R. It is demonstrated that levocetirizine helps to fight difficult urticaria [17]. It is in that respect interesting to mention the fact that this substance inhibits the cytokine expression and viral replication of rhino virus [18]. Closely related to the rhino infection we may note that levocetirizine inhibits Inter Leukine 6 (IL-6) which also occurs in SARS-CoV-2 infection. The SARS-Cov-2 virus furthers the synthesis of IL-6 and along a.o. this route makes a cytokine storm. Note: The pathophysiology of SARS-CoV-2 is complex and largely unknown but is associated with an extensive immune reaction triggered by the excessive production of interleukin 1 beta (IL-1 β), interleukin 6 (IL-6) and others [19]. Both cetirizine (a metabolite of hydroxyzine) and levocetirizine are H1 receptor antagonists. Levocitirizine (pubchem/compound/1549000) and citirizine (pubchem/compound/2678) are stereo-chemically related. In [20] we can read that levocetirizine can imply iatrogenic complications. We surmise that this, because of similarities between the two molecules, most likely is also true for citirizine case.

H2R, the usnic acid/usneate case

Usno or benzyldimethyl-(2-[2-(p-1,1,3,3-tetramethylbutylphenoxy)ethoxy]ethyl)ammonium usneate, is a substance that can be found in lichens. We refer to pubchem/compound/5646. In already older studies it was found to have a biological action [21]. In this latter study molecular information is readily available. Considering the biochemistry, M. Cocchietto, points at the fact that Usno is inhibitory against leukotriene biosynthesis [22]. Leukotienes and histamine are physiologically related. The relationship is also expressed in the response of the H2 receptor behavior. The production of leukotrienes is most of the time accompanied by the production of histamine and prostaglandins [23].

Leukotrienes are a family of lipid inflammatory mediators produced in leukocytes (white blood cells). They are the metabolic oxygenation of arachidonic acid by the enzyme 5-lipoxygenase (5-LO) [24]. Leukotrienes use lipid signaling to perform a regulation of immune response. Interestingly enough

it was reported that the cellular signal substance cAMP, suppresses 5-OL. The leukotrienes exert their biological effects by binding to G-protein coupled receptors (GPCRs).

The histamine receptors, including H4R, are G-protein based. For example, eukotriene LTB4 is a strong attractant for many immune cells.

By the cAMP suppressive action for the synthesis of leukotrienes, it looks as though cAMP might take priority in cellular signaling. Furthermore, H2R activation runs most likely *via* stimulating cAMP synthesis. Referring back to the co-synthesis of histamine and leukotrienes and with an eye on the role of cAMP and leukotrienes under infection, we may note [25] that histamine suppresses the biosynthesis of leukotrienes. This is what both cAMP, histamine and Us no have in common. Human polymorphonuclear leukocytes (PMN) carry H2 receptors and are activated by the leukotriene LTB4. H2 receptor antagonists like cimetidine abrogate the suppression of leukotriene biosynthesis. The inhibition of LT biosynthesis by histamine was characterized by decreased arachidonic acid release and 5-lipoxygenase translocation to the nuclear membrane [25]. An H4 receptor blocker like e.g. thioperamide does not influence the biosynthesis of leukotrienes. This is in slight contrast to the fact that leukotrienes bind to G-protein receptors and H4R is of G-protein type.

Despite this unclarity it could be worthwhile to employ H4 blockers without affecting the synthesis of leukotrienes on the human PMN. Should one want to slightly block the leukotrienes biosynthesis then e.g. Usno can be employed [22] Usno is toxic however (pubchem/compound5646) and therefore might show iatrogenic difficulties. Nevertheless the stereo-chemical similarity to a 2,5-dihydroxyquinone "nucleus" in polyporic acid is most likely the active center [21]. This is perhaps a good starting point for altering the molecule to a less toxic level. The mechanisms of the antibiotic activity of usnic acid (viz. Usno) against Gram-positive bacteria were attributed to its role as an un-coupler of oxidative phosphorylation, inhibiting the synthesis of adenosine triphosphate [26]. The same review reveals that usnic acid delivers apoptosis through the enabling of more protonated molecules to cross the membrane and release protons into the cell. As a result, the intracellular pH decreases and lead to the death (apoptosis) of the cells. This would in particular be interesting for therapies like with Zn where there is the suspicion that viral particles survive in infected cells.

