Hypothesis - antihistamines: relevance updated according to changes in knowledge - observations Dr S. ARMINJON [1], June 2021

Important notice:
This study is only a statement of the elements that should lead to consider the management of Covid through the "histamine route". It is certainly characterised by a certain subjectivity but, how could it be different in view of this observations from a field practitioner's perspective due to the slow progress of the deployment of potential curative treatments, all the polemics, prohibitions and threats. The discerning reader will be able to dismiss the inevitable wear effect of this situation, which is ethnically and intellectually unacceptable, in order to retain only what is essential here: (finally) the opening of an axis of therapeutic reflection and research. Some are theoretically based approaches. It is not a matter of demonstration but only the evocation of the lines of thinking.

At the end of February 2020, at the rise in Europe of what was still an epidemic linked to SARS-Cov2, we formulated, based on the epidemiological, clinical, paraclinical and evolutionary data of CoviD-19, a hypothesis on a pathogenesis of SARS-Cov2 mediated mainly by **the virus-host combination and this from initial contact.**

From the interaction with the pathogen, the host's inflammatory and immune system will sometimes produce **deleterious immune responses** with short, middle or long-term effects.

SARS-Cov2 is highly contagious but above all may have an ability (without a doubt, never yet encountered or seen) **to trigger the excessive uncontrolled response to the host's immune-inflammatory system**, probably encompassing all or part of the pathogeny.

The host's immune-inflammatory system response with its own specificity and susceptibility (from low to very high) after contact with SARS-Cov2 would therefore determine the clinical course and ultimately the severity of the disease (immediate or deferred - long Covid).

This susceptibility of the host to produce the initial defence response, with a more or less rapid harmful response and more or less intensive, could thus explain the different heterogeneities of the Covid-19 both clinical, biological or evolutionary, regardless of stage and time.

Similarly, and in line, the deleterious effects associated with the activation of the immune and inflammatory system are potentially worrying for the "side-effects" they might leave or the reactivation during a second contact.

Therefore, **it is not the intrinsic potential adverse effects of the viral agent (SARS-Cov2) but mainly the host's immune response**, to which the patients would be subjected. The intrinsic reactivity specific to each individual is sharing the way Covid-19 is affecting them in terms of evolutionary kinetics, clinical but above all in gravity and maybe further sequelae.

One way or another, SARS-Cov2 would generate an immune-inflammatory reaction which can evolve progressively (even in a subclinical way) or/and in an explosive and unpredictable way (overreact).

This sometimes explosive and unpredictable character as well as the observed heterogeneities and well-known functions of histamine lead to consideration that this biogenic amine is involved very early or even immediately in an immune response course after SARS-Cov2 contact or could even be involved in a direct viro - induced activation.

Different clinical trials have further confirmed the possible relevance of our hypothesis. Similarly, a more comprehensive knowledge of Covid-19 has bought many elements confirming the possible involvement of histamine and with it, the most probable interest of the antihistamine choice.
Here we discuss all of these elements by updating our previous publications (February-Mars, June 2020) – cf. appendices – in the light of the most recent literature review and acquired new knowledge (June 2021).

Background and initial hypothesis

From the first known Covid-19 cases in France, we have proposed an hypothesis about the pathogenesis related to Covid-19.

In our hypothesis, the participation of the immune-inflammatory system was considered to be the origin, following the initial host-pathogen interaction, of the heterogeneous symptomatology observed and variations in inter-and-intra-individual severity.

Thus, the Covid-19 pathophysiology would result mainly (or even exclusively) of deleterious effects caused by an excessive reaction of the virus-host's interaction induced auto-inflammatory and auto-immune system. The immune-inflammatory system characteristics in terms of "response power" may provide the interpretation of the observations of the heterogeneity that seem to be present in Covid-19.

The virus SARS-Cov2, contagious as it is, appears, in itself, dangerous almost only by its ability to trigger an inflammatory and immune reaction that can become excessive and deleterious in the short, medium or even long-term.

In this Concept, the "indirect" pathogenic effects of SARS-Cov2 would be responsible for the disease. They would also be present in the early stage and "associated" with the "direct" pathophysiological effects of SARS-Cov2.

Therefore, in Covid-19, unlike what is not uncommon to see in viral infection, after a more or less long evolutionary phase, there are immediate pathologic direct effects due to the chain reaction of "indirect" harmful sequelae.

According to this hypothesis, the "indirect" pathophysiological effects linked to SARS-Cov2 could be involved (making it appropriate for target-therapy) from their initiation (and therefore, during the initial contact of the virus). This early targeting could limit the harmful effects, among them, of the runaway inflammation of the immune response, excessive or not.

From this notion, the viral load during contagion could become a less decisive factor in terms of the ability of SARS-Cov2 to induce Covid-19.
Indeed, since it would be the "indirect" physiopathological effects which would come into action via the virus-host interaction, the initial viral load, although potentiating the onset or even runaway, would become less decisive in terms of the disease induction ability (and therefore also in terms of contagiousness). This can be approached with the concepts in force in allergology and according to which, the allergen load, however crucial it might be, is not quantitatively restricted to the triggering of the pathological reaction.

The latter concept may perhaps, in our opinion, reflect different epidemiological and clinical observations that are very heterogeneous.

The Individual sensitivity, the intrinsic "reactivity", is, in fact, of a variable "power" and specific to each individual. SARS-Cov2 could therefore lead to extremely variable individual reactions during the primary but also secondary contact. For better understanding, we will make this analogy: a sort of principal agent with a "universal allergen" behaviour (for the "inducing" behaviour). The prospects for such a hypothetical behaviour in the host-virus interaction would de facto generate implications in the

development of a vaccine and / or in the achievement of protective immunity. In this hypothesis, there would undoubtedly be a viral “stopping” power but little or no action on the Covid-19 “disease” itself with, however, certainly neutralization of certain physio pathological effects, further reinforcing, during subsequent contagions, the clinical heterogeneity already observed which may lead to “bastardized” or non-typical clinical forms or even possibly even more “explosive” forms.

Therefore, the nosological framework of Covid-19 would be largely heterogeneous with regard to the individual (or even intra-individual) specificities of the involvement of the immuno-inflammatory system and its response, in particular, with regard to the initial symptomatology.

This characteristic therefore seemed to be able to fully reflect the observed epidemiological and clinical heterogeneity.

The biological data then available to us, reporting on the “cytokine storm”, also indicated in the involvement of the auto-inflammatory and auto-immune response in severe forms of the disease beyond the comorbidities. The evolution in two phases with worsening on D7-D10 was also totally part of this reactive involvement, and ultimately, the negative impact, on the immuno-inflammatory system of the host.

Based on these facts and according to our hypothesis, it was therefore logical to try to modulate as quickly as possible this abnormally high reactivity of the auto-inflammatory response observed, particularly in certain patients whose predisposition to react in such a way (and it remains to be understood/investigated).

The targeting and the only use of virucidal or / and virostatic molecules, although logical, did not seem to have the capacity to suppress the kinetics of the initiation of the auto-inflammatory and auto-immune reaction, nor to be able to stop the early stages and ultimately, the disease.

From this initial physio-pathogenic hypothesis, the use of certain therapeutic drug classes appeared obvious for their commonly known action against the immune-inflammatory system triggering an acute inflammatory response: antihistamines first and foremost (in particular anti-H1), anti-leukotrienes (leukotriene antagonists), synthetic antimalarial and depressogenic medications or immuno-blockers.

Given its ubiquitous nature within the body, from its early involvement in its known cellular and clinical actions, histamine appeared to us to be the molecule whose appropriate targeting should be a priority. Its involvement may, moreover, arise in addition to its initial activation but also during the evolution of the immuno-inflammatory cascade, along with, beyond its increased release, a possible decrease (whether or not associated with the induction) of the abilities of the human organism, of elimination-neutralisation.

In other words, there would be a possible involvement of histamine by excess release and / or excess production associated or not with a decrease in “physical” or even “functional” clearing capabilities, all induced by the initial (and subsequent) host-virus interaction.

So, antihistamine, with the benefit of long clinical use and its well-known simplicity of use, is more than the logic choice and easily exploitable in our hypothesis as to its possible efficacy during Covid-19 evolution as hypothesized in its physio pathogenicity (immuno-inflammatory system).

In early March 2020, the data search carried out did not show any article on the subject (Histamine - antihistamine - Covid-19).

The other potentially useful therapeutic classes, occurring at different and later times, did not potentially justify stopping the use of antihistamines according to our theorisation, but remained as much as possible a complementary sequential use. In our opinion, the use of antihistamines benefits from a probable stopping power, the other therapeutic classes being administrated, as necessary, to strengthen the AntiH1

role. The therapeutic management of Covid-19 seems to us therefore part of a “multi-class therapy with sequential deployment” of the use of antihistamines as a starting point (and its continuous use).

According to the evolution of the disease, a dedicated therapeutic response targeting the events and elements of the immune-inflammatory cascade in action, with the initial (“promoters”) or sustaining and/or reinforcing effects of histamine. The viral load and/or new contamination is also taking on a possible reinforcing importance. In this hypothesis, it also turns out that conducting clinical trials could de facto be made more difficult to replicate due to the possible bias “phases” in the different study groups (complicating further potential therapeutic strategies).

Subsequently, our various field observations appeared to show (subjectively) a rapid effect of antihistamine (antiH1) on a large part of the initial symptomatology observed when declaring a case of Covid-19 as well as a noticeable shortening of its duration. We then communicated our findings by drawing attention to the earliest possible use of AntiH1 in Covid-19 (without waiting for the triggering of serious forms: at the earliest of the onset of Covid-19 symptoms) in the hope of seeing studies of quality evidence-based research being done[1].

At the same time, we have chosen for clarity of presentation[1] to structure our observations and established a collection of observational data based on the use of a drug (which is an over-the-counter medication in France and many other countries) outside marketing authorisation (MA), as indeed are the majority of drugs used to date for Covid-19 patients, starting with paracetamol. The prescription of drugs, excluding MA, being fully authorised and regulated by the French legislation [2].

Bearing in mind the context, we have compiled the data of our results from the amalgamation of our observational studies and the non-EMA prescription use in order to make the research and proposals in our preliminary communication widely available.

The purpose of this document does not seem to be intended to embrace, ultimately, similar classifications.

The practice guide for the prescription of non-EMA drugs, authorised and overseen according to the terms of the public health and welfare code, is obviously not the usual way for an analysis of therapeutic efficacy but, during a pandemic, the results must benefit from the feedback information from the field by modelling to the strict demonstrative evidence.
Obviously, in the following case studies, we have adopted non-randomized studies, the data presentation and results are not expressed by a desire of research but simply in-field evaluation reproducing our initial theorisation.

Although we are well aware of the weaknesses in both the methodological and the statistical analysis, we have chosen an effective dissemination strategy in order to inform as many medical teams as possible about it, but this time, with more back up "material" than in our initial communication. The pandemic context and the response to be put in place faced (and still face) major challenges unmatched in the past, so different approaches are sometimes needed to launch traditional approaches. The collection of outside MA prescription input was, in our opinion, one of them.

Beyond the methodology, results and concept should indeed be treated and explored to their true potential.

Covid-19, histamine, antihistamines: recent updates and initial hypothesis

The work and proposals conducted in cohort studies in the fight against Covid-19 are numerous and of unprecedented density and speed.

Many of them provided details that we believe could allow progress in the approach and understanding of the possible links between SARS-Cov2, Covid-19, histamine and antihistamines, this was the case in June 2020 during our first update, it is even more relevant a year later ...

As indicated in February 2020, we believe that Covid-19 arises from the virus-host interaction through the various individual reactivities related to histamine. The precocity of interacting with the histamine system had been stressed as paramount. In doing so, histamine has direct but also indirect harmful potentials (mast cell activation, cytokine production, etc.). In order to encompass these two types of effects, we will speak here of the "histamine system" therefore including histamine and the "side effects" linked to histamine (mast cell activation, cytokine production, etc.).

A quick update is therefore made here on the work showing the relationships between Covid-19, “histamine system”, direct antihistamines, active on histamine receptors (of which there are 4 types) and “indirect antihistamines”, in other words, all elements opposing the effects of histamine.

Previously known properties of histamine - antihistamines

Beyond a single theorisation of the possible role of histamine (and its biological implications) in Covid-19, our reflection on the positioning of antihistamines in the therapeutic management of Covid-19 was based on certain properties previously known.
In order to better understand the potential benefit of the fight against histamine and its effects in Covid-19, we will give a brief reminder.

Histamine is released by different cell types and in particular by mast cells and basophils with an action mediated by different types of receptor [3]. It is involved in the immune response with an action of modulating the differentiation of T helper (Th) lymphocytes in Th1 - Th2 [4].
As a reminder, Th1 activates macrophages and cellular immunity and Th2 activates the production of B lymphocytes [5]. B and T cells then interact at the level of secondary lymphoid areas and the production of the specific humoral response of the antigen concerned, begins. The (immunoglobulin E) IgE will then activate the mast cells causing their degranulation and the release of histamine [6].

The links between histamine and IL1, IL6, etc… have been known for a very long time.

Histamine is also involved in the response to certain viral infections with a capacity to release histamine during a viral infection, as has already been well demonstrated in animals for certain viruses [7].

In terms of responses to viral infections, it has been shown that the H1R histamine antagonists have an inhibitory potential on the entry of certain viruses including viruses such as Ebola and Marburg [8] but also influenza [9] viruses.
This potential inhibitory capacity is therefore essential to consider with SARS-Cov2 and, multiple studies to which we will return, have made it possible to establish numerous leads on the inhibitory potential of antihistamines.

It is known that histamine induces the release of certain interleukins by different cell types including in particular endothelial cells [10], the possible involvement of which in the lesional processes of Covid will be the subject of a more specific point below.

Likewise, it is useful to mention the involvement of histamine as a potentiator of other monoamines with ultimately a known pro-thrombotic action [11] (platelet aggregation) [12].
As part of the character of combating thrombotic processes, certain antiH1R antihistamines are known to be able to oppose PAF (Platelet-Activating Factor) with a very particular attraction in their possible repositioning in Covid-19 in order to fight against micro-thrombosis induced in this disease [13].

There are many other implications and consequences (direct or indirect) of histamine in the immune-inflammatory response.
We have mentioned here only known implications useful for the full understanding of the remainder of our presentation.

SARS-Cov2 / Covi-19 - Mast cell activation syndrome

SARS-Cov2 would interact with mast cells and activate them [14]. Thus, SARS-Cov2 could have the ability to cause the release by mast cells of various mediators including TNF-α, prostaglandins, IL1, IL6, leukotrienes and histamine [15].

The activation of mast cells has been demonstrated in Covid-19 by various other studies [16,17,18,19,20,21] and thus seems to be well anchored in the global pathogenesis of Covid-19, confirming our initial hypothesis as to the link between Covid-19 and "histaminergic system".

This notion of mast cell activation in Covid-19 therefore opens up a field of interest in known molecules having a stabilizing action on mast cells, including antihistamines [18,19,20,21].

SARS-Cov2 / Covi-19 - histamine: anatomopathological findings, IL1, IL6 and others

It has been reported that damage to different organs in Covid-19 could be linked to the finding of endotheliitis, in particular in connection with endothelial activation linked to the cytokine storm observed during the course of Covid-19 (direct viral pathogenic role also possible). [22]

It should be noted that the main cellular damage observed was apoptosis. [22] This corresponds to the known in vitro cytotoxicity of histamine. [23]
Thus, correlation does not imply causation and although the extrapolation in vivo of a pro or anti-apoptotic action of histamine on these cell types is not documented here, a possible cytotoxic action of histamine, after prolonged presence and / or at high levels, would remain compatible with the observations made.

In addition, the inflammation of the endothelium, known to be pro-thrombotic, could be the result of an immuno-inflammatory reaction during Covid-19 leading, among other things, to multi-visceral endothelial dysfunction.

Moreover, microvascular and thrombotic damage occurred fairly quickly during Covid-19.[24] As previously mentioned, the involvement of histamine as a potentiator of other monoamines with ultimately a pro-thrombotic action being known [11,12] (platelet aggregation), these findings of microvascular and thrombotic attacks therefore only reinforce the need to better understand the involvement of the "histaminergic system" (with its known links to other pro-coagulant) in the genesis of these abnormalities during Covid-19.

It should be emphasized that this would be one more action, strengthening the pro-coagulant potential of endothelial dysfunction induced by "only" endotheliitis.

Antihistamines could perhaps contribute to the limitation of these microthombotic processes (or even the suppression of their genesis and / or "amplification") as also mentioned by similar more recent hypotheses.[13]

Furthermore, if we consider the cellular expression of antihistamine receptors, in particular H1R, it turns out that endothelial cells could appear to have high expression of this receptor, [25] without prejudicial action induced by histamine.

It has been shown that endothelial cells (in human coronary artery) see an increase in the production of certain cytokines (IL6, IL8) in the presence of histamine with a dose-dependent relationship and over expression in the presence of TNFα in particular. This effect of histamine on cytokine production is blocked by antagonization of H1R receptors (diphenhydramine) and not by that of H2R receptors. [10,23]

It consequently appears possible to consider that, following the activation by SARS-Cov2, in particular of mast cells, a release of histamine may occur. Histamine would then induce, specifically the proximal endothelial cells, an accentuation of the production of cytokines and in particular of IL6 (especially since mast cells are known also to be released also after activation of TNFα[14] which will therefore increase the histamine induced potential).

It also appears that there is a difference in kinetics of the production of these different mediators, with, with regard to histamine, there is a very rapid production since it is stored beforehand, unlike molecules to be synthesized (IL6, IL1, etc.). [14]
A similar phenomenon could also be at work in the event of a reduction, in Covid-19, of the elimination / neutralization capacities physiologically in place within the body.
The latter does not exclude the former, a synergistic origin of the deleterious effects of histamine could this way be at work (in the end: increase of its extracellular concentrations and / or of the presence level in the extracellular environment).

In addition, this action of histamine on IL6 production does not appear to be specific to a cell type but has been highlighted for different cell categories (pulmonary macrophages, monocytes, nasal fibroblasts). [25,26]

It should be noted that, for some cell types (pulmonary macrophages among others), the relationship between IL6 production and histamine is thought to be made in particular as a result on H1R activities [27,28].

In the management of Covid-19, some therapeutic hopes have been placed in a monoclonal IL6 inhibitor tocilizumab [30,31] with relatively encouraging results in terms of the therapeutic potential. [32]

Therefore, it appears that limiting the overproduction of IL6 upstream could thus be a complementary (or even suppressive) route to its elective targeting using tocilizumab. Antihistamines could be of particular interest in doing this. If the use of antihistamines is late, thus not making it possible to avoid the overproduction of IL6, the concept of “multi-class therapy with sequential deployment” then takes on its full meaning (deployment of different therapeutic classes because they are effective at different stages).

It appears to us here that, taking into account, what was previously mentioned, (expression of H1R, involvement of endothelial cells in the synthesis of IL6 in a dose-dependent response to histamine, selectivity of antiH2), it is possible to consider more logically an action mediated by antihistamines antiH1. This still remains to be validated.

