Antihistamines as a therapeutic care plan of Covid-19 About 26 cases

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Conflit d'intérêt : aucun

Summary

We have formulated a hypothesis as to the pathogeny linked to COVID-19.

The implication of the immune-inflammatory system is believed to be the cause, through the host-pathogen interaction, of the heterogeneous symptomatology observed and of the gravity of the inter and intra-individual variables.

Based on this concept, we would like to propose the use of antihistamines as a therapeutic care plan of Covid-19.

The safety profile of the drug, its accessibility and low cost make it an excellent opportunity as long as its proven effectiveness against Covid-19 is demonstrated.

Therapeutic tests for its trial have therefore been carried out.

The data which has been collected and analysed reveal from the outset what we believe to be remarkably effective.

The use of antihistamines has been effective in quickly reducing the patient's symptoms.

The complete and lasting disappearance of symptoms was observed in less than 3 days of use on average.

Similarly, the total duration of Covid-19 disease was shortened, especially due to the fact that the treatment was taken at the earliest stage.

The ability of antihistamines to shorten the progression time of the disease seems relatively effective regardless of the pre-therapeutic time frame.

These findings lead us to the publication of this article, even before the field study had been fully completed, with this in mind aiming to submit as soon as possible a therapy which is solid and easy to apply.

Introduction

This report is not intended' as many of the kind, specialized or not, to address the COVID-19 on an epidemiological, virological or any other clinical term.
There is no need to reassess the current pandemic of SARS-Cov2. Everyone is, like several billion individuals, fully aware of it, especially through the disease that this virus triggers: Covid-19 (Coronavirus Disease 2019) whose potential severity and lethality make it a current (and future) public health threat.

On the other hand, this report aims to bring hope in the way patients with Covid-19 are cared for, a hope carried by field practitioners who provide for their 'common ground': the patient.
It is therefore neither a specialized nor a mainstream article. Some people do it much better than we do. However, by putting on paper the process of our thoughts and then and above all, the findings revealed, it is giving hope in the fight against this pandemic.
Let us wish that this report will be a landmark because it is really a hope of medication therapeutic management of the Covid-19 that we are talking about here.

Sometimes it is the basic elements and their simplicity that makes things change.
Did SARS-Cov2, a straightforward assembly of a few molecules, prove it to us ?

Fully aware of the 'explosive nature of our proposal to use a basic therapeutic drug class in the fight against this disease, the genesis of our reflection must be explained beforehand.

We will firstly set out the initial analytical approach that led to the mention of this therapeutic path, the first test results will then be presented later.

However, for an easy reading, the first part will be presented in the form that we have drawn up without too many details.

Later,an appendix related to this document will set out a complete comprehensive analytical approach of our assertion.
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From heterogeneity to assertion (a postulate)

Based on the epidemiological, clinical, paraclinical and evolutionary paths of Covid-19, our hypothesis formulation of SARS-Cov2 which is conveyed mainly by the virus-host combination and this, from the **initial** contact.

From the interaction with the pathogen, the host's immune-inflammatory system will produce sometimes an exacerbated and deleterious reaction.

SARS-Cov2 has a high contagious strength but above all an ability (without a doubt, never encountered before or comprehended) to cause the host excessive reactions of the immune-inflammatory system, certainly supporting all or part of the pathogenesis.
Depending on the reactive susceptibility of the host's immune system and response to allergies when in contact with SARS-Cov2, it would therefore determine the clinical course and ultimately the severity of the disease.

This susceptibility of the host to produce an abnormal reaction 'turning' more or less against it and in a more or less strong way, could explain the difference in the heterogeneities of Covid-19, whether clinical, biological or evolutionary, regardless of stage/phases and time frame.

From that moment on, it is a potential danger - not of the viral agent (SARS-Cov2) as an inherent part - but simply the reaction induced in the host, to which the patient is subjected.

The intrinsic reactivity specific to each individual is determined in a way by 'his own' Covid19 in terms of evolutionary kinetics, clinical and above all gravity.