H4R

H4R is the newest of the four known histamine receptors. It belongs to the group of G-proteins and is coupled to the Gio protein [27]. H4Rs have been detected in different cell types of the gut, including immune cells, paracrine cells, endocrine cells and neurons. Moreover, H4R expression was reported in human colorectal cancer specimens [16]. A systematic list of H4R contains cells like mast cells, eosinophils, leukocytes, monocytes, CD8+T cells, basophils, dendritic cells, spleen and bone marrow [28]. The H4 receptor is expressed throughout the gastrointestinal tract as well as in the liver, pancreas and bile ducts [29]. H4Rs to modulate the function of mast cells, T cells, dendritic cells and eosinophils, it is natural to foresee a therapeutic potential of H4R antagonists in inflammatory disorders of the GI tract [16].

Eosinophils are stimulated by histamine and so the H4 receptor (H4R) plays an interfering role in generating the eosinophils that can attack intruding agents. In gastrointestinal SARS-CoV-2 infection [30], we can look at the H4 receptor as one of the sources of the cytokine storm. The hypothesis is: to block the H4R in gastrointestinal cells and let the cytokine overproduction, i.e. cytokine storm dies down.

In this respect we note the following. There are mast cells that can fire the cytokine storm *via* interleukine [31]. The latter study was performed with interleukine 33 (IL-33). We note that SARS-CoV-2 furthers the production of interleukine 6 (IL-6) and this also is able to fire and is in fact part of, the cytokine storm. This route of generating the storm is operative without the interference of H4 receptor in gastrointestinal infected epithelial cells. In a medical treatment with an H4R blocker it represents a shunt and is a logical sense bypass to the blocking. It is an interesting question how much the mast cells that employ the interleukin H4R blocking shunt fires the cytokine storm.

An interesting case of an H4 receptor influence is the case of indomethacin. Functional characteristics of the H4R in fibroblasts are associated with inflammatory disorder. This is related to e.g. dermal dexamethasone [32].

Apparently indomethacin can also have a direct anti-inflammatory effect by inhibiting the synthesis of prostaglandins, the signaling molecules. Further, H4R expression occurs in numerous immune and inflammatory reactions and in e.g. gastric acid secretion [27]. Indomethacin is presently under study for fighting COVID-19 [33]. Concerning toxicity, it is most likely that indomethacin is expected to have a low iatrogenic impact [34]. The target protein in SARS-CoV-2 is one of the nonspecific proteins, nsp7. The nsp7 is a co-factor in the expression of the viral RNA [35]. The occurrence of an anti-inflammatory agent in the larger study, supports our quest for studying the role of H4 blocking treatment that can be experimentally researched further.

5-chloro-2-[(4-methylpiperazin-1-yl)carbonyl]-1H-indole (JNJ-7777120) is a specific H4R antagonist. An experimental study of Ballerini [36] suggests that autoimmune diseases are furthered by JNJ-7777120 H4R antagonist and furthered an increase of inflammation. There might be iatrogenic problems in the use of JNJ-777120. Another appropriate not too toxic H4R antagonist is JNJ-10191584 (VUF 6002) [37].

Supportive substances and/or synthetic derivatives

Usno and target leukotrienes: Usnic acid is a secondary metabolite of lichen [26]. Usno is also a substance obtained from lichen. Leukotrienes synthesis can perhaps also be a target of therapeutic intervention with e.g. Usno. General references to leukotriene targets are to be found in [38] and [24]. Direct antiviral activity to the influenza virus is also present in both (+) and (-) Unso/usnic acid [39]. Evidence for anti-viral effect where usnic acid is a repressor of RNA transcription was given early 2000, see: [40,41]. This aspect next to the anti-could inflammatory activity, make usnic acid a proper supportive

substance for diminishing the cytokine storm with histamine response suppression. There is the already mentioned connection between Usno and H2R.

Atranorin and protolichesterenic acid: Another lichen substance, atranorin, is effective against hepatitis C (HC) virus [42]. In this study, the aldehyde group of atranorin was demonstrated to hamper the entry of the HC virus into the host. It is worthwhile to investigate if atranorin is a direct antiviral to SARS-CoV-2. A related matter is the possible blocking of HIV active elements [43]. If a similar some HIV mechanisms are employed in SARS-CoV-2, then the lichen derived protolichesterenic acid is a not toxic frustration for the HIV virus to create nascent DNA from its RNA. This hampers the spreading infection of the HIV virus and could also affect the possible routes via HIV elements on the S spike given those elements are active somehow. We refer again to the possibility of gp41 on SARS-CoV [5].