The fact remains that a complementary and cumulative action of antihistamines can be considered. Indeed, the activation by histamine of the H2R receptors is known to be involved in the greater efficiency of the IL6 gene reflecting an induced enhancement by IL1.[25]

Thus, the production of IL1 by mast cells generates a potentiating effect of IL6 production.
This last notion, very theoretical, however, allows us to better understand the therapeutic interest that may have aroused (at least for a while), by anakinra (competitive inhibitor of IL1 to the type 1 receptor (IL-1RI) [33] in the management of Covid-19.

Beyond that, the involvement of IL1 seems to be partly attributable to a potential histamine induction with regard to, ultimately, the cytokine release. Indeed, in the same way that histamine is "reliable" to

an increase in the production of IL6 (and therefore participates in any case at least to the increase in the levels of IL6), it could participate in the increase of IL1 levels, through its H2R effects. [34]

This involvement, by histamine, of different cytokines (IL1, IL6) including the observations and hopes of therapeutic countermeasures (respectively anakinra, tocilizumab) widely publicised in France in their repositioning as part of the management of Covid-19, can only encourage (only to reinforce) the study of substances known to be active on the direct histamine effects (upstream of its activation of the various cellular receptors) or indirect (or downstream, in connection with the processes linked to the activation of histamine receptors) to and particularly safe use molecules such as antihistamines.

Therefore, all the substances involved in the reduction of the histamine level and / or in the reduction of the effects of histamine should be taken into consideration in the fight against Covid-19 and, of course, as a first choice, antihistamines and other molecules decreasing the production of histamine and / or its effects.

As such, and at this stage of our presentation, it is interesting to point out that a significant number of molecules have been put forward as potentially effective and interesting in the therapeutic response to be deployed in the face of Covid-19.
As we have just seen, some are thought to occur after the release of histamine (anakinra, tocilizumab). This is also the case for other substances for which preliminary work or functional hypotheses have evoked an interest (more or less confirmed) in Codvid-19: vitamin D, [35,36] Quercetine, [36,37,38] Luteolin, [39] Carnosine [40] in particular.
These substances are known to have a stabilizing capacity on mast cells, participating de facto in the reduction of their activation and therefore in the reduction of the release of histamine, this could, put a potential brake (or even stop) to the cascade of events which results in the inappropriate inflammatory response observed in Covid-19 (note that some are known to interact with histamine receptors). [41,42,43,44]

It should be mentioned that, as it is, as indicated in the initial hypothesis, of the extremely variable sensitivity (hyperreactivity or not) in connection with the immuno-inflammatory system specific to each individual, the clinical impact of this type of molecules can take on a great variability.

In any event, the targeting at a given time of a specified effector of this cascade meets the definition of a multi-class therapy with sequential deployment with antihistamines as the initiator and possible "enhancer".

However, it is obvious that, the more time passes, the more the runaway of the immuno-inflammatory cascade and the induced-lesions, ultimately only result from the multiple therapeutic response of all the supposedly active actors. The micro then macroscopic tissue lesions, induced by immuno-inflammatory phenomena, are afterwards taking a pathological role of their own and for which therapeutic countermeasures then become specific (or even non-existent).
For this reason, the initiation of the first therapeutic countermeasures must be as early as possible. Antihistamines, which enjoy a real ease-of-use, a modest cost and the potential blocker effect are therefore the most promising candidate for clinical trials (especially antiH1 but also perhaps an antiH1-antiH2 combination).

The sequence of activation of the physio pathological phenomena induced by SARS-Cov2, appears capable to respond to a cascade of events during which histamine occurs both in the initial phase but also by participating (probably in a dose-dependent manner) to the production of cytokines which, in the end, will act on their own.

It therefore appears most useful to consider the role of histamine from the initial phase of induction of immuno-inflammatory phenomena. The interest of antihistamines (in particular antiH1) thus taking its full meaning.
Any decrease in secretion or effects induced by histamine, logically being of notable importance in reducing, or even stopping, the immuno-inflammatory cascade and its deleterious short, medium and long-term effects in Covid -19.

Thus, in general, any drop in extracellular histamine concentrations or / and any blocking of its effect decreases its cellular and biochemical actions and their consequences.

SARS-Cov2 / Covi-19 - antihistamines: hypotheses regarding potentials, modeling and in vitro study

In vitro Modeling

Various modeling works (molecular binding type, etc.) have underlined the interest of antihistamines at different levels in Covid-19, particularly in their potential for direct anti-viral action.

Thus, the value of repositioning an antihistamine was mentioned in an article published in the Nature Journal in April 2020. [45]

Since then, various modeling work has made it possible to refine the value of antihistamines. We will briefly mention them by schematising their contributions.

Clemastine, azelastine and trimeprazine, antagonists of histamine, have the capacity to oppose the entry of the SARS-Cov2 virus into cellular models. [46]

Loratadine and desloratadine, H1R antihistamines, are believed to have the ability to oppose entry of the SARS-Cov2 virus into cell models by blocking its binding to ACE receptors. [47]

Famotidine and Cimetidine, H2R antihistamines would show an ability to bind to SARS-Cov2 and thus, would be of potential interest in the fight against Covid. [48]

Doxepin, a molecule with strong antiH1R activity, could oppose infection of host cells by SARS-Cov2 by preventing the binding of the virus's Spike protein to the cellular ACE2 receptor. [49]

Ketotifen, an antiH1 antihistamine is believed to be able to reduce viral replication on a cellular model with an additive or synergistic effect when certain other molecules are combined with it (naproxen, indomethacin). [50]

Chlorpheniramine (antiH1) would significantly decrease the viral load of the model, which could suggest a strong virucidal power. [51]

Hydroxyzine and azelastine are believed to have the ability to block the spike-ACE2 interaction. [52]

Antihistamines and useful application in Covid-19

A number of authors have expressed, through different mechanisms of action, the potential interest of various antihistamines in Covid-19, we will show this in a schematic way.

Ebastine as well as Idelalisib molecule for which the anti-allergic potential is known according to the authors (allergic rhinitis), would be of interest in the management of Covid-19. [53]

Rupatadine, an antiH1 antihistamine, is proposed in the prevention of microthrombosis observed in Covid due to both its stabilizing action on mast cells and its anti-PAF (Platelet Activating Factor) activity [54].

The use of antihistamines because of their observed action but also their safety and undisputed convenience appears to be a hypothesis to be promoted in the context of the repositioning of old molecules. [55]

A review of the literature has made it possible to highlight the potential interest of antihistamines (H2R) in Covid. [56]

In a review of the literature carried out on articles published on 27/10/2020 (42 papers) published in February 2021, PEDDAPALLI et. al. helped to consolidate the importance of histamine in the pathophysiological processes of Covid. It was thus better understood the significant potential in the fight against Covid of molecules limiting the effects of histamine or even neutralizing histamine [57]. Histamine would therefore play a major role in the injury mechanisms observed in Covid.

Likewise, a very recent work, published on 26/05/2021, just before the end of writing our update, consolidates the essential role played by the histamine system and antihistamines in the strategic response to Covid-19 [58].

Others have advanced on either observational or theoretical bases and in relation to the known stabilizing effect of antihistamines, the interest of this therapeutic class in the management of Covid-19.

Thus, it was found that in Europe, a small proportion of patients with psychiatric disorders were affected by SARS-Cov2 [59].
Psychotropic drugs have also been targeted as potentially interesting in the management of Covid-19 [60]. It is interesting to note that out of all the therapeutic procedures potentially used in this particular group of patients, almost all of the molecules potentially utilised have known exclusive or partial antihistamine activity (phenothiazine, chlorpromazine, promethazine, thiethylperazine, triflupromazine, cyamemazine, levopromazine, propericiazine, pipotiazine, metopimazine, loperamide, mequitazine, tiotixene, flupentixol, zuclopenthixol, pimozide, haloperidol, astemizole, pipamperone, clomipramine, amitriptyline, benztropine, paroxetine).

As a reminder, many studies focus on mast cell stabilizers, cells whose direct and indirect link with histamine is well established.

SARS-Cov2 / Covi-19 - antihistamines: observations, clinical studies and field practice

Epidemiological aspects

To the question of whether in this pandemic, the use of antihistamines could appear to be "protective", certain epidemiological data have allowed for 16 months, to incorporate certain elements in the answer.

First of all, it should be noted anecdotally that, quickly after the start of the epidemic in France, some expressed their (subjective) observation as to a lesser impact in severe cases (resuscitation).

A small Italian pediatric unit reported that allergy and controlled asthma may appear "statistically" protective against Covid-19. [61]

In the USA, a study on a panel of more than 219,000 people showed a decrease in the incidence of positivity rate to SARS-Cov2. [52]

Likewise, in Spain, a retrospective study on 79,000 people would have made it possible to suggest the possible protective role of taking antihistamine. [62]

Chronic antihistamine intake, however, does not seem to be able to prevent contamination by SARS-Cov2 and the development of Covid-19, due to the very indication of this chronic medication.

Indeed, there seems to be a balance between "level" of histamine and "disease". In fact, chronic antihistamine intake is linked to the "allergic" disease which (already) corresponds to a "high" (or easily elevated) level of histamine. Therefore, the absence of symptoms is related to the compensation with the antihistamine of this high or reactive level of histamine.
Thus, there is (or not) a "residual" capacity for compensation, a "reservoir" of more or less significant antihistamine effect depending on each person. The Covid increasing (to simplify) histamine, if this residual capacity makes it possible to compensate, it could in our hypothesis, not develop Covid-19 otherwise it is necessary in theory (and in our clinical findings), to either increase the dose or change the molecule.
To this end (type of molecule) some antihistamines could have more ability to inhibit SARS-Cov2 replication but, remember that the viral load may not be, for some, the only element impacting the onset of Covid-19 infection. It turns out that, even if some antihistamines were found to be protective in vivo, there could be an overflow of this protective capacity in the face of high viral load or individual sensitivity / reactivity.
In other words, “chronic” allergies treated with antihistamines have a balance between spontaneous allergic process (and more or less permanent) and the effectiveness of the antihistamine treatment. Therefore, they do not develop symptoms, thanks to this balance. After contagion, SARS-Cov2 would, according to our primordial hypothesis, cause a release of histamine, the starting point of the immuno-inflammatory cascade ("corridor theory"). Thus, although on an antihistamine, some treated patients with chronic allergy would see their amount of histamine exceed that of HRH1 blockers and the immuno-inflammatory cascade would begin (with more or less power depending on the "antihistamine leeway" available).
Thus, to manage these patients, it is necessary either to increase the dose of antiH1 or to change the antiH1 (or to combine it with an antiH2).

Clinical studies

Since February 2020, clinical studies have confirmed the finding made in our observational work.

The potential benefit of certain H2R antihistamines in the management of Covid-19 has thereby been demonstrated. This way famotidine would have shown an ability to reduce the number of intubations and deaths in hospitalised patients. [63]

The use of antiH1 and antiH2 antihistamines has shown interest by utilising antihistamines in Covid. [64]
The use of antihistamine and azithromycin has been shown to significantly improve the prognosis of patients with Covid. [65]
Taking antihistamines for prophylaxis in contact subjects would also seem to show significant efficacy.

Note that recently, a South African team reported its results which seem more than encouraging in the management of Covid-19 by means of antihistamine (unpublished).

Despite the paramount importance of the histamine system seems to us to represent in Covid-19, to date, few clinical studies have been carried out.

The incomprehensible reluctance to reposition old molecules in the therapeutic regimen that can be deployed in Covid-19 may seem to be the reason. This obviously does not only concern antihistamines, but the latter seem to be largely ignored for their true potential ... strategic ignorance, ignorance of their efficacy or total lack of interest in the Covid-19. Time will tell.

SARS-Cov2 / Covi-19 - antihistamines: non-HR dependent activity, links and antihistamine-like activity of other therapeutic classes

The activity of antihistamines may also be mediated by a nonreceptor dependent action.
Thus, certain antiH1 antihistamines have an anti-inflammatory action through certain interactions on the production of prostaglandins 2 (PG2), without this activity being only performed by the sole H1R activity. [66]
Note that histamine also has a dual effect on inflammation with pro or anti-inflammatory capability depending on the cell types and the types of receptor involved. Histamine would as well be involved in the inhibition of leukotriene synthesis (LT) with reduction of the action of 5-lipoxygenase [67]. This effect, mediated by the antiH2 receptors, is antagonized by ramitidine (antiH2) which induces a more or less complete suppression of LT biosynthesis reduction. [67]
Thus, the actions of antiH2 could induce a relative increase in LT production and, with it, reduce the active potential of antiH2 on a part of the immuno-inflammation.

AntiH1 do not appear to interfere with this suppressive or diminishing anti-inflammatory effect sometimes observed. Consequently, and in a purely theoretical way, it could result from it either a slower or partial action of the antiH2 compared to the antiH1.

We can therefore also see the potential interest of antileukotrienes through their positioning, mentioned in the initial hypothesis, within the potential anti-inflammatory countermeasures and this, regardless of their possible and associated action on viral adhesion. [68] The action of anti-leukotrienes can also be supplemented by their known ability to reduce production, among others, of IL6 [69] which we have addressed in the very likely involvement in Covid-19.

These data obviously need to be deepened. The notions of possible partial affinities and cross activations taking on all their importance here, as well as that of the functional duality of histamine.

These possibilities of "cross" action and functional duality of histamine further complicate the known actions of the various specific histamine receptors. The concept of feedback control and interdependent effects is also to be considered, like what can be observed at the neuronal level between RH3 and RH1. [70]
Likewise, the expression of variable cell receptors (including the time relation) as well as the effects of co-activations (for example RH1 and RH4) is also possibly a source of differentiated actions. [71]

Beyond the complex relationships of histamine with its various specific receptors - RH 1 to 4, this biogenic amine is also known to enter into a relationship with other receptors, in particular cytokine receptors.
This opens a possible action on the immuno-inflammatory responses in connection with, perhaps, T helper lymphocytes CD4 *, T lymphocytes CD8 * and NK [72] whose involvement in the infectious response is obviously to be considered. The interactions of biogenic amines (and particularly histamine), on the cytokine receptors involved in particular in the antiviral response, have moreover been perceived [73], thus paving the way for a complex field of research as to the understanding of the mechanisms at work and the scale of action or differentiation induced factors.

Between action outside dedicated receivers, activation, modulation and other feedback control, understanding the mechanisms at work offers a wide field of reflection and exploration

To this complexity of action of the antihistamine system itself, the contribution of molecules impacting the downstream pathways of primordial histamine activation, further complicates matters in the emergence of a standard treatment.

For example, the role that vitamin D appears to play, the importance of which as a cofactor of antimicrobial control is known [74]. Based on the possible antimicrobial involvement and epidemiological data, the potential usefulness of vitamin D has been highlighted in the management of Covid-19.[75]
Supplementation is therefore, sometimes recommended in order to optimize antimicrobial control, including for SARS-Cov2. [76]
This will be enough for the French Academy of Medicine to issue a recommendation via a press release dated May 22, 2020 to provide a systematic vitamin D supplementation in the event of Covid-19 [77] and

this, even if the beneficial effect of supplementing severe cases of Covid-19 did not demonstrated a tangible efficacy. [78]
In doing so, vitamin D would participate in maintaining the stability of mast cells and its deficit would be associated with their activation. [79]
Supplementation would thus provide, in the event of a deficit, stabilizing aid making the involvement of histamine less effective in the course of Covid-19, this however seems marginal to us but, as indicated, any limitation of the release of histamine appears to us useful.

This notion of a therapeutic class different from that of antihistamines but having an activity which ultimately converges in part on the histamine system is important to address.

It is indeed to consider the action "antihistamine-like" of certain molecules or therapeutic class.

Thus, some antidepressants would seem to be promising in their potential to fight Covid-19.
A multicentre retrospective observational study carried out in France in partnership with AP-HP (Assistance Publique - Hôpitaux de Paris) and INSERM showed a reduced risk of intubation and death in patients with Covid and also treated with certain antidepressants (fluoxetine, paroxetine, escitalopram, venlafaxine and mirtazapine).
It is interesting to note here that these four antidepressants all have known antihistamine action.

Likewise, as of April 2020, some studies seemed to show a decrease in the prevalence of Covid-19 among smokers, raising questions about the possible protective role of nicotine. Note that these studies only addressed the aspect of prevalence and not the severity of smoking in cases of Covid. [81,82]
Here again, a link with the histamine pathways exists since certain studies tend to show that nicotine appears to be able to cause a decrease in the production of histamine, at the cellular and tissue level [83,84].

We can also mention chloroquine and hydroxychloroquine, the media coverage of which makes it unnecessary to expose the possible potential in Covid-19 patients. Here again, there is a known link between these molecules and the histamine system either "downstream" (activation of mast cells) [85,86], more directly linked to histamine. [87]
It will be noted that there is a duality in the effect on the histamine system of chloroquine with, possible reduction of its release by stabilizing effect on mast cells and effect of reducing the elimination of histamine by possible inhibitory effect on the histamine N-methyltransferase.
As a reminder, there is a duality of opinions and findings on the effect of chloroquine on Covid. During the early phase, it would seem useful, while in the more advanced phase some describe it as deleterious. Therefore, we can argue that the early phase does not yet correspond to a "full" activation of mast cells, the stabilizing effect will therefore be fully beneficial while in the late phase, mast cell activation is "launched" with a de facto increase in histamine release and the decrease in histamine degradation does not appear to be very relevant.
Once again, the complexity of the mechanisms at work and the runaway immuno-inflammatory system call for treatment as early as possible.

However, a link does exist between the histamine route and chloroquine.

In the register of convergences of biological action, ivermectin is currently one of the molecules whose activity in Covid-19 seems promising, we will not come back to the multiple studies that have reported its effectiveness in the management of Covid-19 patients, with regard to the controversy currently created, to mention only one, that of Professor KORY [88] for which we have a very special emphasis in connection with a recent controversy emphasizing the current difficulties in terms of scientific communication. [89] It is indeed interesting to point out that Ivermectin ha, in invertebrates, an action on the histamine system according to various in vitro studies.
It would therefore be interesting to refine the possible links, in human biology, with Ivermectin and the histamine pathway system. [90,91]

Furthermore, it should be noted that Ivermectin is structurally close to macrolides (without possessing antibiotic action). This opens up an interesting field of research, in particular in molecular mimicry, with regard to the possible beneficial effects of certain antibiotics of this family.
This notion of molecular mimicry, which is very theoretical, however, has a very special appeal to examine. For example, Molnupiravir, appeared in the mainstream press as the potential "anti-Covid pill" is the prodrug of hydroxycytidine [92]. Hydroxycytidine has been studied with regard to these possible molecular targets, in particular based on neighbouring molecules (molecular conformation) [93]. Azacytidine and adenosine are two of three structurally comparable molecules. However, azacytidine is known to have an affinity with methyltransferase and adenosine is known to have an inhibitory action on the release of histamine by pulmonary mast cells (with a higher concentration and after intracellular penetration (so later), the opposite effect) [94].
Here again, the relationship remains very theoretical and obviously needs to be refined, but there is undoubtedly a relevant research axis in the context of possible molecular mimicry.