One way or another, SARS-Cov2 would generate an immune-inflammatory reaction that can self-exert in a progressive or/and explosive manner.

The occasional explosive and unpredictable nature of the virus leads towards the involment of histamine to deconstruct the activation and runaway behaviour of the immune-inflammatory system perhaps directly viro-induced.

So antihistamine drugs play a role in the therapeutic management of Covid-19 since it allows the modulation of the 'substratum' of pathogenicity as indicated.

- Antigen presentation
- The expressions of pro-inflammatory cytokines
- The early phase production of histamine

From theory to practice

Case definition

The field method of a diagnosis by Real Time PCR cannot be used as a diagnostic support. Let's remember also that its sensitivity is estimated at 60%.
To this date, there are no biomarkers available.
No study is at hand to ascertain the clinical criteria or the association of valid and applicable clinical criteria as to the diagnosis of Covid-19.
The diagnosis criteria used for data inclusion will be purely clinical (usual symptoms found and described in Covid-19 associated with the exclusion by the practitioner of possible differential diagnosis).
Recovery responds to the same lack of actionable objective elements (no biomarker, no significant elements in clinicals terms of a negative interpretation of Real Time PCR results.
The criteria for recovery will also be purely of a clinical trial: cessation of the initial symptomatology within the first 48 hours consolidation.
It should be noted that a persistent fatigue will not be limited to the classification of cases restored to health, in case of isolated persistence (post-infectious asthenia).
No applicable exclusion criteria could be established.
It was thus possible to obtain a small case control study of patients, all volunteers and fully informed of the therapeutic test offered to them, especially as to any expected benefits as it was absolutely not known at the time but all were informed of the very safe nature of antihistamines. All participants were fully aware and accepted the treatment.

Antihistamine treatment

Once the diagnosis is made and the informed patient's approval obtained, a treatment with the standard dose of antihistamine is prescribed. The choice of molecule is left to the practitioner with the only recommendation to select a 2nd generation antiH1.
The initial duration recommended for the treatment was 14 days ; the earlier the patient is diagnosed, the sooner treatment must start.

As an indication, in total we have concluded that:

92% of patients were given Cetirizine 10mg one daily one dose
4% of patients were given Desloratadine 5mg one daily one dose
4% of patients were given Levocetirizine 5mg one daily one dose

Follow-up of patients after inclusion criteria

It was done by telephone contact using an open type questioning. The practitioner was collecting all the patients feedback without leading, which could influence their response. There are no pre-arranged periodicities within the protocol as well as with the patients.
To be noted that some patients have returned their feedback digitally (email-texts)
All feedback was centralised and then analysed.

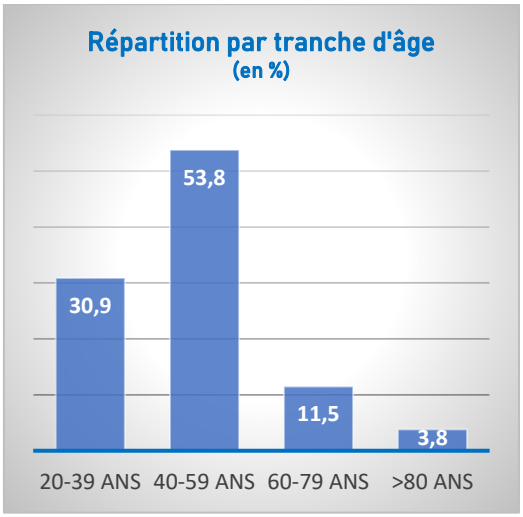
Results

At the time of the analysis process, some data were found to be missing or not fully exploitable. However, they only affected a very small part of the analysis.

The effectual data will be shown (n) when it is not composed of 26 for each element given.

Panel description

Number (n): 26 patients
Sex ratio to 1
Average age (real): 47.42 (23-80)
Age breakdown :



No paediatric population
Few geriatric population T
he vast majority of the population sample (88%) were in the age group identified as most affected by Covid-19 (87% of the Chinese strain).
Our sample is therefore relatively consistent with those of the reference data (except a balanced sex ratio).