Using protolichesterenic acid can be active as a supportive substance for the blocking of the histamine fired cytokine storm. The paper [2] that questions the conclusions of [44] is referred to as well. From the latter we read that the HIV elements are short sections that are not unique to SARS-CoV-2 and HIV. It must be noted that the presence of gp120 on the S spike protein of SARS-CoV-2 is not denied by Zhang cum suis. It is also not demonstrated that those elements are inactive. Therefore looking at how HIV infects, [43], we may still hold that SARS-CoV-2 behaves in some ways similar, cit:"At the initial stage, HIV comes into contact with a CD4-expressing cell (such as a helper T cell or macrophage). The main glycoprotein needed for this interaction is gp120 on the virion surface, which forms a trimer together with a trans membrane component, gp41".

HIV gp120 blocker: Recently Pradhan et al claimed that there are HIV elements in the S spike protein of the SARS-CoV-2 virus [44]. In a paper by Zhang [2] it was contested that "such inserts" were proof of an engineered virus. If we leave that discussion for what it is, then, we note that [2] does not deny that gp120 is present on the S spike of the virus. M. Phillips and J. Svard inform us that gp120 is the main protein needed by the virus to make contact with CD4+ type of cells (helper T cells and macrophage cells). The protein gp120 forms a trimer with the trans membrane gp41 and in this way a virus carrying gp120 can insert its RNA into the host [43]. Because SARS-CoV-2 carries this structure it is likely that it is used in the infection. We explicitly note that [2] did not demonstrate that the gp120 segments on the S spike are not active.

Therefore CD4+ binding disturbing substance like maraviroc may hamper the SARS-CoV-2 virus propagation/multiplication [15]. Interestingly, concerning CD4+ cells we may observe the role of fenbendazole. Fenbendazole is a member of benzimidazole group of anthelminthic like ivermectin (pubchem/compound 6321424). In [9] we read that the administration of fenbendazole to healthy mice stimulated the proliferative response of T-and B-cells to non-specific poly-clonal activators, but partially inhibited the CD4+, CD8 percentage of and +T-lymphocytes. If gp120 in the S spike of SARS-CoV-2 actually targets CD4+, then fenbendazole might hamper the CD4+ infection route. The treatment of nematode infected mice considerably stimulated the proliferative response of B-cells in comparison with T-cells.

Indomethacin: This substance interferes with one of the nonspecific proteins involved in the transcriptase complex. Moreover, indomethacin [45] has a potent antiviral effect against the SARS-CoV virus from beginning of 2000. Indomethacin targets the nsp7 protein of the SARS-Cov-2 virus and is a prostaglandin E2 synthase inhibitor [33].

Zinc: Zinc possesses direct antiviral properties, e.g. against influenza. Zinc is captured in vivo in metallothioneins and it should be noted that metallothioneins, although highly responsive to zinc, have long been classified as interferon (IFN) stimulated genes. IFNs are immune-stimulatory cytokines secreted from infected cells and nearby immune cells that induce the expression of hundreds of antiviral genes [46]. Zn avoids the apoptosis of cells that contain virus material. Some metallothioneins are generated by some viruses as a response to Zn. Not all metallothioneins fire IFN or prevent apoptosis of infected cells but the authors wonder if Zn is not too complicated where we are trying to let a cytokine storm die down.

ACE2 receptor antagonism: On the host cell residing, angiotensin converting enzyme 2(ACE2) is recognized as one of the receptors of the S spike of SARS-Cov-2 RNA infection of the host. Generally angiotensin converting enzyme is related to blood pressure regulation [47]. ACE2 is accountable for human-human infection [48]. In Gordon's research of ≈ 300 protein interactions, captopril [33] is considered a modulator/competitive inhibitor of the ACE2 binding. It decreases the level of angiotensin 2. A search on pubchem showed that there are other competitive inhibitors of ACE2 binding like e.g. fosinopril. Like captopril, fosinopril competitively inhibits ACE thereby it decreases the formation of the potent vasoconstrictor, angiotensin 2. The latter is one of the main factors in in hypertension induced tissue damage (pubchem/compound 172198) and [49]. Diminishing the angiotensin 2 production with suppressing its production implicitly also lowers the cytokine production and the synthesis of new ACE2 receptors [50].