We have previously mentioned the observation by certain teams of the value of antibiotic therapy (azithromycin in particular) in Covid-19, beyond the possible associated bacterial superinfections. This raises questions, in addition to the hypothetical molecular mimicry, about the possible mechanisms of action of antibiotics in this pathology.
It has been argued that the digestive microbiota appears to be involved in the severity of Covid, possibly related to its impact on the host's immune response. It could also be involved in the long-term persistence of symptoms of Covid [95].
A notable link, to be understood better of course, could be the fact that certain bacteria, particularly with an intestinal tropism, are known to have the capacity to secrete histamine [96].

SARS-Cov2 / Covi-19 - risk factors and antihistamines

Finally, let us mention a few possible links highlighting the probable entanglement of the different elements involved on the metabolic level during the attack by SARS-Cov2.
Diabetes has been identified as a serious risk factor in Covid. Here again, the relationship between glucose level and the histamine system may need to be further understood due to the known links between glucose level and histamine.[97,98]
As such, it should be noted that obesity, another known risk factor in Covid, beyond the ventilation disorders that may be involved, certainly has a frequent association with the disorder of glycemic regulation but also, a link with the histamine system and this beyond a central action mediated by H3R since, abdominal fat could be a source of histamine “dysfunction”.
Likewise, as has been observed in the brain during development [99], it would be interesting to assess histamine production, histamine sensitivity and age.

Finally

It seems lawful to us to consider antiH1 antihistamines as a possible therapeutic strategy for Covid-19. The observations are fully in line with the expectations of the theorization initially presented, as well as a good number of recent data resulting from the progress of knowledge and possible emerging therapeutic targets.

However, some results confirm the notion of a sequential therapeutic deployment (or combination) which would be an element that could optimize the management of Covid-19, following the immuno-inflammatory cascades triggered response.
During each phase, some targeted therapeutic countermeasures: antihistamines, antileukotrienes, synthetic antimalarial drugs, corticosteroids and other drugs atc on the immuno-inflammatory event. Their use must be adapted to the most "boisterous" immuno-inflammatory phase.
It is therefore a matter of management with a sort of "multi-class therapy with sequential deployment" according to the biochemical evolutionary stage most intensely at work at the time of the patient's care, de facto making the treatment of Covid-19, a treatment with individual adaptation but for which histamine seems to be the basic common denominator.

In any event, the first issue is the early blocking of SARS-Cov2 contamination from the deleterious effects induced by the host-pathogen interaction.

The efficacy of antihistamines antiH1 during Covid-19 needs to be better understood. Their potential utility in Covid-19 seems to be able to be put to good use in the acute phase but also to consider during the possible long-term complications, which could arise from the action of the immuno-inflammatory system (sometimes infraclinical) - pulmonary fibrosis…

Likewise, the overwhelming forms should consider the persistence of abnormal (and low burst) activation of the immuno-inflammatory system or reinfection without stable immunization. The long-term deleterious effects also remain in the patients, beyond an individual health issue and as a public health issue. The components of these extended forms need to be further explored.

The development of knowledge on the relationship between SARS-Cov2, Covid-19 and histamine only reinforces the usefulness and the urgency of carrying out additional clinical validation studies.

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Hypothèse Covid-19 - antihistaminiques : pertinence actualisée selon évolution des connaissances - observations

ARMINJON S[1]
Juin 2021

Avertissement
Ce travail n'est qu'un exposé des éléments devant amener à considérer la prise en charge du Covid au travers de la « voie histaminique ». Il est certainement empreint d'une certaine subjectivité mais, comment pourrait-il en être autrement face au constat pour un praticien de terrain de la lenteur du déploiement des traitements curatifs potentiels, les polémiques, interdictions et menaces.
Le lecteur avisé saura écarter l'effet d'usure de cette situation éthiquement et intellectuellement inadmissible pour ne retenir que ce qui, ici, est primordial : l'ouverture (enfin) d'un axe de réflexion thérapeutique et de recherche.
Certaines approches sont très théorisées, il ne s'agit là, non pas de démonstrations **mais uniquement de l'évocation d'axe de réflexion**.

Résumé

Fin février 2020, à l'émergence européenne de ce qui était encore une épidémie liée au SARS-Cov2, nous avons, sur la base des données épidémiologiques, cliniques, paracliniques et évolutives du CoviD-19, formulé l'hypothèse d'une pathogénicité du SARS-Cov2 médiée principalement par **la combinaison virus-hôte et ce dès le contact initial.**

De l'interaction avec l'agent pathogène, le système immuno-inflammatoire de l'hôte produirait une **réaction, parfois exacerbée et délétère** à court, moyen voire longs termes.

Le SARS-Cov2 possèderait un pouvoir de contagiosité élevé mais surtout une capacité (sans aucun doute encore jamais rencontrée ou appréhendée) à **provoquer chez son hôte des réactions excessives du système immuno-inflammatoire** ce dernier, supportant vraisemblablement toute ou partie de la pathogénie.

La plus ou moins grande susceptibilité réactive du système immuno-inflammatoire de l'hôte en réponse à son contact avec le SARS-Cov2 déterminerait dès lors l'évolution clinique et in fine la gravité de la maladie (immédiate ou différée (Covid-long)).

Cette susceptibilité de l'hôte à produire une réaction initiale de défense, se « retournant » plus ou moins rapidement contre lui et de façon plus ou moins forte, pourrait ainsi expliquer les différentes hétérogénéités du Covid-19 tant cliniques, que biologiques ou évolutives et ce, quel que soit le stade de la cascade immuno-inflammatoire et/ou et le moment évolutif.

De même, et en droite ligne, les effets délétères en lien avec ces activations du système immuno-inflammatoire sont potentiellement inquiétants pour les « séquelles » qu'elles pourraient laissées ou les réactivations lors d'un second contact.

Dès lors, c'est à **une dangerosité potentielle non pas de l'agent viral (SARS-Cov2) de façon intrinsèque mais bien dans la réaction suscitée chez l'hôte**, à laquelle les malades seraient soumis.

La réactivité intrinsèque propre à chaque individu déterminant en quelque sorte « son » Covid19 en termes de cinétique évolutive, de clinique mais aussi de gravité voire de séquelles ultérieures.

D'une manière ou d'une autre, le SARS-Cov2 génèrerait une réaction immuno-inflammatoire pouvant s'auto-emballer de façon progressive ou/et explosive voire infraclinique.

Ce caractère parfois explosif et imprévisible ainsi que les hétérogénéités observées et les fonctions connues de l'histamine orientent vers la mise en jeu de cette amine biogène lors de l'initiation mais aussi au décours de l'activation et l'emballement du système immuno-inflammatoire voire peut-être de façon directement viro-induite.

Différentes observations cliniques sont venues consolider la possible pertinence de notre hypothèse. De même, les progrès des connaissances dans le Covid-19 ont apporté de nombreux éléments confortant l'implication possible de l'histamine et avec elle, l'intérêt probable des antihistaminiques.

Nous reprenons ici l'ensemble de ces éléments en complétant nos écrits antérieurs (février-mars, juin 2020) -cf annexes - à la lumière de nouvelles recherches bibliographiques et des nouvelles connaissances (juin 2021).

Contexte et hypothèse initiale

Dès l'émergence des premiers cas en France de Covid-19 nous avons formulé une hypothèse quant à la pathogénie liée au Covid-19.

La participation du système immuno-inflammatoire serait à l'origine, au travers de l'interaction agent pathogène-hôte, de la symptomatologie hétérogène observée et de la gravité variable à la fois inter et intra-individuelle et ce, dès les premières interactions agent pathogène-hôte.

Ainsi, la physiopathologie inhérente au Covid-19 serait issue des effets délétères principalement -voire exclusivement- en lien avec une réaction excessive du système auto-inflammatoire et auto-immun de l'hôte. La caractéristique même du système immuno-inflammatoire en termes de « puissance de réponse » pouvant apporter compréhension quant aux observations de l'hétérogénéité qui semblait être de mise dans le Covid-19.

Le virus SARS-Cov2, pour contagieux qu'il soit, apparaît, en lui-même, dangereux quasi uniquement dans sa capacité de déclenchement d'une réaction inflammatoire et immunitaire qui peut devenir excessive et délétère à court, moyen voire long terme.

Dans ce concept, les effets physio pathogéniques « indirects » liés au SARS-Cov2 seraient responsables de la maladie. Ils seraient également présents dès les stades précoces et « fusionnés » avec les effets physio pathogéniques « directs » du SARS-Cov2. Ainsi, dans le Covid-19, les effets délétères viraux ne seraient pas suivis, comme il n'est pas inhabituel de le voir dans certaines viroses **après** une phase évolutive plus ou moins longue, d'effets indirects mais provoqueraient d'emblée la mise en jeu de la chaine de réactions délétères « indirectes ».

Dans cette hypothèse, les effets physio pathogéniques « indirects » liés au SARS-Cov2 seraient impliqués (donc à cibler sur le plan thérapeutique) dès leur genèse (et donc peut-être dès le contact initial hôte-virus). Ce ciblage précoce pouvant permettre de limiter les effets délétères dont le possible emballement immuno-inflammatoire bruyant ou non.
De cette notion, la charge virale lors du contage pourrait devenir moins déterminante en termes de capacité du SARS-Cov2 à induire le Covid-19. En effet, dès lors que ce serait les effets physiopathologiques « indirects » qui entreraient en action via l'interaction virus-hôte, **la charge virale** initiale bien que potentialisant le démarrage voire l'emballement, **deviendrait moins déterminante en termes de capacité d'induction de la maladie** (et donc également en termes de contagiosité). Ceci peut être approché avec les concepts en vigueur en allergologie et selon lesquels, la charge d'allergène, pour cruciale qu'elle soit, n'est pas quantitativement limitative au déclenchement de la réaction pathologique.
Ce dernier concept pouvant peut-être, selon nous, rendre compte des différentes observations épidémiologiques et cliniques très hétérogènes. La sensibilité individuelle, la « réactivité » intrinsèque, est, en effet, d'une « puissance » variable et propre à chaque individu. Le SARS-Cov2 pourrait dès lors provoquer des réactions individuelles très variables en contact primaire mais aussi secondaire. Pour compréhension nous ferons cette analogie : une sorte de fonction d'agent à comportement « allergène universel » (pour le comportement « inducteur »).
Les perspectives d'un tel comportement hypothétique dans l'interaction hôte-virus généreraient de facto des implications dans l'élaboration d'un vaccin et/ou dans l'obtention d'une immunité protectrice. Dans cette hypothèse, il y aurait sans doute un pouvoir « d'arrêt » viral mais peu ou pas d'action sur la « maladie » Covid-19 avec cependant certainement neutralisation des certains effets physiopathologiques renforçant encore, lors de contages ultérieurs, l'hétérogénéité clinique déjà observée pouvant amener à des formes cliniques « abâtardies » ou non typiques voire éventuellement des formes encore plus « explosives ».

Dès lors, le cadre nosologique du Covid-19 serait largement hétérogène aux regards des spécificités individuelles (voire intra-individuelles) de réponse et mise en jeu du système immuno-inflammatoire et, notamment, en ce qui concerne la symptomatologie initiale.

Cette caractéristique semblait dès lors pouvoir rendre compte de l'hétérogénéité épidémiologie et clinique constatée.

Les données biologiques à notre disposition ensuite faisant état « d'orage cytokinique », plaidaient également pour une participation auto-inflammatoire et auto-immune dans les formes graves de la maladie au-delà des comorbidités. L'évolution en deux phases avec aggravation à J7-J10 rentrait également totalement dans cette mise en jeu réactionnelle et in fine, délétère, du système immuno-inflammatoire de l'hôte.

Sur ces bases, il convenait donc de moduler au plus vite cette réactivité anormalement élevée du système auto-inflammatoire constatée et ce, particulièrement chez certains patients dont la prédisposition à réagir est forte et reste à comprendre.
Le ciblage et l'utilisation d'une molécule à effet uniquement virucide ou/et virostatique bien que logique, ne semblait cependant pas permettre de s'opposer à la cinétique de mise en route de la réaction auto-inflammatoire et auto-immune, ni pouvoir stopper sa mise en jeu et au final, la maladie.

De cette hypothèse physio pathogénique initiale, l'utilisation de certaines classes thérapeutiques apparaissait évidente pour leur action et rôles connus dans le système immuno-inflammatoire : antihistaminiques en premier lieu (en particulier anti-H1), anti leucotriènes, antipaludéens de synthèse et immuno-dépressiogènes ou immuno-bloqueurs.

Compte-tenu de son caractère ubiquitaire au sein de l'organisme, de sa mise en jeu précoce dans ses actions cellulaires et cliniques connues, l'histamine nous apparaissait être la molécule dont le ciblage devait être prioritaire.
Sa mise en jeu pouvant du reste, relever d'une activation initiale mais aussi lors de l'évolution de la cascade immuno-inflammatoire avec de plus, au-delà d'une induction augmentée, une possible diminution (associée ou non à l'induction) des capacités de l'organisme des malades, d'élimination-neutralisation.
En d'autres termes, implication possible de l'histamine par excès de libération et/ou production associée(s) ou non à une baisse des capacités de clearance « physiques » voire « fonctionnelles », le tout, induit par l'interaction hôte-virus initiale (et ultérieure).
Les antihistaminiques bénéficiant d'un recul et d'une simplicité d'utilisation, cette simplicité d'utilisation en faisait de plus, des candidats plus que concrets et rapidement exploitables dans leurs potentiels d'effets dans le Covid-19 tels qu'avancé dans sa physio pathogénicité (système immuno-inflammatoire). Début mars 2020, la recherche documentaire effectuée ne montrait aucun article sur le sujet (Histamine - antihistaminiques – Covid-19).

Les autres classes thérapeutiques possiblement utiles, intervenant à des temps différents et ultérieurs, ne comportaient pas le potentiel « d'arrêt » des antihistaminiques selon notre théorisation, mais restaient en possible utilisation séquentielle complémentaire.

La prise en charge thérapeutique du Covid-19 nous semblant dès lors pourvoir relever d'une « thérapie multi-classes à déploiement séquentiel » avec en point de départ (et continu) les antihistaminiques.
A chaque phase de la maladie une réponse thérapeutique dédiée en suivant les évènements et éléments de la cascade immuno-inflammatoire en action, avec de près ou de loin les effets initiaux (« promoteurs ») ou d'entretien et/ou renfort de l'histamine. La charge virale et/ou les nouvelles contaminations prenant également une importance renforçatrice possible.
Dans cette hypothèse, il s'avère par ailleurs que la réalisation d'essais cliniques pouvait de facto se voir rendue plus difficilement reproductible en raison de ce possible biais « de phase » dans les populations étudiées, compliquant encore les éventuelles approches thérapeutiques.

Par la suite, nos différentes observations cliniques semblaient montrer (de façon subjective) un effet rapide des antihistaminiques (antiH1) sur une grande partie de la symptomatologie initiale observée lors de la déclaration d'un Covid 19 ainsi qu'un raccourcissement notable de sa durée. Nous avons alors communiqué ce constat en attirant l'attention sur l'utilisation la plus précoce possible des antiH1 dans le Covid-19 (sans attendre le

déclenchement de formes graves : au plus tôt de l'apparition du Covid-19) dans l'espoir de voir se mettre en place des études de bonnes facture scientifique [1].

Nous avons dans le même temps formalisé nos observations et établi un recueil de données observationnelles basées sur l'utilisation d'un médicament (rappelons-le en vente libre en France et dans de nombreux pays), en dehors de son Autorisation de Mise sur le Marché (AMM), comme du reste tous les médicaments utilisés à ce jour dans le Covid-19, en commençant par le paracétamol. La prescription, hors AMM étant parfaitement autorisée et encadrée par la législation française [2].

Dans ce contexte, nous avons donc mis en forme nos résultats, issus d'un mixte entre recueil observationnel et utilisation hors AMM, afin de rendre nos observations et propositions communiquables. La place précise de ce type d'écrit ne nous semble in fine pas prévu dans les classifications. La pratique médicale de prescription hors AMM, autorisée et encadrée selon les termes du Code de la Santé publique n'étant évidemment pas usuelle en termes d'analyse d'efficacité thérapeutique mais, en période pandémique, les résultats observés se devaient de bénéficier d'une « remontée de terrain » en calquant au mieux aux exigences démonstratives.
Evidemment, aucune randomisation initiale n'a été mise en place, la mise en forme des données et résultats ne relevant pas d'une volonté initiale d'étude mais d'un **constat de terrain** calquant à notre théorisation initiale.

Bien que conscients des faiblesses tant en terme méthodologique que statistique, nous avions fait le choix d'une diffusion le plus large possible afin de sensibiliser le plus d'équipes possibles au sujet, avec cette fois, plus de « matière » que lors de notre communication initiale. Le contexte pandémique et la réaction à mettre en place relevaient (et relèvent encore) de défis non égalés dans le passé, il faut ainsi parfois des approches différentes pour lancer les approches classiques. Le recueil de données de prescription hors AMM en a été, selon nous, à l'évidence l'une d'elle.

Au-delà de la méthodologie, **résultats et concept se devaient en effet de se voir traités et explorés à leurs justes potentiels** entrevus.

Covid-19, histamine, antihistaminiques : apports récents et hypothèse initiale

Les travaux et propositions réalisés dans la lutte contre le Covid-19 sont multiples et d'une densité et rapidité sans précédent.

Nombre d'entre eux ont apporté des précisions qui nous semblent pouvoir permettre d'avancer dans l'approche et compréhension des possibles liens entre SARS-Cov2, Covid-19, histamine et antihistaminiques, c'était le cas en juin 2020 lors de notre première mise à jour, c'est encore plus le cas un an après…

Comme indiqué dès février 2020, nous estimons que le Covid-19 relève de l'interaction virus-hôte au travers des différentes réactivités individuelles en lien avec l'histamine. La précocité d'interagir avec le système histaminique avait été soulignée comme primordiale. Ce faisant, l'histamine revêt des potentiels délétères directs mais aussi indirects (activation mastocytaire, production de cytokines…). Afin d'englober ces deux types d'effets, nous parlerons ici de « système histaminique » englobant donc l'histamine et les « effets secondaires » liés à l'histamine (activation mastocytaire, production de cytokines…).

Il est donc réalisé ici un rapide point quant aux travaux faisant état des relations entre Covid-19, « système histaminique », antihistaminiques directs, actifs sur les récepteurs à l'histamine (dont il existe 4 types) et « antihistaminiques indirects » c'est-à-dire, tous éléments s'opposant aux effets de l'histamine.

Propriétés antérieurement connues de l'histamine – des antihistaminiques

Au-delà d'une seule théorisation du rôle possible de l'histamine (et ses implications biologiques) dans le Covid-19, notre réflexion quant au positionnement des antihistaminiques dans la prise en charge thérapeutique de Covid-19 se basait sur certaines propriétés antérieurement connues.
Afin de mieux appréhender le potentiel intérêt de la lutte contre l'histamine et ses effets dans le Covid-19, nous ferons un bref rappel.