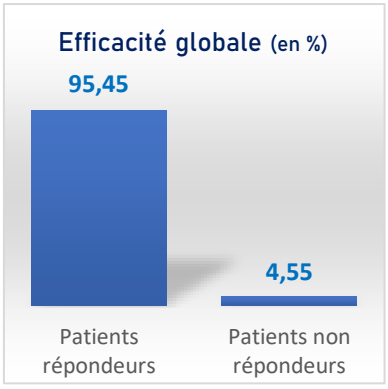
Reported symptoms and their proportion in our panel

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

With an average of 3.36 symptoms per patient

« Efficacité » globale constatée

The 'effectiveness' is considered and defined in this study on the complete and lasting disappearance (-48h) of all the initial symptoms within 5 days from the start of the antihistamine treatment.



95% of patients experienced a consistent disappearance of all symptoms of Covid-19 during the defined treatment period.

However, while encouraging, this does not affirm the effect of the antihistamine treatment. The natural evolution of the disease can, perfectly, lead to the disappearance of the symptomatology during the trial period. It is necessary to refine the interpretation of the data. Some criteria will be further discussed :

- Observed deterioration rate
- Mutative duration from the beginning of the treatment
- Effects on symptomatology ('symptomatic relief')
- Overall evolutionary duration
- Impact of the type of time progression before treatment of the kinetics of relief and the total duration of the disease.

Antihistamine therapy tolerance

Some side-effects were observed which caused treatment discontinuation (Cetirizine). This was a 49-year-old woman who had palpitations within 36 hours of starting the treatment, while at the same time, she reported a complete disappearance of her initial symptoms of the Covid-19 (fever, severe asthenia, chest tightness, dyspnea).

After stopping the treatment, 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.

The incident ultimately shows that the patient considered the adverse effects acceptable to the symptomatic benefit initially perceived. This has led to the addition of our analysis with a notion, certainly subjective but of importance as to the influence on a possible time-related effect-elimination-dose.

In the end, it turned out that the patient had a stress response tachycardia on the onset of the symptomatology Covid-19,

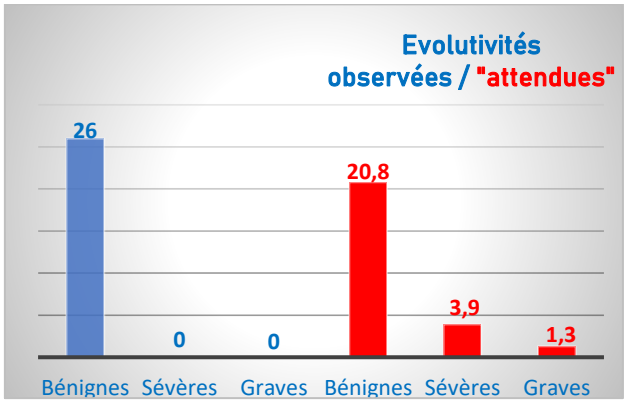
Observed rate of aggravation

It is about getting an idea of the testing changeability observed in the active phase of Covid-19 in our panel treated with antihistamine.
As a reminder, the Chinese strain (10) shows a variation into three groups:

- Benign forms: 80%
- Strong forms: 15%
- Severe forms: 05%

Note that there is no ranking of the initial signs presented but only the evolution rate of Covid-19.
It is clearly demonstrating changes which aggravates the active phase of Covid-19. Severe or harsher forms are described but in much smaller numbers than the evolutionary mutations.
Therefore, our group could legitimately have followed these evolutionary findings (harsh form includes 15% of the panel and in a severe form 5%).

