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Mexican Delphi Consensus to Use Favipiravir in Patients with COVID 19 (Expert Panel)

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SUMMARY

Background and Objectives: The SARS COV2 pandemic in 2020 associated with severe pneumonia has been the most prevalent clinical entity in the morbidity and mortality of the disease. New antiviral treatments have been used under different emergency protocols with the aim of reducing the spread of the virus and reducing its lethality. Since 2013, favipiravir is an antiviral used to treat resistant influenza. Recently, multiple studies in Japan, Russia and China have demonstrated its effectiveness under the inhibitory mechanism of the viral RNA polymerase, effectively reducing the multiplication of the virus. The result of the expert panel using the Delphi method on the use of Favipiravir in patients with COVID 19 in Mexico is presented.

Methods: Using the Delphi method and a panel of experts, a questionnaire was developed that included a block of questions regarding the benefit and non-benefit of the treatment of a patient with COVID 19 since diagnosis, identification of risk factors and comorbidities, as well as the ideal candidate. by consensus to receive the therapy,

its follow-up, laboratory and office studies to be determined. There was consensus on determining the use of Favipiravir in routine clinical practice.

Conclusion: The consensus determined the proper use of Favipiravir in patients with COVID 19 infection under the circumstances of the patient's risk, as well as the benefit of its dosage and monitoring in order to reduce the progression of the disease and reduce the demonstrated morbidity and mortality. in the 2020 pandemic.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) was first identified in Wuhan, Hubei Province, China [1] and is the causative agent of the coronavirus disease 2019 (COVID-19) pandemic. To date, severe pneumonia has been the etiology with the highest morbidity and mortality worldwide. We know that COVID-19 pneumonia is caused by the new virus, so the pathophysiology and treatments are still in the process of demonstrating their effectiveness, tolerability and adverse effects that allow for an ideal treatment for all patients. We can only help ourselves from the different vaccines and the immunity they have created over these 3 years. At this time, new antivirals are urgently required that allow us to treat our patients early and avoid outcomes such as death [2]. SARS CoV-2 is a positive-strand RNA (+RNA) virus and is a member of the coronaviridae family. SARSCoV-2 is a single-stranded RNA beta-coronavirus that encodes an RNA-dependent RNA polymerase (RdRp) and proteases. Favipiravir, formerly known as T-705, is a prodrug of the purine nucleotide favipiravir ribofuranosyl-5′-triphosphate [3]. The active agent inhibits RNA polymerase, stopping viral replication [4]. Favipiravir was approved in 2014 by Japan Pharmaceuticals and Medical Devices Agency under the brand name AVIGAN® for the treatment of new and re-emerging influenza virus infection [5]. Several studies describe its efficacy against other RNA viruses such as Ebola virus [6], as well as efficacy against rhinovirus and respiratory syncytial virus [7].

In vitro, the 50% effective concentration (EC50) of favipiravir against SARS-CoV-2 was 61.88 μM/L in Vero E6 Cells. Therefore, favipiravir has high potential for the treatment of patients with COVID-19 [8-11]. However, the research has been carried out in Asian countries with good clinical results, which is why there has been good efficacy and safety, even without being able to record the effect of favipiravir in patients with COVID-19 within the Mexican population [12]. The objective of this panel is to generate a consensus on the use of Favipiravir in Mexican patients with COVID 19 infection, identifying needs and opportunities in the universe of patients who to date do not have established guidelines or standard treatment present in the country. Identifying the group of patients who can benefit from antiviral treatment in the early stage and reduce the morbidity and mortality presented in the pandemic [13-17].

Methodology

The RAND/UCLA methodology was used to generate consensus, which uses scientific evidence, along with the judgment and opinion of a modified Delphi panel, online asynchronously. The panel was made up of 13 experts, from the specialty of pulmonology and non-pulmonologists present in the practice of respiratory medicine in different centers of the country, taking into account the clinical experience and management of patients with COVID infection, as well as the use of Favipiravir in its dose, treatment, monitoring and taking into account their experience as decision makers and treating patients with these characteristics. A questionnaire will be prepared with a total of 10 questions, the structure of the questionnaire included 2 sections, to be completed online and in person. Once the panelists agree to participate in the panel, the questionnaire will be shared with them so they can answer the questions based on their experience. The point of consensus will be reached when 80% of the panelists agree on the answer. If consensus is not reached on any question, a proposal will be made on the topic, reaching consensus. The final results will be accepted as agreements of the expert panel and will constitute the core of the consensus report. The statistical analysis will be carried out using measures of central tendency and dispersion: maximums and minimums. The first three indicate the central tendency of the distribution or set of expert responses, while the maximum and minimum indicate the extreme responses to have a characterization of the set of results obtained in each of the questions. The median response will be identified with its dispersion indicators.

Questionnaire

The authors of this study constituted the scientific committee of the project due to their career and professional experience in this field. Together with the collaboration of an external methodological advisor, they developed the contents of the Delphi questionnaire. To this end, a bibliographic search was carried out, in which meta-analyses/systematic reviews and other types of critical synthesis of scientific literature were prioritized, through the consultation of common bibliographic databases, as well as a manual review of the bibliographic references obtained to identify others that could be of interest from keywords such as COVID 19, antivirals, pandemic, Favipiravir. Each survey item submitted to the panel's assessment was written taking into account whether it was an assertion, affirmative or negative, as a professional criterion or clinical recommendation, that responded to aspects of interest or controversy in the clinical management of patients with COVID 19. The final version of the questionnaire a block of questions as follows:

1) Current COVID 19 management algorithm.