L'histamine est libérée par différents type cellulaires et notamment par les mastocytes et les basophiles avec une action médiée par différents types de récepteur [3]. Elle intervient dans la réponse immunitaire avec une action de modulation de la différenciation des lymphocytes T helper (Th) en Th1 – Th 2[4].
Pour mémoire, les Th1 activent les macrophages et l'immunité cellulaire et les Th2 activent la production de lymphocytes B [5]. Les cellules B et T interagissent ensuite au niveau des aires lymphoïdes secondaires et la production de la réponse humorale spécifiques de l'antigène concerné, débute. Les IgE vont alors activer les cellules mastocytaires causant leur dégranulation et la libération d'histamine[6].

Les liens entre histamine et IL1, IL6..etc…sont connus de longue date.

L'histamine est également impliquée dans la réponse à certaines infections virales avec une capacité de libération d'histamine lors d'une infection virale comme cela a, du reste, été bien démontré chez l'animal pour certains virus [7.]

Au titre des réponses aux infections virales, il a été montré que les antagonistes RH1 de l'histamine avaient un potentiel inhibiteur sur l'entrée de certains virus dont les virus, Ebola et Marburg [8] mais aussi les virus influenza [9].
Cette potentielle capacité inhibitrice est donc primordiale à considérer avec le SARS-Cov2 et, de multiples études sur lesquelles nous reviendrons, ont permis d'établir de nombreuses pistes sur le potentiel inhibiteur des antihistaminiques.

Il est connu que l'histamine induit la libération de certaines interleukines par différents type cellulaires dont notamment les cellules endothéliales [10] dont l'implication possible dans les processus lésionnels du Covid fera l'objet d'un point spécifique ci-après.

De même, il est utile de mentionner l'implication de l'histamine comme potentialisateur d'autres monoamines avec au final une action pro thrombotique connue [11] (agrégation plaquettaire)[12].
Au titre du caractère de lutte contre les processus thrombotiques, certains antihistaminique antiRH1 sont connus comme pouvant s'opposer au PAF (Platelet Activating Factor) avec un attrait tout particulier dans leur éventuel repositionnement dans le Covid-19 afin de lutter contre les micro-thrombose induites dans cette maladie [13].

Il existe bien d'autres implications et conséquences (directes ou indirectes) de l'histamine dans la réponse immuno-inflammatoire.
Nous n'avons fait mention ici que des implications connues utiles à la pleine compréhension du reste de notre exposé.

SARS-Cov2/Covi-19 – Syndrome d'activation mastocytaire

Le SARS-Cov2 interagirait sur les mastocytes et les activerait [14]. Ainsi, le SARS-Cov2 aurait la capacité de provoquer la libération par les mastocytes de différents médiateurs dont le TNFα, des prostaglandines, l'IL1, l'IL6, des leucotriènes et de l'histamine [15].

L'activation des cellules mastocytaires a été mis en évidence dans le Covid-19 par différents travaux [16,17,18,19,20,21] et semble ainsi bien ancré dans la pathogénie globale du Covid-19, confortant notre hypothèse initiale quant au lien entre Covid-19 et "système histaminique ».

Cette notion d'activation des cellules mastocytaires dans le Covid-19 ouvre donc un champ d'intérêt sur les molécules connues ayant une action stabilisatrice des mastocytes dont les antihistaminiques [18,19,20,21].

SARS-Cov2/Covi-19 – histamine : constats anatomo-pathologiques, IL1, IL6 et autres

Il a été rapporté que les atteintes de différents organes dans le Covid-19 pouvaient être mis en relation avec le constat d'endothélites notamment en lien avec une activation endothéliale liée l'orage cytokinique observé au décours du Covid-19 (rôle pathogène viral direct possible également) [22].
Soulignons que l'atteinte cellulaire principale observée était l'apoptose [22]. Ceci correspond à la cytotoxicité connue in vitro de l'histamine [23].
Ainsi, sans pour autant en donner lien de causalité et bien que l'extrapolation in vivo d'une action pro ou anti-apoptotique de l'histamine sur ces types cellulaires n'est pas ici documentée, une possible action cytotoxique de l'histamine, après présence prolongée et/ou à des taux élevés, resterait compatible avec les observations faites.

Par ailleurs, l'inflammation de l'endothélium, connue pro-thrombotique pourrait être le résultat d'une réaction immuno-inflammatoire lors du Covid-19 entrainant entre autres, une dysfonction endothéliale multi-viscérale.
Les atteintes microvasculaires et thrombotiques ont, du reste, été assez rapidement décrites lors du Covid-19 [24].
Comme précédemment mentionné, l'implication de l'histamine comme potentialisateur d'autres monoamines avec au final une action pro thrombotique étant connue [11,12] (agrégation plaquettaire), ces constats d'atteintes microvasculaires et thrombotiques ne font donc que renforcer la nécessité de mieux appréhender la mise en jeu du « système histaminique » (avec ses liens par ailleurs connus sur d'autre pro coagulant) dans la genèse de ces anomalies lors du Covid-19.
Soulignons qu'il s'agirait là d'une action de plus, renforçatrice du potentiel pro coagulant de la dysfonction endothéliale induite par la « seule » endothéliite.
Les antihistaminiques pourraient peut-être, contribuer à la limitation de ces phénomènes micro-thombotiques (voire en supprimer la genèse et/ou « l'amplification ») comme également évoqué par des hypothèses similaires plus récentes[13].

Par ailleurs, si l'on considère l'expression cellulaire des récepteurs antihistaminiques, en particulier RH1, il s'avère que les cellules endothéliales semblent exprimer fortement ce récepteur [25], sans que cela ne préjuge de l'action induite par l'histamine.
Il est démontré que les cellules endothéliales (artère coronaire humaine) voient accroitre la production de certaines cytokines (IL6, IL8) en présence d'histamine avec une relation dose-dépendante et une sur expression en présence notamment de TNFα. Cet effet de l'histamine sur la production de cytokines étant bloqué par l'antagonisation des récepteurs RH1 (par la diphenhydramine) et pas par celle des récepteur RH2 [10,23].

Il apparait dès lors possible d'envisager que, suite à l'activation par le SARS-Cov2 notamment des mastocytes, Il se produise une libération d'histamine. L'histamine induirait ensuite, notamment sur les cellules endothéliales de proximité, une accentuation de la production de cytokines et en particulier d'IL6 (ce d'autant que les mastocytes sont connus pour libérés après activation également du TNFα[14] qui augmentera donc le potentiel inducteur de l'histamine).

Il apparait également qu'il existerait une différence de cinétique dans la production de ces différents médiateurs, avec, en ce qui concerne l'histamine une production très rapide puisque stockée préalablement au contraire des molécules devant être synthétisées (IL6,IL1…) [14].
Un phénomène similaire pourrait également être à l'œuvre en cas de réduction, dans le Covid-19, des capacités d'élimination/neutralisation physiologiquement en place au sein de l'organisme. L'un n'excluant pas l'autre, une synergie dans l'origine des effets délétères de l'histamine pourrait ainsi être à l'œuvre (au final : augmentation de ses concentrations extracellulaire et/ou de son temps de présence dans le milieu extracellulaire).

De plus, cette action de l'histamine sur la production d'IL6 ne semblerait pas spécifique à un type de cellules mais a été mis en évidence pour différentes catégories cellulaires (macrophages pulmonaires, monocytes, fibroblastes nasaux)[25,26].

Il est à noter que, pour certains types cellulaires (macrophages pulmonaires entre autres), la relation entre production d'IL6 et l'histamine se ferait au travers notamment de son activité sur les RH1 [27,28].

Dans la prise en charge du Covid-19, certains espoirs thérapeutiques ont été placé dans un inhibiteur monoclonal de l'IL6 le tocilizumab [30,31] avec des résultats relativement encourageants quant au potentiel thérapeutique [32].

Dès lors, il apparait que limiter, en amont, la surproduction d'IL6 puisse ainsi être une voie complémentaire (voire suppressive) à son ciblage électif par le tocilizumab. Les antihistaminiques pourraient avoir un intérêt tout particulier pour ce faire. Si l'utilisation des antihistaminiques est tardive, ne permettant ainsi pas d'éviter la surproduction d'IL6, le concept de « thérapie multi-classes à déploiement séquentiel » prend alors tout son sens (déploiement de classes thérapeutiques différents car actives à des temps différents).

Il nous apparait ici que, compte tenu de ce qui a été précédemment mentionné, (expression des RH1, implication des cellules endothéliales dans la synthèse d'IL6 en réponse dose dépendante à l'histamine, sélectivité des antiH1), il soit possible d'envisager plus logiquement une action médiée par des antihistaminique antiH1. Ceci demeurant à démontrer.

Il n'en demeure pas moins qu'une action complémentaire et cumulative des antihistaminiques puisse être envisagée. En effet, l'activation par l'histamine des récepteurs RH2 étant connue impliquée dans la plus grande efficience d'expression du gène de l'IL6 induit par l'IL1[25].
Ainsi, la production d'IL1 par les mastocytes engendre une action de potentialisation de la production d'IL6. Cette dernière notion, très théorique nous permet cependant de mieux appréhender l'intérêt thérapeutique qu'a pu susciter (un temps du moins), l'anakinra (inhibiteur compétitif de l'IL1 à son récepteur de type 1 (IL-1RI)) [33] dans la prise en charge du Covid-19.
Au-delà de cela, la mise en jeu de l'IL1 semble pouvoir en partie relever d'un potentiel inductif de l'histamine quant à, in fine, la libération de cette cytokine. En, effet, de la même manière que l'histamine est « reliable » à une augmentation de la production d'IL6 (et donc participe en tout état de cause au moins à l'augmentation des taux d'IL6), elle pourrait participer à l'augmentation des taux d'IL1, au travers ses effets RH2 [34].

Cette mise en jeu, par l'histamine, de différente cytokines (IL1, IL6) dont les observations et espoirs des contre-mesures thérapeutiques (respectivement anakinra, tocilizumab) largement médiatisés en France dans leur repositionnement dans le cadre de la prise en charge du Covid-19, ne peut qu'inciter (que conforter) l'étude des substances connues actives sur les effets histaminiques directs (en amont de son activation des différents récepteurs cellulaires) ou indirects (ou d'aval, en liens avec les processus liés à l'activation des récepteurs à l'histamine) à et particulièrement les molécules d'utilisation sécuritaire tels que les antihistaminiques.

Ainsi, toutes les substances participant à la baisse du taux d'histamine et/ou à la réduction des effets de l'histamine nous apparaissent à prendre en considération dans la lutte contre le Covid-19 et, bien évidemment, en premier lieu les antihistaminiques et autres molécules diminuant la production d'histamine et/ou ses effets.

A ce titre, et à ce stade de notre exposé, il est intéressant de souligner qu'un nombre conséquent de molécules ont été avancées comme potentiellement efficaces et intéressantes dans la réponse thérapeutique à déployer face au Covid-19.
Comme nous venons de le voir, certaines interviendraient en aval de la libération d'histamine (anakinra, tocilizumab). C'est le cas également d'autres substances pour lesquelles des travaux préliminaires ou hypoyhèses fonctionnelles ont évoqué un intérêt (plus ou moins confirmé) dans le Codvid-19 : vitamine D[35,36], Quercétine[36,37,38], Luteolin[39], Carnosine[40] notamment.
Ces substances sont connues comme ayant une capacité stabilisatrice sur les mastocytes, participant de facto à la réduction de leur activation et donc à la diminution de la libération d'histamine, mettant en cela, un possible frein (voire arrêt) à la cascade d'événements qui aboutit à la réponse inflammatoire inappropriée observée dans le Covid-19 (à noter que certaines sont connues comme pouvant interagir avec les récepteurs à l'histamine)[41,42,43,44].
Notons que, s'agissant, comme indiqué dans l'hypothèse initiale, d'une susceptibilité extrêmement variable (hyperréactivité ou non) en lien avec le système immuno-inflammatoire propre à chacun, l'impact clinique de ce type de molécules peut revêtir une grande variabilité.

Quoiqu'il en soit, le ciblage à un temps donné, d'un effecteur donné de cette cascade répond à la définition d'une thérapie multi-classe à déploiement séquentiel avec en initiateur et « amplificateur » possible les antihistaminiques.

Il est cependant évident que, plus le temps passe et plus l'emballement de la cascade immuno-inflammatoire et les lésions qu'elle induit, relèvent à terme d'une mise en jeu thérapeutique multiple de l'ensemble des acteurs supposés actifs. Les lésions tissulaires micro puis macroscopiques, induites par les phénomènes immuno-inflammatoires, prenant ensuite un rôle pathologique qui leur est propre et dont les contre-mesures thérapeutiques deviennent ensuite spécifiques (voire inexistantes).
C'est la raison pour laquelle, la mise en route des premières contremesures thérapeutiques se doit d'être la plus précoce possible.
Les antihistaminiques, dont la simplicité d'utilisation, le coût modeste et l'effet bloqueur potentiel sont ainsi des candidats des plus prometteurs se devant de bénéficier d'essais cliniques (antiH1 notamment mais également peut-être combinaison antiH1-antiH2).

La séquence d'activation des phénomènes physiopathologiques induits par le SRAS-Cov2, semble bien pouvoir répondre à une cascade d'événement durant laquelle l'histamine intervient à la fois à la phase initiale mais également en participant (sans doute de façon dose dépendante) à la production de cytokines qui, in fine, agiront en elles-mêmes.

Il apparait donc des plus utile d'envisager le rôle de l'histamine et ce **dès la phase initiale d'induction des phénomènes immuno-inflammatoires**. L'intérêt des antihistaminiques (en particulier antiH1) prenant ainsi son plein sens.
Toute baisse de la sécrétion ou des effet induits par l'histamine, étant logiquement d'une importance notable dans la réduction, voire l'arrêt, de la cascade immuno-inflammatoire et ses effets délétères à courts, moyens et longs termes dans le Covid-19.

Ainsi, de façon générale, toute baisse des concentrations extracellulaires d'histamine ou/et tout blocage de son effet diminue ses actions cellulaires, biochimiques et leurs conséquences.

SARS-Cov2/Covi-19 – antihistamines : hypothèses quant aux potentiels, modélisation et étude in vitro

Modélisation– effets in vitro

Différents travaux de modélisation (type binding moléculaire…) ont souligné l'intérêt des antihistaminiques à différents niveau dans le Covid-19 notamment dans leur potentiel d'action antivirale directe.

Ainsi, l'intérêt du repositionnement d'antihistaminique était évoqué dans un article paru dans la revue Nature dès avril 2020[45].

Depuis, différents travaux de modélisation ont permis d'affiner l'intérêt des antihistaminiques. Nous les mentionnerons de façon succincte en schématisant leurs apports.

Clemastine, azelastine et trimeprazine, antagonistes de l'histamine, possèderaient une capacité à s'opposer à l'entrée du virus SARS-Cov2 dans les modèles cellulaires[46].

Loratadine et desloratadine, antihistaminiques RH1, possèderaient une capacité à s'opposer à l'entrée du virus SARS-Cov2 dans les modèles cellulaires en bloquant sa liaison avec les récepteurs ACE[47].

Famotidine et Cimetidine, antihistaminiques RH2 montreraient une capacité à se fixer sur le SARS-Cov2 et ainsi, comporteraient un intérêt potentiel dans la lutte contre le Covid[48].

La doxepine, molécule ayant une activité antiRH1 forte pourrait s'opposer à l'infection des cellules hôtes par le SARS-Cov2 en venant empêcher la fixation de la protéine Spike du virus sur le récepteur ACE2 cellulaire[49].

Le Ketotifen, antihistaminique antiH1 serait en capacité de réduire la réplication virale sur modèle cellulaire avec un effet additif ou synergique lorsqu'on y associe certaines autres molécules (naproxene, indomethacine)[50].

Chlorpheniramine (antiH1) réduirait de façon très notable la charge virale du modèle, ce qui pourrait laisser supposer un fort pouvoir virucide[51].

Hydroxyzine et l'azelastine auraient la capacité de bloquer l'interaction spike-ACE2[52].

Antihistaminiques et intérêt d'utilisation dans le Covid-19

Un certain nombre d'auteurs ont avancé au travers de différents mécanismes d'action l'intérêt potentiel de divers antihistaminiques dans le Covid-19, nous en ferons ici état de façon schématique.

L'ébastine ainsi que l'Idelalisib molécule dont le potentiel anti-allergique est connu selon les auteurs (rhinite allergique) présenteraient un intérêt dans la prise en charge du Covid-19 [53].

La Rupatadine, antihistaminique antiH1, est proposée dans la prévention des microthromboses observées dans le Covid en raison à la fois de son action stabilisatrice sur les cellules mastocytaires et son activité anti PAF (Platelet Activating Factor)[54].

L'usage des antihistaminiques en raison de leur action constatée mais aussi de leur sécurité et facilité d'emploi apparait une hypothèse à promouvoir dans le cadre du repositionnement d'anciennes molécules[55].

Un travail de synthèse de la littérature a permis de mettre en avant l'intérêt potentiel des antihistaminiques (RH2) dans le Covid [56].

Dans une revue de la littérature effectuée sur les articles publiés au 27/10/2020 (42 articles) parue en février 2021, PEDDAPALLI et al ont permis de consolider l'importance de l'histamine dans les processus physiopathologiques du Covid. Il a été ainsi mieux appréhendé le potentiel important dans la lutte contre le Covid des molécules limitants les effets de l'histamine ou neutralisant même l'histamine[57]. L'histamine jouerait ainsi donc un rôle majeur dans les processus lésionnels observés dans le Covid.

De même, un travail tout récent, publié le 26/05/2021, juste avant la fin de rédaction de notre mise à jour, permet de consolider le rôle primordial joué par le système histaminique et les antihistaminiques dans la stratégie de réponse face au Covid-19 [58].

D’autres ont avancé sur des bases soit observationnelles soit théoriques en lien avec l’effet de stabilisation connu des antihistaminiques, l’intérêt de cette classe thérapeutique dans la prise en charge du Covid-19.

Ainsi, il a été constaté qu’en Europe, une faible proportion des patients avec troubles psychiatriques était affectée par le SARS- Cov2 [59].
Les médicaments psychotropes ont également été ciblés comme potentiellement intéressant dans la prise en charge du Covid-19 [60].
Il est intéressant de noter que sur l’ensemble des thérapeutiques potentiellement impliquées chez ce groupe particulier de patients, la quasi-totalité des molécules potentiellement impliquées ont une activité antihistaminique exclusive ou partielle connue (Phénothiazine, chlorpromazine, prométhazine, thiethylperazine, triflupromazine, cyamémazine, levopromazine, propericiazine, pipotiazine, metopimazine, lopéramide, mequitazine, tiotixene, flupentixol, zuclopenthixol, pomozide, haloperidol, astemizole, pipamperone, clomipramine, maitriptyline, benztropine, paroxetine,)

Pour rappel, de nombreux travaux mettent l’accent sur les stabilisateurs des mastocytes, cellules dont le lien direct et indirect avec l’histamine n’est plus à démontrer.