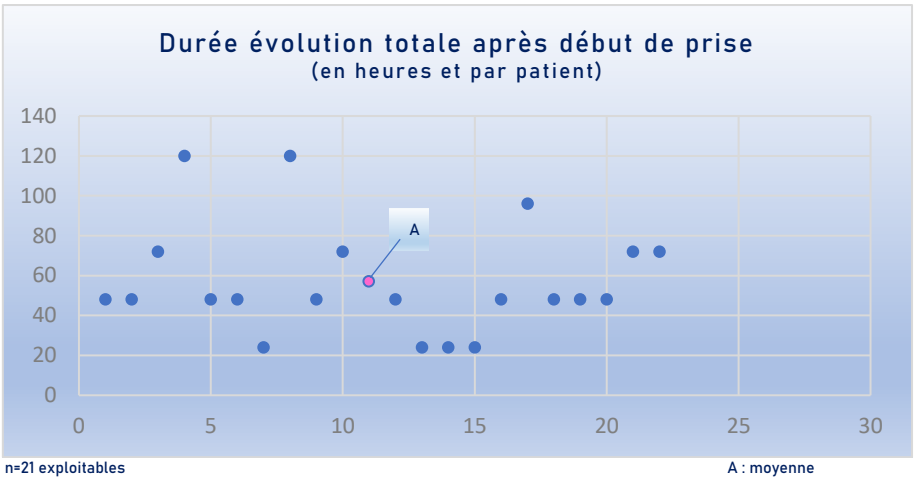
This was not observed, as no patient condition worsened while taking antihistamines.



Evolutionary time after the start of the treatment

It is a question of understanding the total disappearance of symptoms after the start of the treatment.

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



Observation of improvement during treatment and kinetic enhancement

It is a question of estimating the presence and, if necessary, the speed at which treated patients have presented 'symptomatic amelioration'. By amelioration we mean :

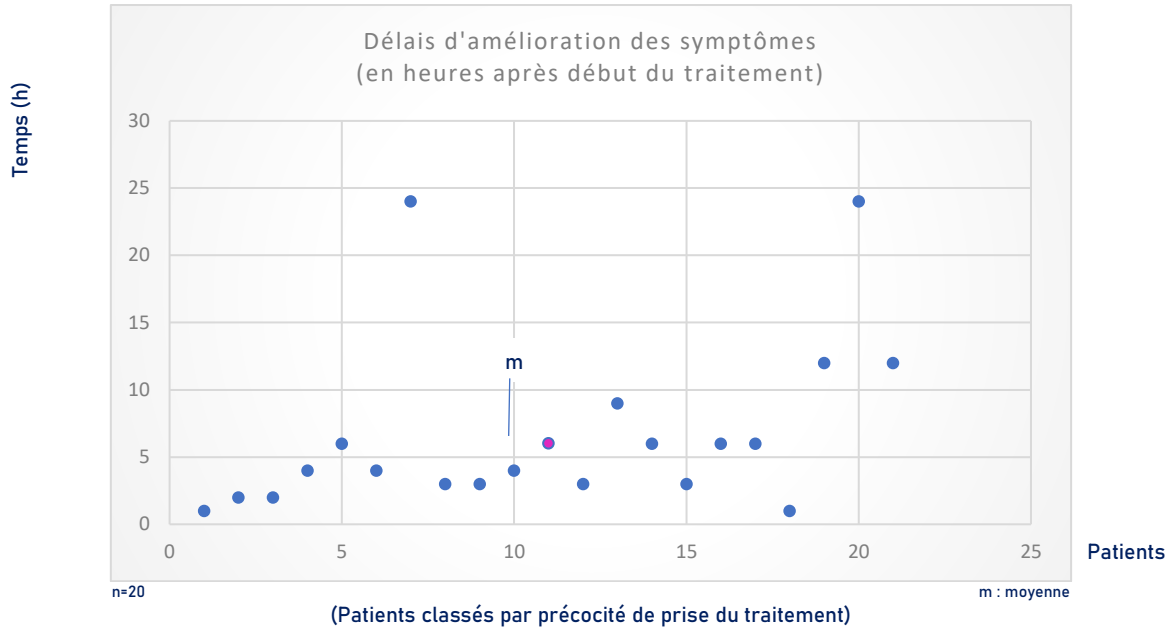
- either a decrease in one or more symptoms
- either disappearance of certain symptoms with or without any decrease in the remaining symptoms