DISCUSSION

Histamine has a direct modulating effect. We mention upfront a study where histamine is coupled to the immune-regulation of HIV infected patients [51]. In our theoretical paper we focused on histamine 1,2 and 4 receptor types. Although histamine 3 receptor also occurs in lung tissue and neuroendocrine gastrointestinal tissue, we have not inspected it very deeply. H3 receptors are more associated to neuro endocrine tissue. This will most likely warrant a subsequent study.

Looking at a possible gp120 to CD4+ infection route of SARS-C0V-2, the lowering of histamine is immediately hampering CD4+ activity. Perhaps it is too simple to say *in vivo*; less histamine less CD4+ and therefore less gp120-CD4+ infection. However, the direct influence already shows the importance of antihistamines in hampering SARS-CoV-2. In the analopgous virus, SARS-CoV, the RNA genome replication is a crucial step

in SARS-CoV propagation and is mediated by the RNA replicase [52]. The S spike of SARS-CoV-2 also contains the replicase necessary cofactor nsp7. So it makes sense to believe that the virus propagation can run similar to SARS-CoV. From the study done by [2] we may observe that SARS-CoV does not contain the HIV elements such as SARS-CoV-2. It therefore makes sense to hypothesize that SARS-CoV-2 also has ways to propagate that differ from SARS-CoV. Nevertheless, interference with indomethacin therewith targeting cofactor nsp7 is a genuine possibility to hamper SARS-CoV-2 virus propagation.

The role of histamine in the generation of interleukins IL-1 and IL-6 that also may further the possibility of infection *via* ACE2 is another more indirect effect of histamine and provides reason to look at the possibility of antihistamines next to competitive inhibitors of ACE2. Competitive anti-angiotensin also may suppress the creation of ACE2 receptors on the host cell. We note here that indomethacin (pubchem/compound 3715) shares a 2D structural indol resemblance with serotonin (pubchem/compound 160436). In this case we are looking at the indol skeleton and the OH substitute at the same 2D indol structure. Interestingly enough in HIV-1 we have LEDGF/p75 integrase inhibitors; a strong binding partner of HIV-1 integrase [43]. There are a group of rationally designed small molecules containing the indol skeleton [53] that targets the LEDGF/p75-IN. All of those molecules, like e.g. CHIBA-3000, have an indole skeleton [53].

In the indol (Figure 1) the OH group resides at another position relative the N than serotonin and indomethacin. Perhaps that the indol sharing also points to the use of the CHIBAn molecules in SARS-CoV-2 originally targeted for LEDGF/p75-IN (integrase) in HIV-1. LEDGF/p75 is by far the most extensively studied co-factor in HIV study. It is a 74 kD protein ubiquitously expressed, chromatin associated protein in HIV-1 infection. Because certain HIV elements are on the S spike it could pay to look at substances that hamper the gp120 binding of the virus to CD4+ cells. It is noted here that the N-terminal domain structure (amino acids 1-49) of the HIV-1 IN protein resemble the zinc finger [46] with a His, Cys, Cys combination [43]. The S of cystine provide the binding place for e.g. Mg^{2+} or Zn^{2+}, there is a connection with the LEDGF approach to hamper the integrase in which in HIV-1 the IN protein participates. With this way of looking at an alternative binding *via* the gp120 on the S spike (which presence is confirmed by Zhang et al., we are obviously not forgetting the ACE2 binding but merely mention other possible ways of infection. Before entering more deeply into the possibilities of antihistamines, we note that there were already objections against what is called the non-steroidal anti-inflammatory drugs (NSAIDs). No conclusive evidence against their use could be concluded however [54].

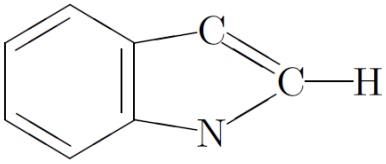

Figure 1: Basic Indol structure [24].