SARS-Cov2/Covi-19 – antihistaminiques : observations, études cliniques et pratique de terrain

Aspects épidémiologiques

A la question de savoir si dans cette pandémie, l’utilisation d’antihistaminiques pourrait apparaitre comme « protectrice », certaines données épidémiologiques ont permis depuis 16 mois, débaucher certains éléments de réponse.

Une petite série pédiatrique italienne faisait état que l’allergie et l’asthme contrôlé apparaissait possiblement « statistiquement » protecteur face au Covid-19 [61].

Aux USA, une étude sur un panel de plus de 219 000 personnes a permis de mettre en évidence une diminution de l’incidence de la positivité au SARS-Cov2 [52].

De même, en Espagne, une étude rétrospective sur 79 000 personnes aurait permis d’avancer un rôle protecteur possible de la prise d’antihistaminique[62].

La prise chronique d’antihistaminique ne semble cependant pas pouvoir empêcher la contamination par le SARS-Cov2 et le développement du Covid-19 et ce en raison même de l’indication de cette médication chronique.
En effet, il semblerait exister une balance entre « niveau » d’histamine et « maladie ». En fait, la prise chronique d’antihistaminique est liée à la maladie « allergie » qui correspond (déjà) à un niveau « élevé » (ou facilement élevable) d’histamine. Dès lors, l’absence de symptôme est liée à la compensation par l’antihistaminique de ce niveau d’histamine élevé ou réactif.

Ainsi, il existe (ou non) une capacité « résiduelle » de compensation, une « réservoir » d'effet antihistaminique plus ou moins important selon chacun. Le Covid augmentant (pour schématiser) l'histamine, si cette capacité résiduelle permet de compenser il pourrait dans notre hypothèse, ne pas y avoir développement du Covid-19 sinon il faut en théorie (et dans nos constats cliniques), soit augmenter la dose soit changer la molécule.
A ce titre (type de molécule) certains antihistaminiques pourraient avoir plus de capacité à inhiber l'infestation par le SARS-Cov2 mais, rappelons que la charge virale pourrait ne pas être, pour certains, le seul élément impactant le déclenchement de la maladie Covid-19. Il s'avère alors que, même si certains antihistaminiques s'avéraient in vivo protecteurs, il pourrait y avoir débordement de cette capacité protectrice face à la charge virale importante ou la sensibilité/réactivité individuelle.
Autrement dit, les allergiques « chroniques » traités par antihistaminiques ont un équilibre entre processus allergique spontané (et plus ou moins permanent) et efficacité du traitement antihistaminique. Ils ne développent donc pas de symptômes, grâce à cet équilibre. Après contage, le SARS-Cov2 engendrerait selon notre hypothèse primordiale, une libération d'histamine, point de départ de la cascade immuno-inflammatoire (« théorie du couloir »). Ainsi, bien que sous antihistaminique, certains patients allergiques chroniques traités verraient leur quantité d'histamine dépasser celle des bloqueurs HRH1 et la cascade immuno-inflammatoire débuterait (avec une puissance plus ou moins grande selon la « marge de manœuvre antihistaminique » disponible).
Ainsi, pour prendre en charge ces malades il faut soit augmenter la dose d'antiH1 soit changer d'antiH1 (soit l'associer à un antiH2).

Etudes cliniques

Depuis février 2020, des études cliniques sont venus en confirmation du constat fait dans nos travaux observationnels.

Il a été ainsi démontré l'intérêt potentiel de certains antihistaminiques RH2 dans la prise en charge du Covid-19. La famotidine aurait ainsi montré une capacité à réduire le nombre d'intubation et de décès chez les patients hospitalisés[63].

L'utilisation antihistaminiques antiH1 et antiH2 a montré un intérêt quant à l'utilisation des antihistaminiques dans le Covid[64].
L'utilisation d'antihistaminique et d'azithromycine s'est montré en capacité d'améliorer de façon notable le pronostic des patients atteints de Covid[65]. Une prise en prophylaxie des antihistaminiques au niveau des sujets contact semblerait montrer également une efficacité notable.

A noter que récemment, une équipe sud-africaine a fait état de ses résultats qui semblent plus qu'encourageant dans la prise en charge du Covid-19 au moyen d'antihistaminique (non publié).

Malgré l'importance primordiale que nous semble représenter le système histaminique dans le Covid-19, à ce jour, peu d'études cliniques ont été réalisé.

Les réticences, incompréhensibles, face aux repositionnements d'anciennes molécules dans le schéma thérapeutique déployable dans le Covid semblent en être peut-être la cause. Cela ne concerne bien évidement pas

que les antihistaminiques, mais ces derniers semblent largement ignorés dans leur potentiel…ignorance stratégique, méconnaissance de leur potentiel ou total inintérêt dans le Covid, le temps jugera.

SARS-Cov2/Covi-19 – antihistaminiques : activité non RH dépendante, liens et activité antihistaminique-like d'autres classes thérapeutique

L'activité des antihistaminiques pourrait également être médiée par une action non récepteur dépendant.
Ainsi, certains antihistaminiques antiH1 possèderaient une action anti-inflammatoire au travers de certaines interactions sur la production des prostaglandines 2 (PG2), sans que cette activité ne soit dévolue qu'à leur seule activité RH1[66].
Soulignons que l'histamine présente également une dualité d'effet sur l'inflammation avec une capacité pro ou anti-inflammatoire selon le type cellulaire et le type de récepteur considéré. L'histamine serait ainsi impliquée dans une inhibition de la synthèse des leucotriènes (LT) avec réduction de l'action de la 5-lipopoxygénase [67.] Cet effet, médié par les récepteurs antiH2, est antagonisé par la ramitidine (antiH2) qui induit une suppression plus ou moins complète de la réduction de biosynthèse des LT [67.]
Ainsi, les actions des antiH2 pourraient induire une augmentation relative de la production de LT et, avec elle, réduire le potentiel actif des antiH2 sur une part de l'immuno-inlammation.
Les antiH1 ne semblent pas se heurter à cette effet suppresseur ou diminuant de l'action anti-inflammatoire parfois observée. Dès lors, et de façon purement théorique, il pourrait en résulter une action soit moins rapide soit partielle des antiH2 par rapport aux antiH1.

Nous pouvons dès lors entrevoir également l'intérêt potentiel des anti leucotriènes au travers de leur positionnement, évoqué dans l'hypothèse initiale, au sein des contre-mesures anti-inflammatoires possibles et ce, indépendamment de leur action possible et associée sur l'adhésion virale[68]. L'action des anti leucotriènes peut par ailleurs également être complétée par leur capacité connue à baisser la production, entre autres de l'IL6 [69] dont nous avons abordé le très probable implication dans le Covid-19.

Ces données, se doivent bien évidement d'être approfondies. Les notions d'éventuelles affinités partielles et activations croisées prenant ici toute leur importance de même que celle de la dualité fonctionnelle de l'histamine.
Ces possibilités d'action « croisée » et de dualité fonctionnelle de l'histamine viennent complexifier encore les actions connues des différents récepteurs spécifiques de l'histamine. Le concept de rétrocontrôle et d'effets interdépendant est également à considérer, à l'instar de ce qui peut être observé au niveau neuronal entre RH3 et RH1 [70]. De même, les expressions cellulaires variables (y compris sur le plan temporel) des récepteurs ainsi que les effets de co activations (par exemple RH1 et RH4) est également possiblement source d'actions différentiées[71].

Au-delà des relations complexes de l'histamine avec ses différents récepteurs spécifiques -RH 1 à 4-, cette amine biogène est également connue pour entrer en relation avec d'autres récepteurs et notamment des récepteurs aux cytokines.
S'ouvrent ainsi, les actions possibles sur les réponses immuno-inflammatoires en lien avec, peut-être, lymphocytes T helper CD4*, lymphocytes T CD8* et NK[72] dont l'implication dans la réponse infectieuse est

évidement à considérer. Les interactions des amines biogènes (et particulièrement de l'histamine), sur les récepteurs cytokiniques impliqués notamment dans la réponse antivirale, ont du reste été appréhendées[73,] ouvrant ainsi un champ complexe de recherche quant à la compréhension des mécanismes à l'œuvre et des balances d'action ou de différenciation induites.

Entre action hors récepteurs dédiés, activation, modulation et autres rétrocontrôles, la compréhension des mécanismes à l'œuvre offre un vaste champ de réflexion et d'exploration.

A cette complexité d'action du système antihistaminique lui-même, l'apport de molécules impactant les voies d'aval de l'activation primordiale histaminique, complexifie encore les choses dans l'émergence d'un traitement de référence.

Par exemple, le rôle que semble jouer la vitamine D dont l'importance en qualité de cofacteur de la lutte antimicrobienne est connue[74]. Partant de l'implication antimicrobienne possible et de données épidémiologiques, la possible utilité de la vitamine D a été mise en avant dans la prise en charge du Covid-19 [75.]
Une supplémentation est ainsi, parfois conseillée afin d'optimiser la lutte antimicrobienne y compris pour le SARS-Cov2 [76].
Cela suffira à l'Académie Française de Médecine pour recommander via un communiqué en date du 22 mai 2020 d'apporter une supplémentation systématique en vitamine D en cas de Covid-19[77] et ce, même si l'effet bénéfique d'une supplémentation des cas sévères de Covid-19 n'aurait cependant pas démontré d'efficacité tangible[78] .
Ce faisant, la vitamine D participerait au maintien de la stabilité des mastocytes et son déficit serait associé à leur activation[79].
Une supplémentation apporterait ainsi, en cas de déficit, une aide stabilisatrice rendant moins effective la mise en jeu de l'histamine au décours du Covid-19, cela nous semble cependant marginal mais, comme indiqué toute limitation de la libération d'histamine nous apparait utile.

Cette notion de classe thérapeutique différente de celle des antihistaminiques mais ayant une activité qui, au final converge en partie sur le système histaminique est importante à aborder.

Il est en effet à considérer les actions « antihistaminique-like » de certaines molécules ou classes thérapeutiques.

Ainsi, certains antidépresseurs sembleraient être prometteur dans leur potentiel de lutte contre le Covid-19. Une étude observationnelle rétrospective multicentrique menée en France en partenariat AP-HP et INSERM a montré une diminution du risque d'intubation et de décès chez les malades atteints de Covid et bénéficiant d'un traitement par certains antidépresseurs (fluoxétine, paroxétine, escitalopram, venlaflaxine et mirtazapine).
Il s'avère intéressant de souligner ici que ces quatre antidépresseurs ont tous une action antihistaminique connue.

De même, dès avril 2020, certaines études semblaient montrer une diminution de la prévalence du Covid chez les fumeurs amenant à s'interroger sur le rôle protecteur possible de la nicotine. Soulignons que ces études n'abordaient que l'aspect de prévalence et non la gravité liée au tabagisme en cas de Covid[81,82].
Là encore, un lien avec les voies histaminiques existe puisque certaines études tendent à montrer que la nicotine semblerait en capacité de provoquer une diminution la production d'histamine, au niveau cellulaire et tissulaire[83,84].

Nous pouvons également évoquer la chloroquine et l'hydroxichloroquine dont la médiatisation rend inutile l'exposé du possible potentiel dans le Covid. Il existe en effet là encore un lien connu entre ces molécules et le système histaminique soit « d'aval » (activation des mastocytes)[85,86] soit plus directement lié à l'histamine[87].
On remarquera qu'il existe une dualité dans l'effet sur le système histaminique de la chloroquine avec, possible réduction de sa libération par effet stabilisateur des mastocytes et effet de diminution de l'élimination de l'histamine par possible effet inhibiteur sur l'histamine N-methyl transferase.
Pour rappel, il existe une dualité d'avis et constats dans le Covid sur l'effet de la chloroquine. En phase précoce, elle semblerait utile alors qu'en phase plus avancée certains la décrive délétère. Dès lors, nous pouvons avancer que la phase précoce ne correspond pas encore à une activation « pleine » des mastocyte, l'effet stabilisateur sera donc pleinement bénéfique tandis qu'en phase tardive, l'activation mastocytaire est « lancée » avec une augmentation de facto de la libération d'histamine et la baisse de la dégradation de l'histamine n'apparait pas très pertinente.
Encore une fois, la complexité des mécanismes à l'œuvre et l'emballement du système immuno-inflammatoire plaident pour une prise en charge la plus précoce possible.
Quoiqu'il en soit un lien existe bien entre voie histaminique et chloroquine.

Dans le registre des convergences d'actions biologiques, l'ivermectine fait actuellement partie des molécules dont l'activité dans le Covid semble prometteuse, nous ne reviendrons pas sur les multiples travaux ayant rapporté son efficacité dans la prise en charge du Covid, au regard de la polémique crée actuellement pour n'en mentionner qu'un, celui de P. KORY [88] pour lequel nous avons un regard tout particulier en lien avec une récente polémique mettant l'accent sur les difficultés actuelles en termes de communication scientifique[89]. Il est en effet intéressant de signaler que les avermectines possèdent, chez les invertébrés, une action sur le système histaminique selon diverses études in vitro.
Il serait donc intéressant d'affiner les éventuelles liaisons, en biologie humaine, avermectine et système histaminique[90,91].

Par ailleurs, soulignons que les avermectines sont structurellement proche des macrolides (sans posséder d'action antibiotique). Ceci ouvre un champ intéressant de recherche notamment de mimétisme moléculaire, quant aux constats d'actions bénéfiques possible de certains antibiotiques de cette famille.
Cette notion de mimétisme moléculaire, très théorique revêt cependant un attrait tout particulier à bien considérer. Par exemple, le Molnupiravir, présenté dans la presse grand public comme la potentielle « pilule anti-Covid » est la prodrogue de l'hydroxycytidine[92]. L'hydroxycytidine a été étudiée quant à ces cibles moléculaires possible notamment en se basant sur des molécules voisines (conformation moléculaire)[93]. L'azacytidine et l'adénosine sont deux des trois molécules structurellement comparables. Hors, l'azacytidine est connue pour avoir une affinité avec les methyltransferase et l'adénosine est quand à elle connue pour avoir une action inhibitrice de la libération d'histamine par les cellules mastocytaires pulmonaires (avec à plus forte concentration et après pénétration intracellulaire (donc plus tard), un effet inverse)[94].
Ici encore, la relation reste très théorique et demande bien évidement à être affinée mais il existe indubitablement un axe de recherche pertinent dans le cadre de possibles mimétismes moléculaires.

Nous avons précédemment mentionné le constat par certaines équipes de l'intérêt de l'antibiothérapie (azithromycine notamment) dans le Covid et ce, au-delà des éventuelles surinfections bactériennes associées. Cela amène à s'interroger, outre l'hypothétique mimétisme moléculaire, sur les mécanismes possibles d'action des antibiotiques dans cette pathologie.

Il a été avancé que le microbiote digestif semble impliqué dans la sévérité du Covid, probablement en lien avec son impact sur la réponse immune de l'hôte. Il pourrait également être impliqué dans la persistance à long termes de symptômes du Covid[95].
Un lien notable, à mieux appréhender bien évidement, pourrait être le fait que certaines bactéries notamment à tropisme intestinal, sont connues comme ayant la capacité de sécréter de l'histamine[96].

SARS-Cov2/Covi-19 – facteurs de risque et antihistaminiques

Mentionnons enfin quelques pistes de liens possibles soulignant l'intrication probable des différents éléments impliqué sur le plan métabolique lors de l'atteinte par le SARS-Cov2.
Le diabète a été identifié comme étant un facteur de risque de gravité dans le Covid. Là encore, la relation entre taux de glucose et système histaminique emble devoir être appréhender plus avant en raison des liens connus entre taux de glucose et histamine[97,98].
A ce titre, il faut remarquer que l'obésité, autre facteur de risque connu dans le Covid, au-delà des troubles de ventilation qui peuvent lui être imputés, comporte certes une fréquente association avec un trouble de régulation glycémique mais également, un lien avec le système histaminique et ce au-delà d'une action centrale médiée par les RH3 puisque, la graisse abdominale pourrait être source de dysproduction d'histamine.
De même, à l'instar de ce qui a pu être observé au niveau cérébral lors du développement[99], il serait intéressant d'évaluer production d'histamine, sensibilité à l'histamine et âge.

Au total

Il nous apparait licite de considérer les antihistaminiques antiH1 comme une stratégie thérapeutique à envisager dans le Covid-19.
Les observations entrent pleinement dans les attendus de la théorisation initialement présentée de même que bon nombre de données récentes issues des progrès des connaissances et de cibles thérapeutiques émergentes possibles.

Certains résultats nous confortent cependant dans la notion d'un déploiement (ou combinaison) thérapeutique séquentiel qui serait un élément pouvant optimiser la prise en charge du Covid-19, suivant en cela les cascades du système immuno-inflammatoire.
A chaque phase, certaines contre-mesures thérapeutiques ciblées : antihistaminiques, anti leucotriènes, antipaludéens de synthèse, corticoïdes et autres médicaments s'opposant aux phénomènes immuno-inflammatoires. Leur utilisation devant être adaptée à la phase immuno-inflammatoire la plus « bruyante ».
Il s'agit donc d'une prise en charge avec une sorte de « **thérapie multi classe à déploiement séquentiel** » selon le stade évolutif biochimique le plus intensément à l'œuvre au moment de la prise en charge du malade, faisant de facto du traitement du Covid-19 un traitement à adaptation individuelle mais pour lequel l'histamine semble être le fil conducteur basal.

Quoiqu'il en soit, l'enjeu premier est bien le blocage **au plus précoce de la contamination par le SARS-Cov2** des effets délétères induit par l'interaction hôte-agent pathogène.

L'efficacité des antihistaminiques antiH1 au cours du Covid-19 se doit d'être mieux appréhendé. Leur potentiel d'utilité dans le Covid-19 semblant pouvoir être mis à profit dans la phase aigüe mais également envisager dans

les possibles complications à long termes, qui pourraient découler d'une mise en jeu (parfois infra clinique) du système immuno-inflammatoire (fibrose pulmonaire…).

De même, les formes à évolution prolongée doivent faire envisager la persistance d'une activation anormale (et à bas bruit) du système immuno-inflammatoire ou des réinfections sans immunisation stable. Les effets délétères à long terme demeurent également chez ses patients, au-delà d'un enjeu de santé individuelle, un enjeu en termes de santé publique. Il convient d'explorer plus avant les composantes de ces formes prolongées.

L'évolution des connaissances sur la relation entre SARS-Cov2, Covid-19 et histamine ne viennent que conforter l'utilité et, **l'urgence de réaliser des études complémentaires de validation clinique**.

Conflit d'intérêt : aucun

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Hypothesis for Covid-19 - Antihistamines drug :
Updated according to recent knowledge - Synthesis of observed cases

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Abstract

At the end of February 2020, at the rise in Europe of what was still an epidemic linked to SARS-Cov2, we formulated, based on the epidemiological, clinical, paraclinical and evolutionary data of CoviD-19, a hypothesis on a pathogenesis of SARS-Cov2 mediated mainly by the virus-host combination and this from initial contact.

From the interaction with the pathogen, the host's inflammatory and immune system will produce deleterious immune responses with short, middle or long-term effects.

SARS-Cov2 is highly contagious but above all may have an ability (without a doubt, never yet encountered or seen) to trigger the excessive uncontrolled response to the host's immune-inflammatory system, probably encompassing all or part of the pathogeny.