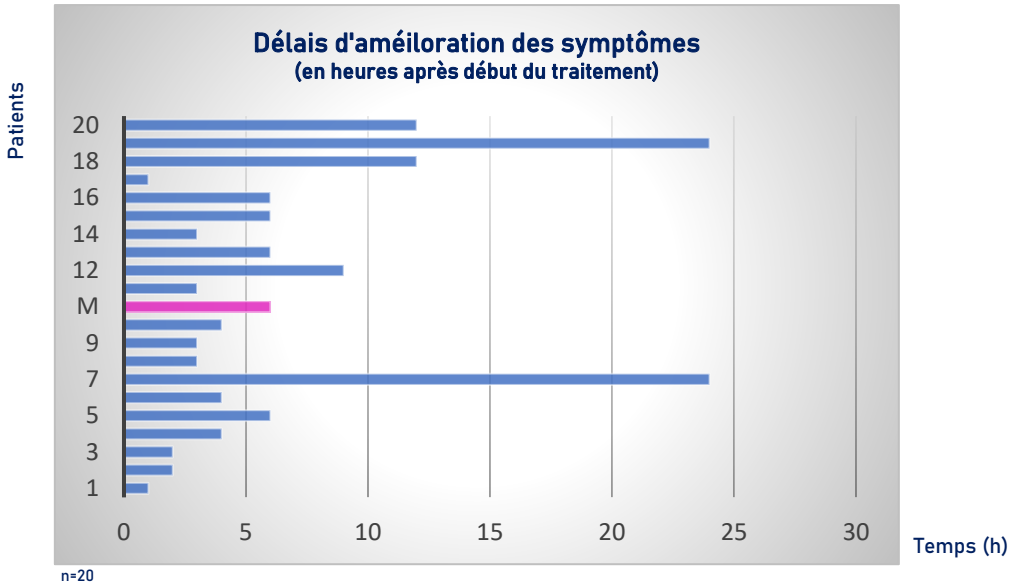
The data of our panel (n=22) shows that:

- 88% of patients will report an improvement as defined,
- 8% will experience a disappearance of symptoms which will ultimately prove to be an end of evolution (without insensibility perception)
- 4% ineffective

Which gives 96% positive change in the symptomatology of the patients after taking the antihistamine. Among patients who reported an improvement as indicated in the average observation time, is 6.1 hours (extreme: 1-24).

The grouping by patient points toward a more homogeneous categorization.





Correlation of the total duration and time before the use of antihistamine / to the first sign of symptoms

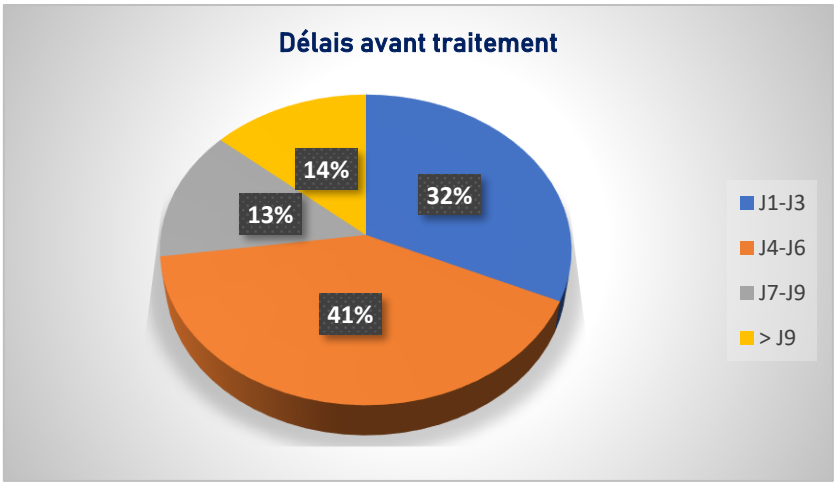
It is difficult to establish the natural evolutionary duration of Covid-19, as references give very little consolidated data.

However, it is well documented regarding the existence of a viral rebound between 07th and 10th day.

The HCSP reports a duration of 2 weeks.

