EVIDENCE SUMMARY

Should Oseltamivir be used in the treatment of COVID-19?

Antonio L. Faltado Jr., MD FPCP, FPSEDM, MSc (cand) and Anna Angelica Macalalad-Josue, MD, FPCP, FPSEDM, MSc (cand) and Maria Teresa Sanchez-Tolosa, MD, D Clin Epi, FPDS

RECOMMENDATION

We recommend against the use of oseltamivir as treatment for patients with COVID-19 infection. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

The panel made a strong recommendation against the use of oseltamivir noting that the mortality rate among patients given the drug is higher compared to those given standard of care (i.e., 27% vs 6%). Likewise, results showed that the progression to severe disease is five times more likely among patients taking oseltamivir.

Key Findings

Based on the five retrospective cohort studies included in this review, oseltamivir was associated with increased risk of mortality ((Odds Ratio (OR), 4.20; [95%CI 4.03, 4.38], very low quality of evidence). Moreover, it was associated with risk of disease progression (OR 5.22; [95% CI, 2.00, 13.02], low quality of evidence) as well as longer time to viral clearance (standard mean difference (SMD) of 1.65 days longer (95% CI 1.27, to 2.03, low quality of evidence). Currently, there are five ongoing clinical trials on the efficacy of oseltamivir as treatment for COVID-19.

Introduction

Oseltamivir, a neuraminidase inhibitor, has been effective in treating influenza A and influenza B [1]. It has been hypothesized to inhibit SARS-CoV-2 proteases involved in the degradation of polyproteins that control viral replication [2]. However, an in-vitro study failed to show effectivity of oseltamivir against SARS-CoV-2 [3] while several other observational studies have conflicting results in terms of mortality benefits of oseltamivir in COVID-19 [4-6].

Review Methods

We performed a comprehensive systematic search of related literature from Medline, CENTRAL, Love Platform App and the COVID-19 NMA database. We also searched for preprint articles on medXriv, and searched for ongoing clinical trials using ClinicalTrial.gov, Clinicaltrialsregister.eu and Chinese Clinical Trial Register. Freehand search using Google was also done to check for other sources of information. Search was conducted using the following search terms: “COVID-19,” “SARS-CoV-2” and “Oseltamivir.” There was no limit with regard to the date, language and country of publication.

Eligible articles were evaluated using the following criteria:

Population	COVID-19 patients any age, co-morbidities and severity
Intervention/Exposure	Oseltamivir
Comparison	Usual standard of care, placebo, any active control
Outcomes	Mortality, clinical improvement, progression free survival, need for mechanical ventilation and adverse effects
Methodological filter	randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available

Results

We found no randomized controlled trials in our search. We obtained a total of five retrospective cohort studies: two from the search on Medline, CENTRAL, Love Platform App and COVID-19 NMA database, and three preprint articles on medXriv. We also found five ongoing clinical trials from our search of trial registries.

A total of five retrospective cohort studies with a total of 130,867 patients were included in this review, the pertinent details of which are shown in Appendix 1. The studies of Mancilla-Galindo et al., Chen et al. and Liu et al. were pre-prints and have not been peer reviewed. All of the studies enrolled confirmed COVID-19 patients by RT-PCR. The dose and duration of oseltamivir were not reported in all of the studies. The studies used electronic medical records and nationwide COVID-19 databases to collect data. There was no limit in terms of severity, although majority of patients included in the study of Chen et al. had mild to moderate COVID-19. All of the studies used statistical adjustments to reduce potential confounding and selection bias. The study of Mancilla-Galindo et al. used propensity score matching. All of the studies had adequate follow up. In this review, we found that oseltamivir use was associated with increased risk of mortality (Odds Ratio (OR), 4.20; [95% Confidence interval (CI) 4.03, 4.38], very low quality of evidence). Moreover, its use was associated with disease progression (OR, 5.22; [95% CI, 2.00, 13.02], low quality of evidence). In terms of time to viral clearance, Chen et al. showed that oseltamivir use had a standard mean difference (SMD) of 1.65 days longer (95% CI 1.27, 2.03) than the control group (low quality of evidence). However, Hu et al. reported that patients on oseltamivir had a lower risk of prolonged viral shedding (≥20 days) (Hazards Ratio (HR), 0.416; 95% CI, 0.279 to 0.620) compared to the control group (low quality of evidence).

Recommendations from other groups

There was no mention on the use of oseltamivir as treatment for COVID-19 in the Infectious Diseases Society of America (IDSA) treatment guidelines (April 14, 2021), World Health Organization (WHO) living guideline (March 31, 2021), US-NIH treatment guideline (Feb. 16, 2021) and Australian Living Clinical Practice Guidelines (May 20, 2021).

Research gaps

Currently, there are five ongoing clinical trials on the use of oseltamivir as treatment for COVID-19.