The host's immune-inflammatory system response with its own specificity and susceptibility (from low to very high) after contact with SARS-Cov2 would therefore determine the clinical course and ultimately the severity of the disease, immediate or deferred.

This susceptibility of the host to produce the initial defense response, with a more or less rapid harmful response and more or less intensive, could thus explain the different heterogeneities of the Covid-19 both clinical, biological or evolutionary, regardless of stage and time.

Similarly, and in line, the deleterious effects associated with the activation of the immune and inflammatory system are potentially worrying for the "side-effects" they might leave or the reactivation during a second contact. Therefore, it is not the intrinsic potential adverse effects of the viral agent (SARS-Cov2) but mainly the host's immune response, to which the patients would be subjected.

Therefore, it is the potential dangerous nature and not the elemental viral agent (SARS-Cov2) but indeed in the reaction aroused in the host, to which the patients would be subjected. The intrinsic reactivity specific to each individual is shaping the way Covid19 is affecting them in terms of evolutionary kinetics, clinical but above all gravity and maybe further sequelae.

One way or another, SARS-Cov2 would generate an immune-inflammatory reaction which can evolve progressively (even in a subclinical way) or/and an explosive and unpredictable way (overreact).

This sometimes explosive and unpredictable character as well as the observed heterogeneities and well-known functions of histamine lead to consideration that this biogenic amine is involved very early or even immediately in an immune response

course after SARS-Cov2 contact or could even be involved in a direct viro-induced activation.

Different clinical trials have further confirmed the possible relevance of our hypothesis. Similarly, a more comprehensive knowledge of Covid-19 has brought many elements confirming the possible involvement of histamine and with it, the most probable interest of antihistamines choice. Here we discuss all of these elements by updating our previous field reports in the light of the most recent literature review and acquired new knowledge.

Background and initial hypothesis

From the first known Covid-19 cases in France, we have proposed a hypothesis about the atherogenesis related to Covid-19.

In our hypothesis, the participation of the immune-inflammatory system was considered to be the origin, following initial host-pathogen interaction, of the heterogeneous symptomatology observed and variations in inter-and intra-individual severity.

Thus, the Covid-19 pathophysiology would result mainly (or even exclusively) of deleterious effects caused by an excessive reaction of the virus-host's interaction induced auto-inflammatory and auto-immune system. The immune-inflammatory system features in terms of "response power" may
provide the interpretation of the observations of the heterogeneity that seem to be in Covid-19 cases.

The virus Sars-Cov2, contagious as it is, appears, in itself, dangerous almost only by its ability to trigger an inflammatory and immune reaction that can become excessive and deleterious in the short, medium or even long term.

In this concept, the "indirect" pathogenic effects of SARS-Cov2 would be responsible for the disease. They would also be present in the early stage and "associated" with the "direct" pathophysiological effects of SARS-Cov2.
Generally, it is not uncommon to see in viral infection, after a more or less long evolutionary phase, the pathologic indirect effects due to chain reaction of indirect harmful sequels induced this viral infection. Here, according to our hypothesis, the direct deleterious effects of the virus would not be followed after a notable time infectious evolution by his indirect effects would immediately (or very early) cause a chain reaction of harmful sequels (usually observed after a long evolution time).

Under these circumstances, the "indirect" pathophysiological effects linked to SARS-Cov2 could be involved (therefore appropriate for target-therapy) in their initiation (and therefore, during the initial contact of the virus). The early targeting could limit the harmful effects, among them, the runaway inflammation of the immune response, excessive or not.

From this notion, the viral load during control could become a less decisive factor in terms of the ability of SARS-Cov2 to induce Covid-19. Indeed, from this it would be the

pathophysiological indirect effects that would come into action via the virus-host interaction, the initial viral load although significant at the beginning or even the runaway reaction, therefore would become less decisive in terms of the ability to induce the disease (and therefore also in terms of contagiousness).
This can be related to the existing allergology concepts and according to which, the allergen load, however crucial it may be, is not in a quantitative manner restricted to the triggering of the pathological reaction.
The latter concept may perhaps, in our opinion, reflect different epidemiological and clinical observations that are very heterogeneous. The individual susceptibility, the intrinsic "reactivity", is, in fact, of a variable "power" and specific to each individual. Sars-Cov2 could therefore lead to extremely variable individual reactions during the primary but also the secondary contact. For better understanding, we will explain by analogy: a kind of principal agent with "universal allergen" behaviour (for inductive behaviour).

The prospects for such a hypothetical behaviour in the host and virus interaction would de facto generate implications in the development of a vaccine and/or in the achievement of protective immunity. In that scenario, there would probably be a virus "stopping" power but little or no action on the "disease" Covid-19 with, however, certainly neutralization of some pathophysiological effects further reinforcing, in the subsequent counts, the clinical heterogeneity already observed which may lead to "bastardized" or not typical clinical forms.

Therefore, the Nosological framework of Covid-19 would be largely heterogeneous with regard to the individual (or even intra- individual) specificities of the involvement of the immune-inflammatory system and its response, in particular, with regard to the initial symptomatology.

This characteristic therefore seemed to be able to fully reflect the epidemiological and clinical heterogeneity observed.

The biological data already provided, then reporting on the "cytokine storm", also advocated the involvement of the auto-inflammatory and autoimmune response in severe forms of the disease beyond the comorbidities. The two-phase evolution with worsening effect at day 7-10 was also totally part of this reactive involvement, and ultimately, negative impact, of the host's immune-inflammatory system.

Based on these facts and according to our hypothesis, it was therefore logical to try to modulate as soon as possible this abnormally high reactivity of the auto-inflammatory response observed, especially in some patients with strong predisposition to react in such a way (this predisposition remains to be investigated).

The targeting and use of virucidal or/and virostatic molecules, although logical, did not seem in capacity to suppress the initial kinetics of the inflammatory response, nor to be able to prevent cellular or anatomopathological deleterious effects.

From our initial physio pathogenetic hypothesis, the use of certain therapeutic drug classes appeared obvious for their commonly known action against the immune system triggering an acute inflammatory response: antihistamines first and foremost

(in particular anti-H1), antileukotrienes (leukotriene antagonists), synthetic antimalarial and depressogenic substance or immuno-blockers.

Because of the ubiquitous nature of the organism, its early onset within the known cellular and clinical mechanisms, histamine would appear to be an appropriate priority target molecule. Its involvement may, in addition to its initial action also be noted during the evolution of the immuno-inflammatory cascade, with in addition, beyond its increased release, a possible decrease (maybe both associated) of the abilities of the human organism, of elimination-neutralization.
In other words, there would be a possible involvement of histamine by excess release and / or excess production associated or not with a decrease in "physical or functional" degradation capabilities, all induced by the initial (and subsequent) host-virus interaction.

So, antihistamines, with the benefit of long clinical use and a well know simplicity of use, are more than the logic choice and easily exploitable in our hypothesis as to a possible efficacy during Covid-19 evolution.
In early March 2020, there was no literature available showing any articles on the subject (Histamine - antihistamines - Covid-19).
It should be noted that, in our initial thinking, the possible use of different treatments, at different intervals, did not mean the possibility of stopping (or not starting) the use of antihistamines according to our theory, but meant addition to the sequential use of other medication. In our opinion, only antihistamines benefit from a probable stopping power, the other therapeutic classes coming, if necessary, to strengthen them.

The therapeutic management of Covid-19 therefore seems to fall within a "multi-class therapy with sequential deployment" with an initial management (and continuous) use of antihistamines.
According to the evolution of the disease, a dedicated and complementary therapeutic response (which would try to target certain events and the elements of the immune response and the inflammatory cascade), maybe could prove useful in complementarity with antihistamines (because perhaps coming from oppose histamine-mediated actions). The viral load and/or new contaminations can also play here potential important reinforcement (antihistamine at all evolutionary stages). Under hypothesis, it also turns this out that the conduct of clinical trials could de facto be made more difficult to replicate due to this possible "phase" biases in the different studied groups (complicating further potential therapeutic strategies).

Subsequently, our various field observations appeared to indicate (subjectively) a rapid effect of antihistamines (antiH1) on much of the initial symptomatology observed when declaring a case of Covid-19 as well as a noticeable reduction of the duration. We then communicated our findings by drawing attention to the use of antiH1 in Covid -19 patients at an early stage (without waiting for a progression to a serious form: at the earliest of the onset of Covid-19) in the hope of seeing the implementation of a quality evidence-based research.

At the same time, we have chosen for clarity of presentation [1] to structure our observations and established a collection of observational data based on the use of a drug (which is an over-the-counter medication in France and many other countries) outside marketing authorization (MA), as indeed are all drugs used to date in Covid-19

patients, starting with paracetamol. The prescription of drugs, excluding MA, being fully authorized and regulated by the French legislation [2].

Bearing in mind the context, we have formatted the data of our results from the amalgamation of our observational studies and the non-EMA prescription use in order to make the research and proposals in our preliminary communication widely available. The purpose of this document does not seem to be intended to embrace, ultimately, similar classifications. The practice guide of prescribing non-EMA, authorized and overseen according to the terms of the public health and the welfare code, is obviously not the usual way for an analysis of therapeutic efficacy but, during a pandemic, the results must benefit from the feedback information from the field by modelling to the strict demonstrative evidence. Obviously, in the following case studies, we have adopted non-randomized studies, the data presentation and results are not expressed by a desire to study but simply state our field findings.

Although we are aware of the weaknesses in both the methodological and statistical analysis, we have chosen an effective dissemination strategy in order to inform as many medical teams as possible about it, but this time, using more backup material than in our initial communication.

Beyond the methodology, the results and the concept had to be addressed and explored correctly to their full potential.

The statistical power of the study, despite its weaknesses and the unclassified methodology, participated in undermining the progress toward a full consideration (especially in France).

The current pandemic context and the measures to be put in place in response, constitutes an unprecedented challenge, so sometimes new approaches are needed to further traditional approaches. The non-EMA prescription data collection is, in our view, clearly one of them.

Covid-19, histamine, antihistamines: quick update on recent research or not, proven facts and hypotheses

The work and proposals conducted in cohort studies in the fight against Covid-19 are numerous and of unprecedented analytical sensitivity and adaptability.

Many of them gave further clarifications which could provide us with additional of information for our approach and understanding the possible link between Sars-Cov2, Covid-19, histamine and antihistamines.

A rapid, Covid-19, histamine, antihistamine relationships, with regard to the new bibliography but also of the interaction between current improvement of our knowledge on Covid-19 and some previously known properties.

Histamine is produced by cells especially such as mast cells and basophils with an action mediated by different types of receptors [3]. Sars-Cov2 could interact with mast cells and activate them [4]. Thus, Sars-Cov2 could develop the ability by mast cells to

release various mediators including TNF-alpha, prostaglandins, IL1, IL6, leukotrienes and histamine [5]. This ability to release histamine during a viral infection has, besides, been well documented in animal studies for some viruses [6].

The histamine release during Covid-19 seems to contribute as one of the physio pathological elements at work after the infection by Sars-Cov2 and, both histamine and antihistamines seem to us the most impactful in particular regarding a possible therapeutic approach.

The possible interest of antihistamines in the management of Covid-19 and/or the control of SARS-Cov2 was confirmed recently as being part of the potential tracks to follow [7]. In addition to this, it has recently been argued that taking certain antihistamines (famotidine, class of H2R) may have a significant modulating effect on the severe evolution of Covid-19 from Sars-Cov2 [8] infection. Some clinical trials are still in progress.

The understanding of the possible links between famotidine, an antihistamine H2R, and Sars-Cov2 / Covid-19 have recently made a significant contribution [9]. The direct antiviral activity of the antihistamines does not appear to be a potential approach in vitro models [9].

Famotidine has a high H2 blockers activity[10] as well as an important selectivity for H2R [11], its affinity for H1R seems on the other hand very low or even nil [9].

Furthermore, it was reported that different lesions in the organs in patients with Covid-19 could be related to the finding of endotheliitis in particular in connection with an endothelial cell infection activation associated to the cytokine storm observed during Covid-19 (direct viral pathogenetic role also possible) [12].

In terms of anatomopathological diagnosis, it should be noted that the main cell involvement observed was apoptosis [12]. Shown in vitro cytotoxicity of histamine results in apoptosis [13]. Correlation does not imply causation and although the extrapolation in vivo of a pro or anti-apoptotic action of histamine on these cell types is not documented here, a possible cytotoxic action of histamine, after prolonged presence and / or at high levels, would remain compatible with the observations made.

In addition, the endothelial inflamed response, known as prothrombotic state could be the result of an immune-inflammatory reaction in patients with Covid- 19 leading, among others, to multi-visceral endothelial dysfunction. Microvascular pulmonary thrombosis has been reported by other medical teams during Covid-19 [14]. The involvement of histamine as a potentiator of other monoamines with ultimately a prothrombotic action is known [15] (platelet aggregation), these findings of microvascular pulmonary thrombosis only reinforce the need to better understand the involvement of the histaminergic system with its known linkage to other pro coagulant) in the genesis of these abnormalities. It should be emphasized that this would be one more action, reinforcing the potential of pro coagulant factor of endothelial dysfunction induced by endotheliitis.
Antihistamines may contribute to the limitation of these microthombotic processes (or even the suppression of their genesis and / or amplification).

Furthermore, if we consider the cellular expression of antihistamine receptors, especially RH1, it turns out that the endothelial cells could appear as highly endowed in RH1 [9], without prejudicial action induced by histamine. It is shown that human coronary artery endothelial cells see an increased production of certain cytokines (IL6, IL8) in the presence of histamine with a dose-dependent relationship and an overexpression in the presence of TNF-alpha in particular. This effect of histamine on cytokine production is blocked by antagonization of RH1 receptors (diphenhydramine) and not of RH2 receptors (famotidine) [16,17].

It consequently appears possible to consider that, following the activation by Sars-Cov2, particularly the mast cells, there is a release of histamine. Histamine would then induce, specifically on the endothelial cells by proximity, an accentuation of the production of cytokines and in particular IL6 (this especially since the mast cells are known to also release after activation TNFα [4] with a histamine-induced increase).

It also appears that there would be a difference in the kinetics of production of these different mediators, with reference to histamine, there is a very rapid stored production but quite the contrary for molecules to be synthesized (IL6, IL1...) [4]. A similar phenomenon could also be caused, in case of reduction of the physiological elimination/neutralization capabilities within the organism, in relation to Sars-Cov2 in Covid-19. The latter not excluding the former, a synergistic origin of the deleterious effects of histamine could this way be at work (in the end: increase of its extracellular concentrations and / or the level of presence in the extra cellular medium).

Besides, this action of histamine on IL6 production would not appear to be specific to this type of cell but has been highlighted for different cell categories (pulmonary macrophages, monocytes, nasal fibroblasts) [18,19].

It should be noted that, for some cell types (pulmonary macrophages among others), the relationship between IL6 production and histamine would be through in particular as a result of RH1 activities [20,21].

In the management for Covid-19 patients, some therapeutic hopes were placed in monoclonal IL6 inhibitors: tocilizumab [22,23] with a potential for encouraging therapeutic results [24].

The benefit of antihistamines in order to limit the synthesis of IL6 by targeting monoclonal antibodies brings benefits recognized in Covid-19, as a consequence, it appears to us the most promising and this, through this only confined potential of cytokine synthesis. Reducing the overproduction of IL6 is a de facto supplementary protocol for its selective targeting with tocilizumab. The concept of "multi-class therapy with sequential controlled deployment" gaining meaning through this notion (temporal sequence deployment of different therapeutic classes).

It appears here that, given what has been previously mentioned, (expression pattern of H1R, involvement of IL-6 synthesis by endothelial cells in dose-dependent response to histamine, selectivity of antiH2), it is possible to consider more logically an action mediated by antihistamine antiH1. This remains to be demonstrated.

Nevertheless, a complementary and cumulative action of antihistamines may be considered. Histamine activation of H2R receptors is known to be involved in the greater efficiency of IL6 gene reflecting an induced enhancement by IL1 [25].

Here again, the production of IL1 by mast cells generates a potentiating effect of IL6 production (known mediated by histamine). This latter notion, very theoretical, however, allows us to better understand the recent interest in anakinra therapy (competitive inhibitor of IL1 to the type 1 receptor {IL-1RI}) [26] in the management of Covid-19 patients.
Beyond this, the involvement of IL1 seems to be partly attributable to a potential histamine induction during the cytokine release. Indeed, in the same way that histamine is "reliable" to an increase of IL6 production (and therefore participates in any case, and at a minimum, in the increase of IL6 levels), it could participate in the increase of IL1 levels, through the H2R effects [27].
Such implementation, by histamine, of different cytokines (IL1, IL6) including observations and hopes of therapeutic countermeasures (respectively anakinra, tocilizumab) which are in full relevance in their repositioning as part of the management of Covid-19 patients, can only encourage to do the same with the known active substances on the effects of histamine. Therefore, all substances involved in the reduction of histamine levels and/or in the reduction of the effects of histamine should be taken into consideration when fighting off covid -19 and, of course, as a first choice, antihistamines and other molecules that decrease the production of histamine and / or its effects.

In doing so, regardless of their type (antiH1, antiH2), antihistamines seem to retain their appeal throughout the course of the immuno-inflammatory cascade within Covid-19.

Similarly, the targeting at a particular time, of a specified effector of this cascade meets the definition of a multi-class therapy with sequential activation with as the initiator and the possible "amplifier": antihistamines.

It is obvious, however, that the excessive immuno-inflammatory cascade and the induced-lesions, may have a level that the only available response will be a multiple therapeutic response using many active actors.

The micro and then macroscopic tissue lesions, induced by immuno- inflammatory phenomena, are afterwards taking a pathological role of their own and whose therapeutic countermeasures are specific (or even non-existent).

For this reason, the start of the first therapeutic countermeasures must be as early as possible.

The easy to use, cost-effective antihistamines with a potential blocking effect are thus the most promising choice to gain from clinical trials (antiH1 in particular, antiH2 already benefiting).

The sequences of activation of the pathophysiological phenomena induced by Sars-Cov2, appears capable of an event cascade response during which histamine intervenes both in the initial phase but also participating (probably in a dose-dependent

manner) in the production of cytokines that, eventually, will take action themselves. It is therefore most useful to consider the role of histamine and this from the initial phase of induction of immuno-inflammatory phenomenon. The interest of antihistamines (especially antiH1) thus taking again its full meaning. Any decrease in histamine-induced secretion or its effects is logically of significant importance in reducing or even stopping the immuno-inflammatory cascade as well as its short, medium and long-term deleterious effects in Covid-19 patients. In general, any decrease in extracellular histamine concentration or/and any blocking effect decreases its biochemical and cellular actions and their consequences.