We will take as an expected natural evolution : 12 to 14 days.

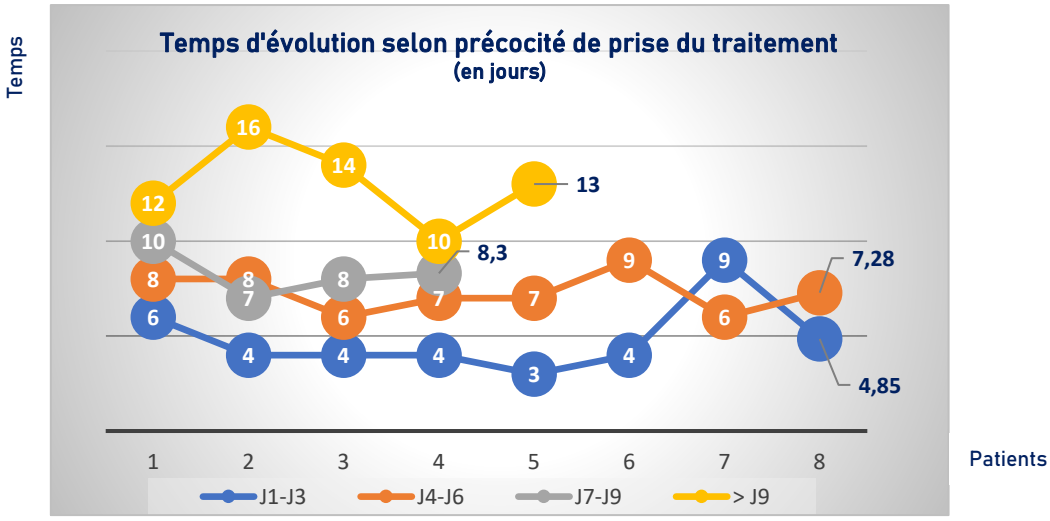
The average time when the treatment was started compared to the beginning of the symptomatology is in our panel of 5.5 days, with the following breakdown :



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

Correlation between the complete evolution time frame and the delay in starting the treatment :

Délais Medical treatment between	**Temps Total d'évolution Covid-19** Covid-19 complete evolution time
1 et 3	4,8
3 et 6	7.2
7 et 9	8.3
> 9	13
In days from the time of symptoms onset	in days



In blue: patients taking antihistamine between 1 and 3 days after the onset of the first signs, average total duration: 4.8 days

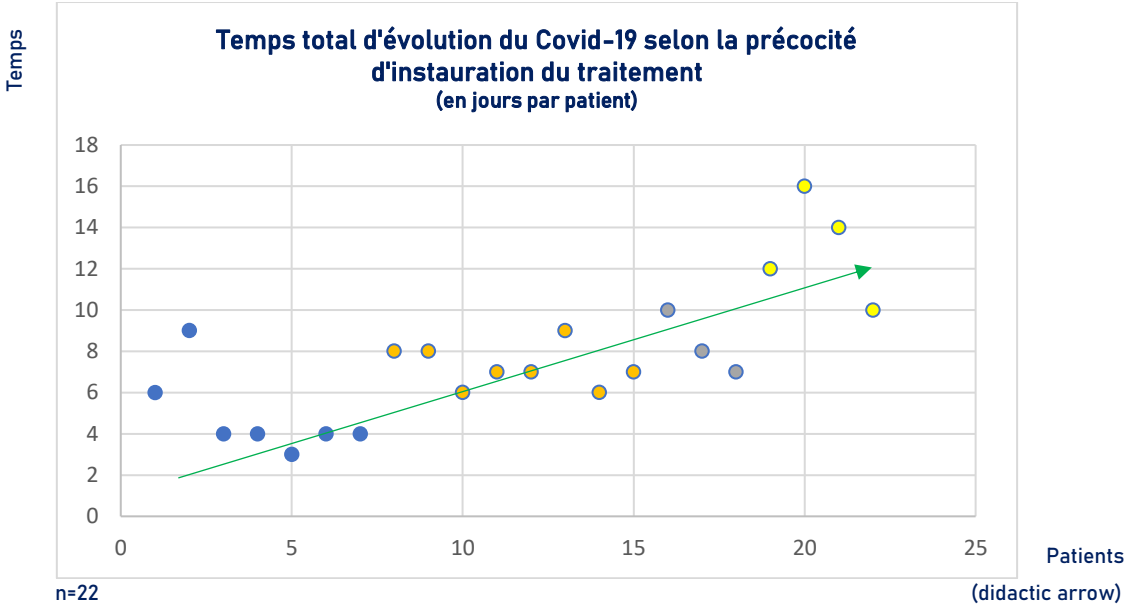
In orange: patients taking the antihistamine between 4 and 6 days after the onset of the first signs, average duration: 7.28 days
In grey, patients taking antihistamine between 7 and 9 days after the onset of the first signs, average duration: 8.3 days
In yellow: patients taking antihistamine more than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