References

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Appendix 1. Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Mancilla-Galido et al 2021	COVID-19 confirmed patients by RT-PCR Any severity (n=122,557)	Oseltamivir or Amantadine or lopinavir/ritonavir or rimantadine or zanamivir or antibiotic only or antiviral+ antibiotic Doses/duration unknown	No Antiviral/Antibiotic/standard of care	All-Cause Mortality	Real World multicenter, Retrospective cohort study
Lee et al 2020	COVID-19 confirmed patients by RT-PCR Any severity (n=7339)	Lopinavir/Ritonavir or HCQ or antibiotics ribavirin, oseltamivir or interferon Doses/duration unknown	Standard of Care	Mortality, Severe COVID-19	Retrospective Cohort study
Liu et al 2021	COVID-19 confirmed patients by RT-PCR Any severity (n=504)	Lopinavir/ritonavir or Arbidol or Oseltamivir	Standard of Care	Primary: In hospital death Secondary: Change in lesion size on CT scan	Retrospective Cohort
Chen et al 2020	COVID-19 confirmed patients by RT-PCR inpatient, any severity, even asymptomatic (n=284)	Oseltamivir or Arbidol or Lopinavir/Ritonavir/ Chloroquine or immunoglobulin or Corticosteroids or antibiotics plus standard of care	Standard of Care	Time to Viral RNA Clearance	Retrospective Cohort
Hu et al	COVID-19 confirmed patients by	Arbidol or Oseltamivir or Lopinavir/Rito	Standard of Care	Viral Shedding	Retrospective Cohort

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
	RT-PCR inpatient, any severity (n=183)	navir or α interferon or Ribavirin plus standard of care			

Appendix 2. GRADE Summary of Findings (SoF) Table

Author(s): Antonio L. Faltado Jr., Anna Angelica Macalalad-Josue
Question: Oseltamivir compared to Standard of Care for COVID-19
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	observational studies	not serious	serious [a]	not serious	not serious	none	2323/8499 (27.3%)	7648/121901 (6.3%)	**OR 4.20** (4.03 to 4.38)	**157 more per 1,000** (from 150 more to 164 more)	⨁◯◯◯ VERY LOW	CRITICAL
Progression to Severe Disease												
1	observational studies	not serious	not serious	not serious	not serious	none	8/19 (42.1%)	919/7520 (12.2%)	**OR 5.22** (2.00 to 13.02)	**299 more per 1,000** (from 96 more to 522 more)	⨁⨁◯◯ LOW	CRITICAL
Time to Viral Clearance (in days)												
1	observational studies	not serious	not serious	not serious	not serious	none	35	245	-	SMD **1.65 SD higher** (1.27 higher to 2.03 higher)	⨁⨁◯◯ LOW	IMPORTANT
Prolonged Viral Shedding >/=20 days												
1	observational studies	not serious	not serious	not serious	not serious	none	76/117 (65.0%)	21/66 (31.8%)	**HR 0.416** (0.279 to 0.620)	**171 fewer per 1,000** (from 217 fewer to 107 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **SMD:** Standardised mean difference; **HR:** Hazard Ratio

Explanations

a. inconsistent results across studies I2=92%

Appendix 3. Characteristics of Ongoing Clinical Trials

Trial ID	Title	Status	Population	Intervention	Comparator	Outcome
EUCTR2020-001610-38-DK	Irbesartan and Oseltamivir treatment of COVID-19 infection. - Covid-19 protection trial	Authorised	COVID 19	Irbesartan, Oseltamivir	Placebo	Preventing patients with Covid-19 infection treated at home in hospitalizing for this disease.
NCT04255017	An Open, Prospective/Retrospective, Randomized Controlled Cohort Study to Compare the Efficacy of Three Antiviral	Recruiting	COVID 19	Abidol hydrochloride, Oseltamivir, Lopinavir/ritonavir	supportive care	Time for lung recovery;Rate of disease remission

	Drugs(Abidol Hydrochloride, Oseltamivir and Lopinavir/Ritonavir) in the Treatment of 2019-nCoV Pneumonia.					
NCT04558463	The Effectivity and Safety of Favipiravir Compared to Oseltamivir as Adjuvant Therapy for COVID-19: An Open Label Trial	Recruiting	Covid19	Favipravir	Oseltamivir	Clinical radiologic changes;Percentage of RT-PCR test convertion
IRCT20201202049566N1	Evaluation of treatment strategy Included : hydroxychloroquine ,naproxen and oseltamivir for outpatient patients with Covid 19	Not Recruiting	COVID 19	naproxen 500 mg twice daily, hydroxychloroquine 200 mg twice daily, and oseltamivir 75 mg twice daily for 5 days .	naproxen 500 mg twice daily, hydroxychloroquine 200 mg twice daily for 5 days	symptoms indicative of cough, shortness of breath, fever
NCT04303299	A 6 Week Prospective, Open Label, Randomized, in Multicenter Study of, Oseltamivir Plus Hydroxychloroquine Versus Lopipinavir/ Ritonavir Plus Oseltamivir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine in Mild COVID-19 AND Lopipinavir/ Ritonavir Plus Oseltamivir Versus Favipiravir Plus Lopipinavir / Ritonavir Versus Darunavir/ Ritonavir Plus	Recruiting	COVID 19	Oseltamivir and other antiviral drugs	conventional quarantine	SARS-CoV-2 eradication time

	Oseltamivir Plus Hydroxychloroquine Versus Favipiravir Plus Darunavir and Ritonavir Plus Hydroxychloroquine in Moderate to Critically Ill COVID-19					