As a reminder, some antihistamines antiH1 possess an anti-inflammatory action through certain interactions on the production of prostaglandins 2 (PG2), without this activity being only performed by the sole H1R process [28]. We emphasize that histamine also has a duality effect on inflammation with a pro or anti-inflammatory capability depending on the cell types and the types of receptor involved. Histamine would as well be involved in the inhibition of leukotriene synthesis (LT) with reduction of the action of 5-lipoxygenase [29]. This effect, mediated by antiH2 receptors, is antagonized by ranitidine (antiH2) which induces a deletion, more or less complete, of LT biosynthesis reduction [29]. Thus, the actions of antiH2 could induce a relative increase in the production of LT and, with it, reduce the active potential of antiH2 on a part of the immuno-inflammation.
AntiH1 do not seem to incur this suppressing or diminishing effect of the anti-inflammatory action sometimes observed. Therefore, and purely theoretically, it could produce an antiH2 action, in its use during Covid-19, either slower or partial compared to antiH1.
We can also see the potential interest of antileukotrienes through their positioning, mentioned in the initial hypothesis, within the potential anti-inflammatory countermeasures and this, regardless of their possible and associated action on viral adhesion [30]. The action of antileukotrienes can also be supplemented by their known ability to reduce production, among others, of IL6 [31], which we have addressed in the expression of interest of Covid-19.

Once again, the notion of multi-class therapy with sequential procedures makes sense.

These data, of course, need a deeper knowledge. The notions of possible partial affinities and cross-activations here, become significant as well as that of the functional duality of histamine. However, famotidine does not appear to have an affinity for H1R[9], the possible action of antiH1 on H2R would be interesting to document or have an experimental research to investigate (we have not yet found any data on the subject in our literature search). These possibilities of "cross" linkage and dual action of histamine further complicate the known actions of different specific histamine receptors. The concept of feedback effect and interdependence effects is also to be considered, similar to the one observed at the neuronal level between H3R and H1R [32]. Likewise, the fluctuating cell surface receptors (including time) as well as the effects of coactivation (e.g. H1R and H4R) is also possibly a source of differentiated actions [33].

Beyond the complex interaction of histamine with its various specific receptors H1R to 4, this biogenic amine is also known to interact with other receptors and in particular cytokine receptors.

This opens a possible action on immuno-inflammatory responses may be related to, among others, T helper lymphocytes CD4*, T lymphocytes CD8 * and NK[34], whose involvement in the infectious response is clearly to be considered.
The interactions of biogenic amines (and particularly histamine), on the cytokine receptors, involved in particular in the antiviral response, were also acknowledged [35], thus paving the way for a complex field of research as to the understanding of the mechanisms at work and the scales of action or differentiation-induced factors.
Among actions outside dedicated receivers, activation, modulation and other feedback loops, the understanding of the mechanisms at work offers wide-angle reflections and fields of exploration. However, the involvement of histamine seems to be perfectly valid in Covid-19 is starting to be recognized by more and more medical teams.
Some observational studies on antiH2 during Covid -19, consolidating the interest in randomized controlled trials [36]. The same interest in dedicated studies emerges from the literature search on the therapeutic classes previously discussed (antihistamines, antileukotrienes) during Covid-19 [37].

It should also be noted that vitamin D appears to play an important role as a cofactor of antimicrobial's control [38]. Based on the possible antimicrobial involvement and epidemiological data, the potential usefulness of vitamin D was highlighted [39]. Supplementation is, therefore, sometimes advised to optimize antimicrobial control including for Sars-Cov2 [40]. In the statement published on May 22nd, 2020, the French Academy of Medicine recommends a systematic vitamin D supplementation in case of Covid-19 (800 to 1000IU /day before age 60 and according to dosage beyond age 60) [41]. No impact of supplementation for severe cases have so far demonstrated tangible results and efficiency [42].

In doing so, Vitamin D would contribute to maintaining the stability of mast cells and its deficiency would be associated with their activation [43].
A supplementation would, therefore, provide, in the event of a deficiency, a stabilizing aid making the implementation of histamine less effective in the development of Covid-19, this seems to us negligible but, as indicated, any limitation of the release of histamine, we believe is relevant.

Observation Case

Various observations have been made regarding the taking antihistamines (antiH1) during covid-19 patients with no known allergies.

They have been put together and processed in a global perspective in order to identify any points of interest.

It is therefore a data collection from outside-MA antihistamines in Covid-19 exposed patients in the practice of primary care on clinical criteria (see case definition). The data from the control group are being processed into meaningful information.

As known cases from primary care, the inclusion of the diagnostic criteria was purely clinical (symptoms found and described in Covid-19, epidemiological context, associated with the differential diagnostic procedures by the practitioner to confirm or eliminate). As a reminder, the diagnostic RT-PCR protocol in the field practice cannot be used as a diagnostic support. Although improvements gradually took place,

accessibility to RT-PCR in France was very limited, and this, until at least 11 May 2020. Therefore, the application of Real Time-PCR in primary care could not be easily and quickly addressed, rendering de facto inclusion purely clinical.
Similarly, the sensitivity at 60% initially estimated appears very generous especially in the initial non-severe forms. The negative predictive value of RT-PCR is subject to caution [44,45,46].

In addition to this, after the original editorial cut-off point (12/04/2020) [47], the result of the only RT -PCR requested in our cohort will return positive. She was a 58-year -old patient with associated pre-existing comorbidities (diabetes and obesity) known risk factors for Covid-19. She was the only patient in our sample who had a risk factor (2 in her case) associated with Covid-19. Its evolution is within the strict average of what is observed for the whole sample.

At the time of care and patient management, to our knowledge, there were no studies that had determined the validation and actionable clinical criteria or combination of clinical criteria for the diagnosis of Covid-19. This is still the case but it is now possible to rely on a more substantiated clinical definition including nonspecific symptoms, of varying severity, after two to fourteen days incubation time.

The clinical diagnosis need:

Shortness breath sensation
or
Cough
And at least two of the following symptoms:
fever, chills, myalgia, headache, rhino-pharyngitis, anosmia, ageusia, thorax pressure or chest pain, abdominal pain, diarrhea, dyspnea, confusion, fatigue, drowsiness.

However, let’s remind ourselves, this clinical definition of Covid-19 has not been validated to date and cannot be transposed or applied to the criteria chosen by us at the time of our initial findings. Thus, in early March 2020, the clinical presentations, especially of non-severe or early-stage forms, included: fever, cough, dyspnoea, myalgia, headache, confusion, pharyngitis, rhinorrhea, chest pain, diarrhoea, nausea and vomiting [46]. Anosmia and ageusia were just be considered to be associated with Covid-19.

The constant evolution of knowledge about this new disease makes any de facto nosology and understanding to constantly evolve.

The chronology of knowledge and its optimization should therefore be carefully considered (as well for the diagnosis techniques such as RT-PCR SARS-Cov2).

The criteria of "healing" responds to the same absence of usable objective elements (no biomarker, no meaning in terms of healing, negative results of RT -PCR). It is therefore purely clinical with a consolidation phase (persistence, at least 48 hours without recurrence).

The healing criteria chosen here were therefore also purely clinical: stopping the initial symptomatology starting within a 48-hour consolidation.

No applicable criteria for exclusion have been defined. None of the patients had a documented allergy (and not known) allergy.

Antihistamines intake occurred after the onset of signs and symptoms.

Treatment using Antihistamine drugs : AntiH1

The molecules used were all newer second-generation H1-antihistamines, at the recommended dosage.
As an indication, it will be noted that in total:

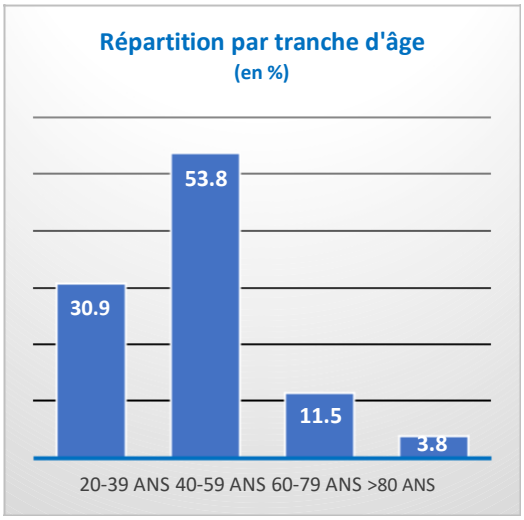
92% of patients were given cetirizine 10 mg per day as a single dose (per os)
04% of patients were given desloratadine 5 mg daily as a single dose (per os)
04% of patients were given levocetirizine 5 mg per day as a single dose (per os)

During the evaluation, some data were missing or not fully exploitable. However, they affected only a very small part of the desired analysis.

The representative material will be reported (n) when it is not the case-control 26 for a given element.

Panel description

Number of patients: 26
Sex ratio to 1
Average Age: 47.42 years (23-80)
Age distribution :



No paediatric population,
Low geriatric population,

Vast majority of the panel participants (88%) is in the identified age group most affected by Covid-19.

Our sample is therefore relatively compatible with those of the literature data (except for the balanced sex ratio in our series).

Reported Symptoms

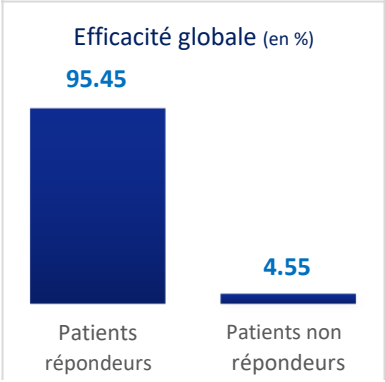
Symptoms	In % of patients
Dyspnea	26.92 % of patients
Pharyngitis	3.84 % of patients
Brutal Anosmia	3.84 % of patients
Diffuse myalgias	38.46 % of patients
Cough	38.46 % of patients
Headache	15.38 % of patients
Fever (sup 38C/100.4F)	23.07 % of patients
Chest tightness	26,92 % of patients
Chills	3,84 % of patients
Asthenia	38.46 % of patients
Diarrhea	26.92 % of patients
Sneeze	3.84 % of patients
Obstructive Rhino	7.69 % of patients
Nausea	3.84 % of patients
Skin eruption	3.84 % of patients
Low back pain	19.23 % of patients

With an average of 3.36 symptoms per patient

Overall effectiveness observed

End of sickness definition is as follows: "efficacy" is considered here and defined as the total
and lasting disappearance (>48h) of all initial symptoms within 5 days from the first administration of antihistamine.

Criteria for end of illness progression observations:



95% of patients experienced a complete disappearance of Covid-19 symptoms during the defined period. The total number of days with antihistamine medication use was 14 days.

With a 70 days gap from the antihistamine treatment end date, the patients did not report or develop any other symptoms.

Since the natural course of the disease could perfectly lead to a symptomatological disappearance during the observation period, it was necessary to refine the study data. Some criteria were therefore explored:

* observational rate of deterioration
* evolutionary duration after therapy initiation
* effect on symptomatology ("symptomatic relief »)
* total evolutionary duration
* impact of time to progression before treatment on the kinetic relief and total duration of the disease

Observed worsening rate

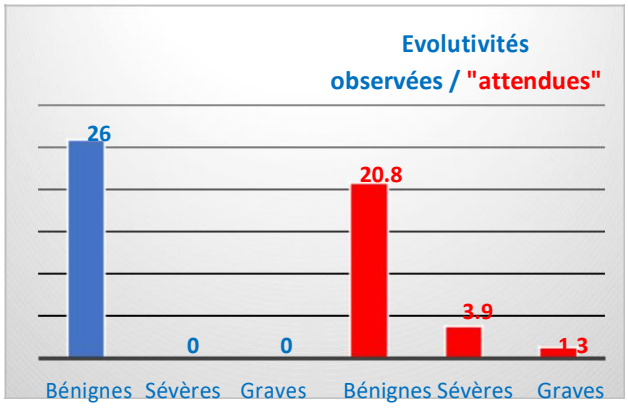
It is a question of getting an idea of the scalability observed in the active phase of Covid-19 ("per critic") in our sample treated with antihistamine.

As a reminder, it is reported as an overall distribution of Covid-19 into 3 groups:

- mild form: 80%
- severe forms: 15%
- harsh /extreme forms: 5%

There is no reference made about the initial sign classification, but only the Covid-19 global evolution.
Therefore, our case series could follow these evolutionary findings (transition to a severe form for 15% of the panel and to a serious form for 5%).

This was not the case with observed/expected comparative findings:

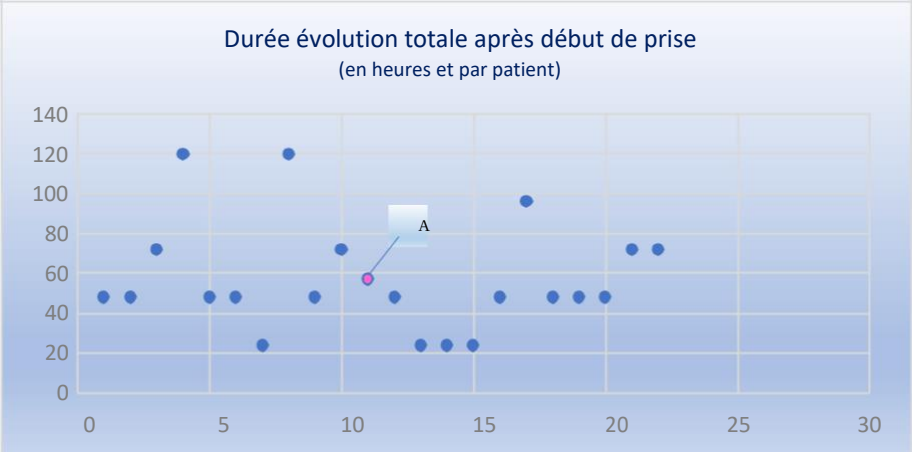


There was therefore no evolution towards a severe and / or a serious form within the panel, different from the expected theoretical average.

Evolutionary time after starting the treatment

It is a question of understanding the delay in the total disappearance of symptoms after starting the antihistamines treatment.

The average is found at 50.3 hours or 2.1 days (utmost 1-5 days) with a homogeneous distribution.



n=21 exploitables A : moyenne

Presence of improvement and kinetic improvement during treatment

The aim is to estimate the presence and, if any, the rate at which treated patients experienced "symptomatic relief ".

By relief we mean:

- a decrease in one or more symptoms
- either a disappearance of certain symptoms with or without a decrease in the remaining symptoms.

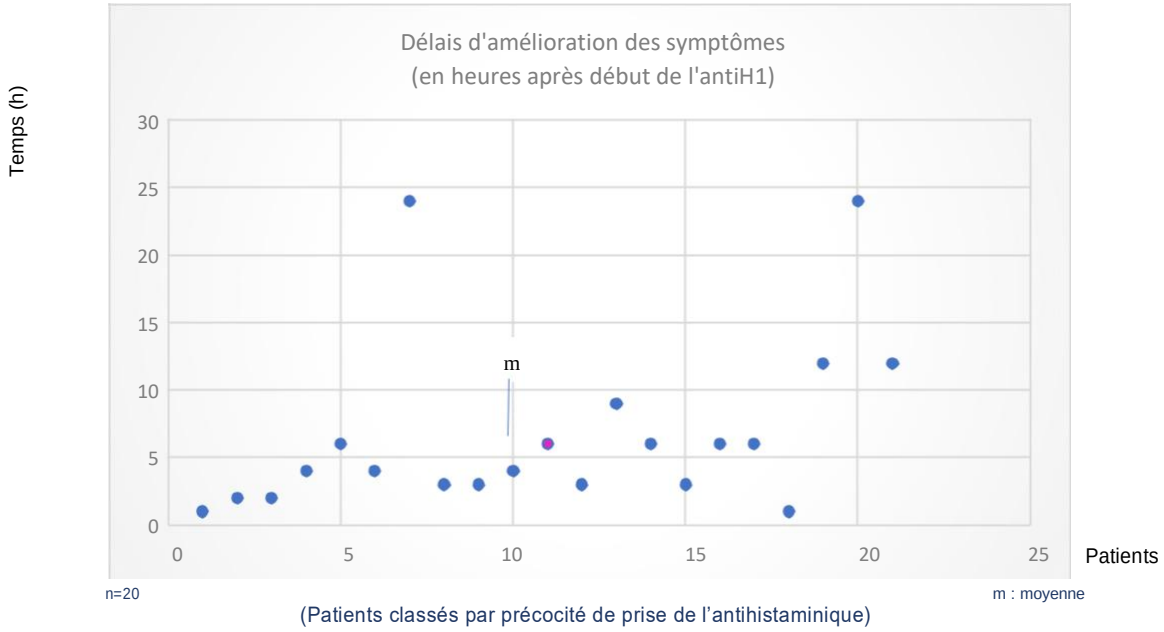
Data from our Series (n=22) show that:

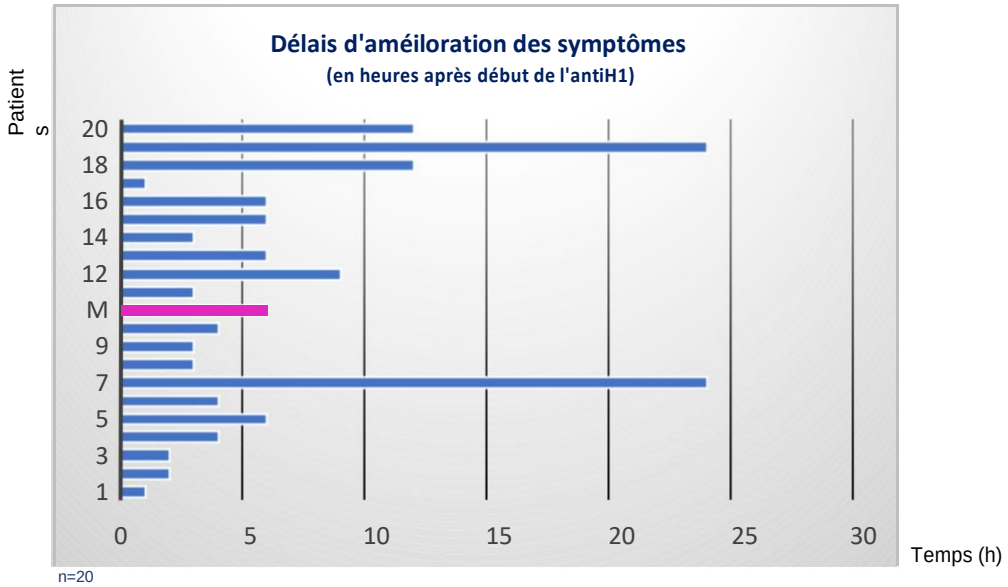
- 88% of patients will report improvement as defined,
- 8% will have a disappearance of symptoms that will ultimately prove to be an end of evolution without sensation of " decrease »)

- 4% no effect

Among patients who reported improvement as defined, the average observed time (from first symptom improvement) is 6.1 h (extreme: 1-24).

The distribution by patient shows a homogeneous distribution.