There is therefore a correlation between the total duration of evolution and the early start of the treatment.
Beyond 9 days of development of the Covid-19, the average value of the total duration links with the known value of 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 - 8.3 - 13)

In our view, without therapeutic reaction, we should obtain in general similar data in each of the groups. Administering an inactive drug between J1 J3 should not influence the total duration of an infectious disease such as Covid-19 (or among a small proportion if we allow a value from the placebo effect in such a pathology).

This is not the case. We observe a clear decrease related to the different time of the administration of the treatment.

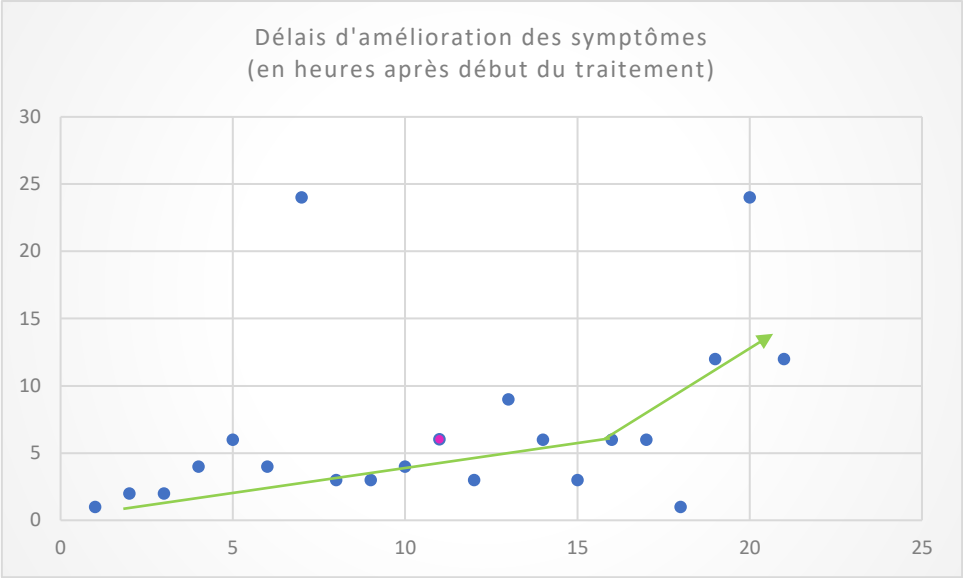
The antihistamine have the ability to reduce the evolutionary sequence of Covid-19



In blue : taking the antihistamine between 1 and 3 days after gradual onset symptoms, average duration:4.8 days. In orange :taking the antihistamine between 4 and 6 days after gradual onset symptoms, average duration: 7.28 days.
In grey : taking the antihistamine between 7 and 9 days after gradual onset symptoms, average duration 8.3 days.
In yellow: taking the antihistamine more than 9 days after gradual onset symptoms, average duration: 13 days.

Thus, there is a very clear interrelation between the total time of evolution and the earliest stage of taking the antihistamine.

This is also reflected in the distribution of kinetics above-mentioned in terms of time lapse for recovery.