The more general aim of the study was:

Find means to let the cytokine storm for at least gastrointestinal infection die down

To provide supportive substances that hamper the virus replication

Use e.g. IgE 'trained' to attack the virus when the attack is most effective. To our minds it is most effective after the cytokine chaos is resolved

We studied possible routes. E.g., it is possible to (1) suppress H4R in gastrointestinal cells with JNJ-7777120, to use (2) maraviroc to hamper infection *via* gp120 and use (3) IgE trained cells to eradicate the SARS-CoV-2 virus. In Table 1 we present a number of combinations that may look interesting for further experimental research. Another route is to replace (2) with indomethacin and keep (3) as it is. Obviously JNJ-7777120 can be replaced with thioperamide. Therefore we can obtain a combinatorial matrix of possibilities. It is noted that substances like atranorin and usnic acid can also play a role in (2). Concerning the supportive substances we mention the following. Lichen substances show weak antiviral activity. The role of Zn is somewhat confusing. Especially the role of metallotrienes needs to be sorted out further.

Lowers the cytokine storm with H4R

Hampers the virus multiplication and

Eliminates the virus

If necessary :

It can be supplemented with cetirizine or levocetirizine to block the H1R and we may also look at leukotrienes.

It can be supplemented with atranorin to hamper other aspects of virus multiplication.

Most likely there are other ways of obtaining objective number three.

Concerning (3) we acknowledge that this aspect is not studied very deeply either. Therole of IgE, IgM and IgA might also necessitate a follow up if it is possible. Interestingly, Adami [55] found that the H4R antagonist JNJ-7777120 is able to undo the gastric damage of indomethacin. The "ok" in the tox column of Table 1 is based on their finding. Perhaps that a similar situation is valid for JNJ-10191584. It is hence possible to block the cytokine storm, hamper the nsp7 guided infection and undo the damage of indomethacin.

Contrary to JNJ-7777120, the H4R antagonist thioperamide does not have an indol (Figure 1) skeleton. Moreover, there are two N atoms in the five ring and this ring is not connected to a benzene structure. Thioperamide allow LTB4 and there is most likely a larger role for the H4 receptor in LTB4 production [56].

It must be noted that we did our theoretical study in the field of applying non-steroidal anti-inflammatory drugs. Although there could be sceptical reactions towards this approach, we believe that it is a valid one in early treatment to prevent the cytokine overproduction. There is literature to support this [57-59].

Table 1: Some H4 antagonists with supportive substances and remarks made on 2D structural chemistry and a column, designated toxicity (tox), which is only indicative for what the authors know about the combination of those substances. ok is explained in the text, "?" means we don't know yet.

H4R substance	Supportive substance	Remarks	Toxicity (tox)
JNJ-7777120	Indomethacin	Blocks c-storm & hampers nsp7 infection. indol shared structure	ok
JNJ-10191584	Indomethacin	c-storm blocking & hampers infection. aldehyde group demonstrated to hamper the entry of the Hepatic C virus. no 2D structural chemical relatedness	?
Thioperamide	Indomethacin	Blocks c-storm & hampers nsp7 infection. double N 5 ring twisted but related JNJ-10191584	?
JNJ-7777120	Atranorin	c-storm blocking & hampers infection. aldehyde group demonstrated to hamper the entry of the Hepatic C virus. no 2D structural chemical relatedness	?
JNJ-10191584			
Thioperamide			
JNJ-7777120	CHIBA-3000	Blocks c-storm & interferes with integrase in HIV-1 LEDGF. indol shared structure	?
Antihistamine like JNJ-7777120	Captopril	Interferes with ACE2 production *via* cytokine IL-6 similar as H4R antagonist N containing 5 ring is not indol like	?
Antihistaminelike JNJ-7777120	Fosinopril	Interferes with ACE2 production *via* cytokine IL-6 similar as H4R antagonist N containing 5 ring is not indol like similar to captopril	?

CONCLUSION

We end this discussion section by noting that to our minds the structural 2D resemblance with an indol (Figure1) skeleton between some of the antiviral substances explored and serotonin cannot be altogether accidental. Especially because of nsp7 is a cofactor in the polymerase of the enzyme. The chemical similarity between the indol skeleton of indomethacin and the indol skeleton of CHIBA-3000 can be an indication of a similar way of the SARS-CoV-2 virus propagation and the HIV virus. Perhaps this allows us to gain insight into possible other ways of infection besides the ACE2 route. Of course quantum chemical electron cloud density studies, e.g., or e.g. hydrogen bonding in DNA base pairs can provide more insight into the idea of indol skeleton similarity.

ACKNOWLEDGMENT

We would like to thank Dr. Ivoyl P. Koutsaroff (Wisol Japan KK, Osaka, Japan), Ad Popper, MSc and Bert vd Bos, BSc and for their support during this paper preparation.

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