Correlation between entire duration and time before initiation of antihistamine / to thefirst sign of symptoms

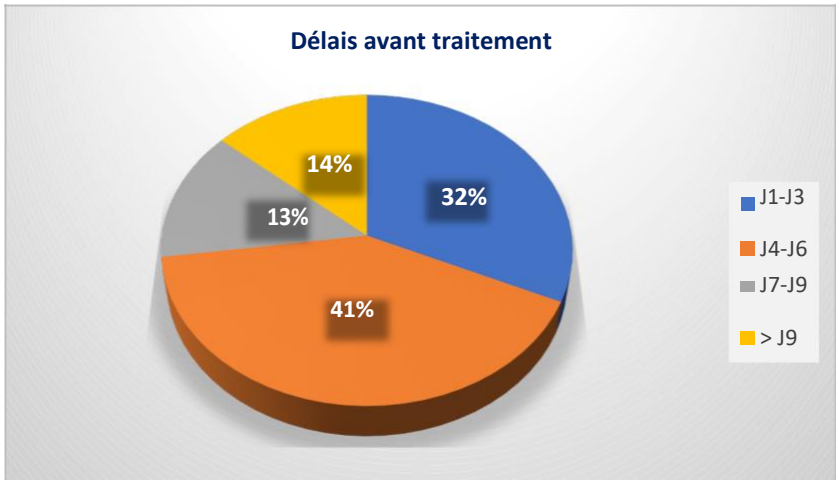
It is difficult to establish a natural evolutionary duration of Covid-19, as the literature gives little consolidated data at the time of the study (March 2020).

However, the existence of an activity rebound between the 7th and the 10th day is well documented.

The French HCPH reports a duration of 2 weeks [46].

We fixed an expected natural evolution value: 12-14 days

The average time when the treatment was started compared to the onset of symptomatology is in our 5.5 day series, with the following breakdown:



This brings the complete termination of the symptomatology to 7.6 days (average consultation time of 5.5 days and average long-term disappearance of symptoms after initiation of treatment of 2.1 days).

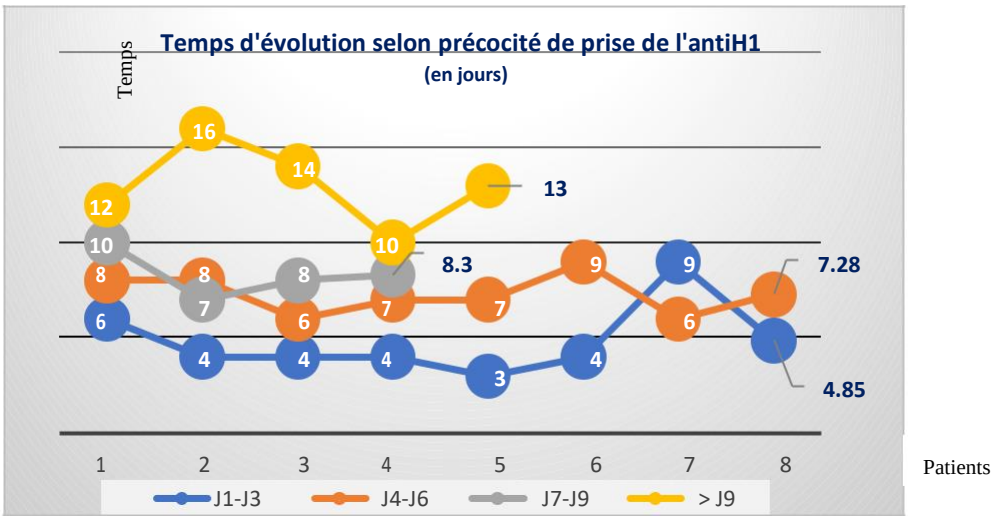
As we are resuming the initial writing of the data, the update in relation to the current growth of knowledge, the natural evolutionary duration cannot always be defined by consensual agreement, but would seem to be equal or superior within the fixed range presented. Indeed, it would appear that the average duration of 14 days for the natural evolution of Covid-19 remains a low estimate compared to some practical data reporting that the “average recovery time of symptomatic forms is 25 days with a high value of 35 days” [47].

It seems that an extended period has been recently highlighted (Hotel Dieu study, Paris). This period estimated to be sometimes over 60 days might tie in with a chronic inflammatory immune system activation which develops insidiously. No clinical and biological data have been submitted.

None of the patients in our study developed a recurrence of the symptoms (taking into account a 70 day after the end of the 14 days initial treatment period).

Relationship between the complete evolution time frame and the delay in starting antihistamine

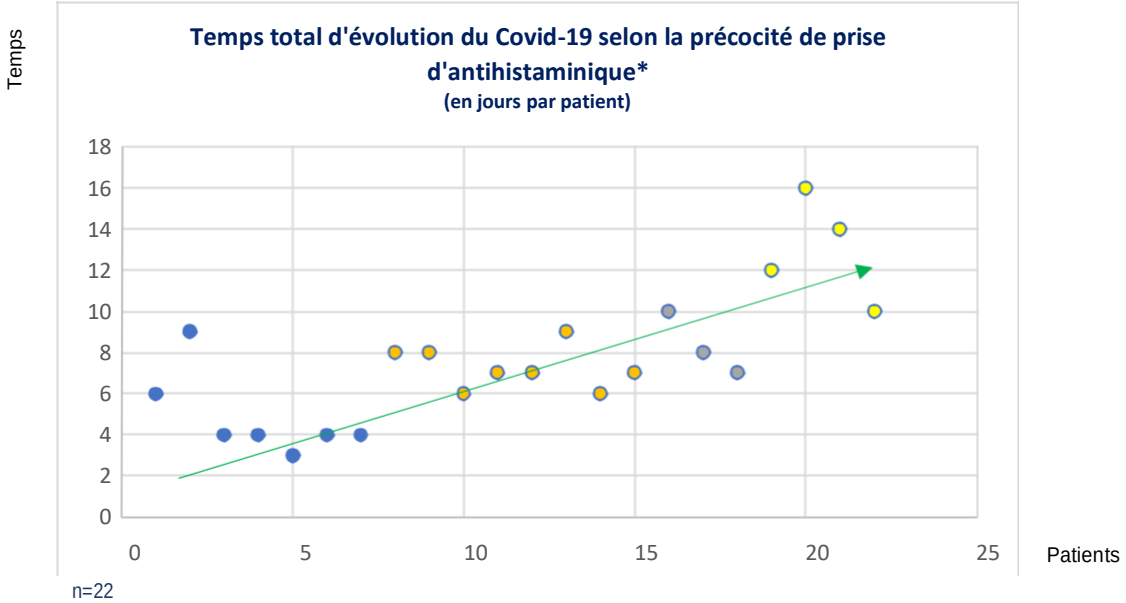
Taking antihistamine between	Total Time Evolution Covid-19
1 and 3	4,8
3 and 6	7.2
7 and 9	8.3
> 9	13
In days since early symptoms	In days



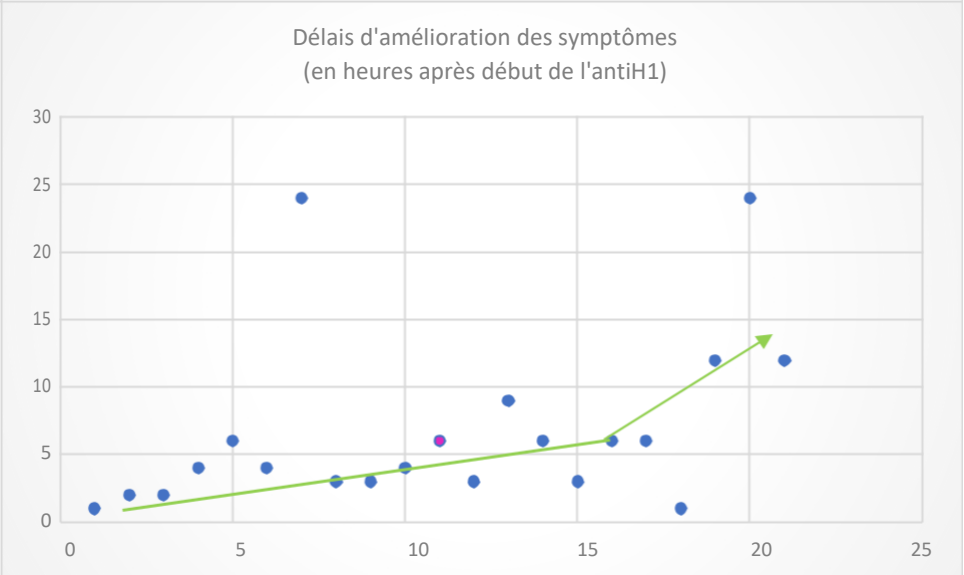
In blue: patients taking the antihistamine between 1 and 3 days after the onset of the first signs, average total duration: 4.8 days
In orange: patients taking antihistamine between 4 and 6 days after onset of the first signs average total duration: 7.28 days
In grey : patients taking antihistamine between 7 and 9 days after onset of the first signs average total duration: 8.3 days
In yellow : patients taking antihistamine more than 9 after the onset of the first signs average total duration: 13 days

There is therefore a correlation between the total duration of the evolution and the early start of treatment. Beyond 9 days of development of Covid-19, the average value of the total duration links with the known value of the control (12-14 days).

The patients who are treated at an early stage show a shorter symptomatic duration in total (4.85 days vs 7.2-4.85 days vs 8.3 - 4.85 days vs 13).



*Timeline depending on early treatment (in days)
(didactic arrow)



(didactic arrow)

There is therefore a clear inter-relation between the total duration of evolution and the earliest stage of the antihistamine treatment. This aspect of the study is also reflected in the distribution of kinetics presented above in terms of time lapse for recovery.

Tolerance of antihistamine therapy

In an observed case, the side effects required temporary cessation of the treatment (cetirizine 10mg per 24h in one dose).

This was a 49-year-old woman who had palpitations within 36 hours of starting the antihistamine treatment, while at the same time she reported a complete disappearance of her initial Covid-19 symptomatology (fever, severe asthenia, chest tightness, dyspnea).
After treatment discontinuation (<48), the patient reported a recurrence of the initial symptoms with a reduced intensity during self-assessment.
After 48 hours of therapeutic interruption, she resumed the antihistamine treatment which showed the disappearance of symptoms in less than 48 hours.
In the end, it turned out that the patient had a stress response tachycardia on the onset of the symptomatology Covid-19 could cause posteriori doubt in relation to the iatrogenic component

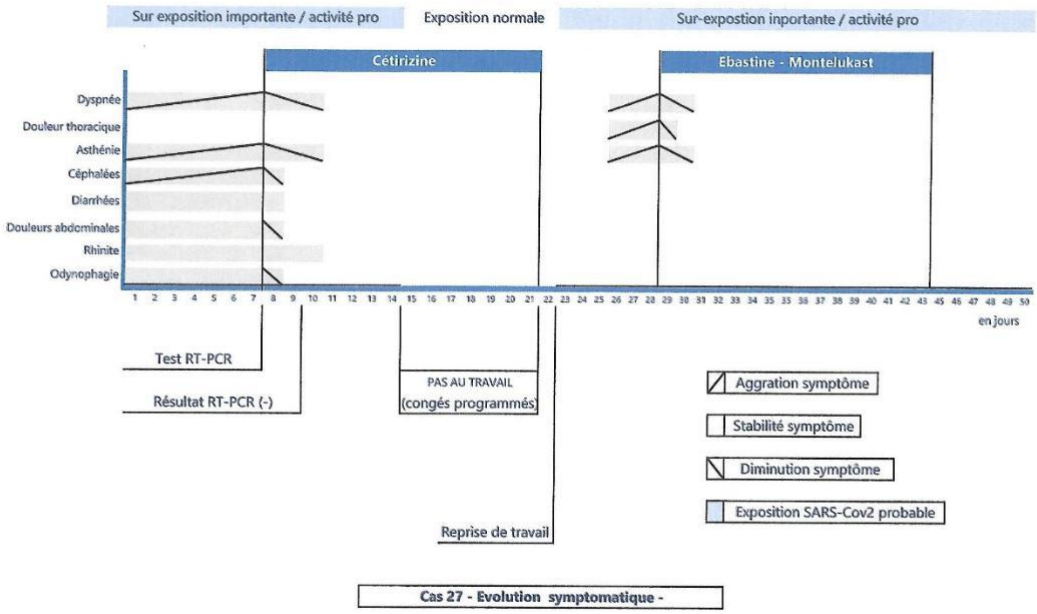
Other findings

It was often assessed, from several patient feedback, of what can be described as a calming effect during the first 48 hours: indicating that they were feeling the benefits the longer the administration of the medication time frame increased.

Complementary case study example:

We will report a case which was not included in the initial data because it was observed at a later date. In light of the information provided, its specificity had to be considered. We will therefore use it as a sidelines data and in addition to the 26 cases.
She is a 22-year-old woman, with no significant history (in particular no known allergies or asthma), a nurse working in pre-admission screening ("Advanced Medical Post" dedicated to the assessment of suspected Covid-19 patients) in the emergency room of a hospital complex (and she sometimes has to work in Covid-19 unit). She developed (D0) the following symptomatology: dyspnea, intense fatigue, headache, rhinitis, odynophagia, abdominal pain and diarrhea, (fever not documented). The intensity of the symptoms (except diarrhea increased within a few days and in particular dyspnea. On the seventh day (D7) of the onset of symptoms, she was tested by nasal swab (RT-PCR). She started the same day (D7) taking cetirizine 10 mg one tablet every 24 hour. She reported within 2 to 3 hours after taking the medication, a reduction in some of the symptoms: abdominal pain, headache, odynophagia, dyspnea with persistence of fatigue unchanged. She described a total disappearance of symptoms within 72 hours after administering the first dose.
The RT-PCR returned negative on D9. She was still allowed to work as it was authorised by the occupational health services, also retaining the diagnosis of Covid-19 on the clinical signs but followed the instructions regarding non-isolation according to the recommendations (negative RT-PCR result and non-evolution more than 8 days)[46].
She did not have a recurrence of symptoms for the next 11 days (taking cetirizine for 14 days in total) and took some scheduled annual leave. Her professional activity resumed on the 22nd day (D22). Around the 25th day (D25), she had chest pain associated with dyspnea and severe asthenia. She continued working (occupational medicine decision). On the 28th day (D28), She felt a progressive increase in dyspnea and chest pain, she had sought medical advice again. She then took a combination of

ebastine 10 mg every 12 hours - montelukast 10 mg one dose per day. The symptoms then regressed within 12 hours and disappeared within 48 hours of the first doses. After 14 days of taking the medication, there was no sign of symptoms recurrence (professional activity maintained).
No signs or symptoms were reported 10 days after cessation of therapy (D24 beginning of ebastine- montelukast association and D10 of cessation of the latter). However, despite a total recovery, she reported dyspnea on exertion, something that is not normal for her.



(indicative schematic representation)

It should be noted that the exposure, in the course of her professional duties, involves a high risk of viral contact with in addition multiple possible contagions. The availability of personal protective equipment (mask, protective gown, etc.) would have been difficult (1 mask for 12 hours and no protective gown), but the accessibility of hand-sanitiser was satisfactory. The lack of protection mentioned as well as the management of known positive RT-PCR patients increased the possibilities of contagion for this nurse. (Serology test pending and clinical monitoring of dyspnea).

Discussion

The finding of a clear homogeneity within these time limits does not seem to us to fall within a stochastic distribution or a distribution related to a placebo effect. The different values that randomly appear, under those conditions, should be much more heterogeneous. The homogeneity of the nature of the duration of improvements and cessation of symptoms, could therefore be due to a pharmacological action in

connection with the administration of antihistamines. This should be explored through clinical trials.

Similarly, the existence of a link between the period of action and the number of days before the treatment probably confirms a pharmacological action. In the absence of any effect from antihistamines, we should have obtained globally similar data in each of the groups established according to the timeframe for starting the antihistamines treatment (compared to the onset of symptoms). The taking of an inactive drug should not, logically, influence the total duration of a disease according to the initial latency before starting treatment. The findings of a clear relationship between earliness and duration argue in favor of a possible extrinsic activity, in this case the antihistamines.
Note that there is an almost linear relationship (a continuum) between the groups classified according to early treatment stage. An adherence effect (placebo effect) does not seem to us to be the mechanism at work here on symptoms and a pathology, which the evolutionary characteristics are known to all.

The order of magnitude and the existence of a distinct link cannot, in our opinion, be due to chance or a placebo effect, including from a small sample, but here again, tests must be conducted in order to verify the possible action of antihistamines.

The low statistical power and the methodological weakness of the points made, however open to criticism, cannot however exclude the action of antihistamines on the symptoms of the Coronavirus (Covid-19) from previous data but to be achieved by appropriate research.

Our findings met the expectations of the initial theorization which cannot therefore be invalidated by these observations. The administration of antihistamines might therefore have the ability to reduce the total period of Covid-19 but also the duration of the various symptoms presented here. This option should be explored.

It is interesting to note, the incident of tolerance, although, not sure if it is, (symptomatology ultimately already existent before starting the treatment), shows that the patient considered herself that the adverse effects were acceptable in view of the symptomatic benefit initially felt.

The pathophysiological mechanism related activity chosen here in relation with Covid-19 seems to us the correct selection and calls for further studies including clinical trials regarding the introduction of antihistamines antiH1(logical leading medication seems to be: cetirizine) for a Covid-19 treatment.

Finally

It seems lawful to us to consider antihistamines antiH1 as a possible therapeutic strategy in Covid-19. Our observations don’t contradict the expectations of theorization initially presented. However, some of the results lead us to continue looking for a therapeutic deployment or combination, in sequence, because it seems to be an element that can maximize the management of Covid-19, following the immune-inflammatory response triggering a series of cascades. During each phase, some therapeutic targeted countermeasures: antihistamines, antileukotrienes, synthetic

antimalarial drugs, corticosteroids and other drugs act on the inflammatory phenomenon. They are used trying to counter the highest immuno-inflammatory response. It is therefore a medical management with a kind of multi- class therapy with a sequential deployment according to the biochemical evolution stage during the medical care of the patient, with an individual and adaptive Covid-19 treatment, for which histamine seems to be the basic common thread. As such, maybe n on-steroidal anti-inflammatory drugs NSAID with a theoretical
risk more important remain a likely option associated with a subsequent use of antihistamines but are likely to be capable of complementary perspectives at a later stage using appropriate clinical supervision (strict medical vigilance). Notwithstanding this, the main issue is to block as early as possible the contamination caused by SARS-Cov2, of the deleterious effects induced by host pathogen interaction.
The likely effectiveness of antihistamines AntiH1during the covid-19 pandemic must be better understood.
Their potential for therapeutic application in covid- 19 which can be effectively used in the acute phase but also considered during the possible long-term complications, (sometimes infra clinical) of the inflammatory and immune system (pulmonary fibrosis …). Similarly, the prolonged evolutive form must contemplate the abnormally persistent activation (and less noisy) of the immune and inflammatory system or of the re-infections without the development of a stable immunization. The evolution of knowledge about the link between SARS-Cov2, Covid- 19 and histamines only reinforces on this basis the importance or urgency to carry out further research. The long-term deleterious effects also remain in these patients, but beyond an individual health issue, a considerable public health issue. We must further explore the component of these long-term forms. Therefore, by taking into account the coherence between the initial theorization, inflow of new knowledge and observations, randomized intervention studies must be implemented as soon as possible.

No conflict of interest to declare.

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