(didactic arrow)

Debate

Taking in consideration the results, it appears that the homogeneous nature of the duration of improvements (6 hours on average) and the disappearance of symptoms (2.1 days on average), the outcome can probably be linked to pharmacological action.

The finding of the logical homogeneity in these times seems to us to be related to the distribution of a stochastic process or the distribution in relation to a placebo effect. The distribution of a possible placebo or/and stochastic effect would have been spread more widely in our view.

Similarly, the existence of a link between the period of action and the number of days before the treatment probably confirms a pharmacological action.

Again, the proportion and the existence of an explicit link, cannot be a matter of chance or a placebo effect, in our view (even taking into consideration our small panel).

Despite the known lack of statistical power and the methodological complete accuracy for our critics, it does not seem to be able to rule out the efficacy of antihistamines in the prevention of adverse reactions/symptoms of Covid-19 in terms of data.

Finally, as already reported, the patient satisfaction rate was a strongly noticeable and unexpected element in its proportion.

The perceived benefit, for the most part in the first 48 hours after the start of the treatment is regularly reported. Combined with what might correspond to a dose effect curves response, some patients report a degradation the longer time elapses from the moment the medication was taken.

Conclusion

It should be noted that for almost all of them, the symptoms initially presented by the patients in this case study (not known to be allergicals symptoms) are usualy not reactive to an antihistamine treatment, except if we take into consideration the immune-inflammatory reaction in Covid-19.

A placebo effect does not seem to us to be a mechanism having effect on symptoms and pathology of which we all know the evolutionary characteristics.

Taking into account the above, an activity related to the pathophysiological mechanisms proposed here in relation to Covid-19, appears to us to be continued as well as the use of antihistamines.

Our results suggest that this therapeutic strategy should be considered effective. The benefit/risk ratio being very favourable to the use of antihistamines in Covid-19. Let's agree that randomized controlled trials and complementary studies will confirm our findings but in the meantime there is a health emergency leading us to consider and weight up the benefit/risk factors every minute.

Antihistamines have a very significant pull back in its use leading to a full drug safety in mass use.
Our results indicate that :

- No aggravation was observed
- 88% of the patients experienced an improvement in their symptoms between 4 and 6 hours after taking the treatment.
- 95% of patients experienced the disappearance of the symptoms within an average of 2 days after starting the treatment.
- There is a clear link between take-up time and symptomatic improvement speed.
- There is a clear link between take-up time and recovery time.
- The total time frame of change is on average decreased in relation to the reference value (-4.4 days if ref. at 12 and -6.4 days if ref. at 14)

All in all, our conviction can only be reinforced by this data converging into our theoretical expectations.

Theoretical expectations of molecules, little was expected at first.

Let us believe that the treatment of Covid-19 will be easy to action so that no difficulty in accessing potential treatment will add dark times to this pandemic.

Some previous results, however, allows us to think that combination therapy seems to be an interesting element in the management of Covid-19, in the network of the immune-inflammatory system.
At each stage, some counter-measures : hydroxychloroquine, corticosteoids, are taking all their place in this flight in our opinion. Similarly, the approach using anti-leukotrienes seems likely to open up complementary perspectives.

Special thanks to our patients and to mister CASSANI.

REFERENCES

(1) Specialist in general medicine, DliuEA Systemic Diseases and Arthritis, Graduate of Grenoble School of Medicine, FRANCE
(2) General Medicine, Trained in Emergency Medicine and Disaster Medicine, Graduate of Nice School of Medicine, FRANCE
(3) General Medicine, Geriatric Capacity, Graduate of Pavie and Dijon Schools of Medicine, ITALIA-FRANCE
(4) General Medicine, Graduate of Paris School of Medicine, France
(5) Guan W-J et al , NEJM 28/02/2020
(6) Wang D et al, JAMA 07/02/2020
(7) CHEN N et al, Lancet 29/01/2020

(8) HUANG C et al, Lancet 2401//2019
(9) HCSP, High Council of Public Health publication of 05/03/2020, Notice management of confirmed Sars-Cov2 infections,
(10) London, GB

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