2) Opinion on the relative importance of risk factors taken into account when prescribing and monitoring treatment with Favipiravir.

3) Opinion on the safety profile of Favipiravir.

4) Recommendations for the selection of treatment for the ideal candidate to benefit from the use of Favipiravir in patients with COVID 19.

All questions had to be answered, in order to obtain the opinion of all the panelists participating in both rounds on all the questions raised. However, in the second round, only those items for which consensus was not obtained in the previous round were consulted, that is, those questions that did not obtain at least 80% grouped responses. Finally, extend the recommendation in a final consensus under the following statements (Strong: >80% agreement and Weak <80% agreement) ending in determining the doctor's criteria according to the clinical case witnessed.

Expert Panel Selection

The experts on the panel were proposed by their clinical experience and medication management as leaders in prescribing in patients with COVID 19. Be representatives of their medical specialty with decision-making on the clinical situation of the study, professional recognition for their experience and scientific criteria. (leadership in the field) and special interest in the field of COVID 19 infection. The field work of the study was carried out between June-July and August 2023. With headquarters in Mexico City in Mexico and Tokyo City in Japan.

Analysis and Interpretation of Results

To analyze the group opinion regarding each question raised and give a numerical score to the agreement of the statement or question. Consensus was defined when at least 80% of the panelists had responded in agreement or disagreement. The data were analyzed globally, establishing a consensus of statements that resulted in:

a) STRONG Recommendation: Agreement more than 80%

b) WEAK Recommendation: Agreement less than 80%.

Results

13 experts who participated in the study, 100% were specialist doctors. (82% Pulmonologists, 14% Non-Pneumologists (Geriatrics and Otorhinolaryngology). Of the total participating experts, 70% have been in professional activity for more than 15 years and 80% treated on average more than 10 patients for COVID 19 in one week. There was consensus (agreement of >80% of the panelists) in more than 90% of the questionnaire and only 10% went to the second round. Consensus was concluded in 15 recommendations for the use of Favipiravir in patients with COVID infection 19 in Mexico for use at any level of medical care in our country (Table 1).

Table 1: Recommendation on the use of favipiravir in patients with covid 19 infection.

Indication	Recommendation
1. Fever, Cough, Nasal congestion and Dyspnea are the cardinal symptoms in COVID 19 infection	Strong
2. Odynophagia, Headache, Myalgia, fatigue, anosmia, dysgeusia and diarrhea are secondary symptoms to COVID 19 infection.	Strong
3. The Use of Favipiravir should be initiated in patients with Comorbidities and Symptoms.	Strong
4. The use of Favipiravir should be initiated in all immunosuppressed patients.	Strong
5. In patients with COVID 19 infection, imaging study is no required.	Strong
6. In the treatment of COVID 19 infection, the use of Favipiravir is recommended for 14 days.	Strong
7. In the treatment of COVID 19 infection, the use of Favipiravir is recommended for 10 days if the case warrants it.	Weak
8. In patients with COVID 19 infection and a decrease in oxygen below 90%, it is suggested to perform a Chest Tomography.	Strong
9. In the patient who has responded to Favipiravir. It is not recommended to perform an antigen test as a way to resolve the disease.	Strong
10. In the dosage of Favipiravir, the number of Tablets is not an obstacle to completing the treatment regimen.	Strong
11. Patients with comorbidities, over 60 years of age, high risk of complications and unvaccinated with COVID 19 infection are ideal candidates for the use of Favipiravir.	Strong
12. In the treatment scheme in patients with COVID 19 and use of Favipiravir, it is recommended that it can be used after 5 days of the beginning of the infection if the case warrants it.	Weak
13. In all patients with COVID 19 infection, it is recommended to perform laboratory studies such as blood count, C-reactive protein and D- dimer.	Strong
14. It is considered with clinical and scientific experience that Favipiravir should be the initial antiviral treatment in COVID 19 infection.	Strong
15. Favipiravir is considered within the Treatment of COVID 19 in National and International Guidelines	Weak

Discussion

During the presence of the different waves of the pandemic from 2020 to 2023, different outcomes have been observed in patients with COVID 19, mainly in patients with severe pneumonia. This case demonstrates the effectiveness of Favipiravir in patients with pneumonia and comorbidities. To date, in Mexico there is no treatment established by guidelines for the treatment of acute COVID 19. Favipiravir is a good option for patients with acute clinical symptoms and comorbidities that allows us to initiate appropriate therapy before presenting progression or deterioration. of the disease taking into account that we do not have tools to determine the severity and that the patient will certainly present with fatal progression of the disease. Favipiravir is a good option as a treatment for COVID 19. In this consensus panel of experts, there was agreement that Favipiravir should be used in certain patients who present risk factors. There was consensus on most of the statements, but there were disagreements regarding the time of use of Favipiravir, since clinical experience has seen the improvement a few days after starting the treatment, which makes us reflect on whether the treatment should be less days, but there is still no scientific evidence to establish it. An important fact that has shown approximation in the severity of the disease is hypoxemia and the use of chest tomography, which in this area already exists evidence to determine the severity of patients.

Conclusion

Favipiravir is a good therapeutic option in patients with COVID 19 pneumonia and comorbidities with clinical results of symptomatic improvement of patients and prevention of disease progression in the short term. In summary, the data from this panel showed a consensus to use of Favipiravir in patients with COVID 19 infection and risk of deterioration. The consensus meets the established goals of having an initial document of evidence for recommendation on the use of Favipiravir in patients with COVID 19 infection in Mexico.

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