IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Drug Efficacy & Safety In Covid-19

A REVIEW ON FAVIPIRAVIR , MOLNUPIRAVIR & CORTICOSTEROIDS.

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ABSTRACT

This review asseses the side effects of three drugs-Favipiravir,Molnupiravir, and Methylprednisolone used in COVID-19 patients. As the virus spread rapidly,several treatments were explored,but none offered a definite cure. Favipiravir, an antiviral drug initially approved for influenza treatment & Molnupiravir, another antiviral with broad spectrum activity, were repurposed for COVID-19. Methylprednisolone , a corticosteroid was also administered to reduce inflammation. However , the effectiveness & safety remains the subject of the efficacy & major side effects.

KEYWORDS :- COVID-19, SARS-CoV-2, Favipiravir, Molnupiravir, Methylprednisolone, Antiviral, Efficacy, Drug, Corticosteroids.

INTRODUCTION

An unpredictable novel pneumonia-like disease outbreak in Wuhan, China, in December 2019, named Coronavirus disease (COVID-19), which was caused by a novel coronavirus coined the severe acute respiratory syndrome (SARS)-CoV-2, has swept China and was spread across the globe . As of mid-June, 215 countries or regions have reported confirmed cases, with more than 6,800,000 confirmed cases and 400,000 deaths, and a death rate over 5.84% worldwide . Patients with COVID-19 showed primary symptoms similar to those with SARS and Middle East respiratory syndrome (MERS), such as fever, dry cough, myalgia, and fatigue .

In addition, severe pneumonia caused by the coronavirus can increase the levels of inflammatory cytokines, resulting in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) .

Since the first appearance of coronavirus disease (COVID-19) in Wuhan, China ,this disease has evolved into a global pandemic. It is associated with a wide clinical spectrum of conditions, ranging from asymptomatic disease to fatal pneumonia. Treatment protocols remain limited to guideline recommendations and clinical studies. No specific treatment or prophylaxis has been introduced for use.

OBJECTIVE

In this review, we aimed to assess the safety & potential side effects of drugs Favipiravir, Molnupiravir & Methylprednisolone used in treatment among patients diagnosed with COVID-19 , in order to discuss its role as a therapeutic option.

WHAT IS FAVIPIRAVIR ?

Favipiravir, an antiviral agent in the nucleotide-analogue class, has been approved for influenza treatment in Japan. Its activity profile against influenza, Ebola and many other RNA viruses has been established as consisting of prevention of viral replication via inhibition of viral RNA polymerase.[10] It is used as a pro-drug, with 94% bioavailability, 54% protein binding and low volume of distribution.

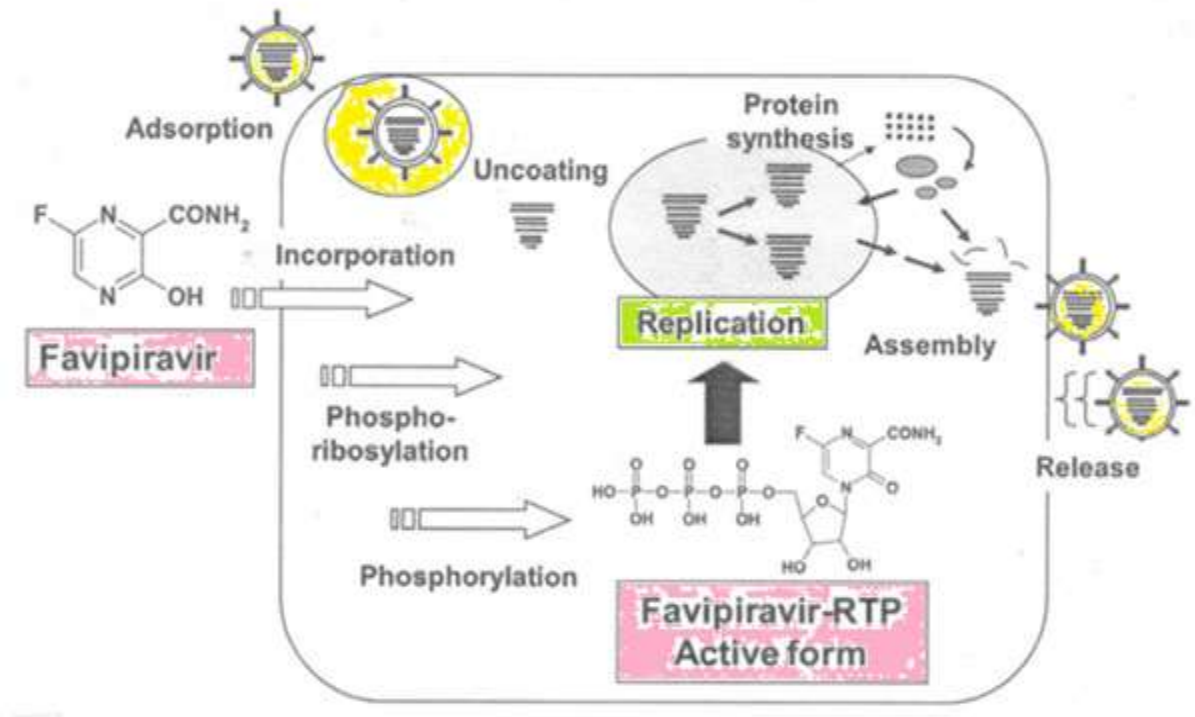


Figure : Illustrative diagram of intracellular activation and mechanism of action of favipiravir

Review

This retrospective study was conducted on patients admitted to hospital and hospitalized due to confirmed COVID-19. COVID-19 was diagnosed using the reverse-transcription polymerase chain reaction (RT-PCR) test. In this retrospective study, data on clinical characteristics, along with laboratory and chest computed tomography (CT) findings, were retrieved from digital databases and patient files. Patients > 18 years of age were deemed eligible if complete laboratory and chest CT data for them were available, along with a COVID-19 diagnosis via real-time RT-PCR; or if they showed highly suspicious disease based on clinical-radiological findings, despite RT-PCR negativity.

In accordance with the treatment guidelines for adult COVID-19 patients endorsed by the Turkish Ministry of Health, these patients received a loading oral favipiravir dose of 1600 mg twice daily, followed by a maintenance dose of 600 mg twice daily, for a total duration of 5 to 10 days.[5]

Demographic data, underlying conditions, clinical signs and symptoms, laboratory and radiological findings, oxygen support requirement, supportive treatments and side effects arising during favipiravir treatment were recorded.

Side effects were defined as elevated transaminases, gastrointestinal symptoms (nausea, diarrhea or abdominal pain), high blood sugar or thrombocytopenia.

Table no-01.

Demographic characteristics of the patients

	No side effects (n = 320)	**With side effects (n = 37)**	**P-value**
Age, years, n ± SD	62.88 ± 13.9	58.95 ± 13.08	0.102
Gender, n (%)			
Male	203 (63.4%)	25 (67.6%)	0.753
Female	117 (36.6%)	12 (32.4%)	
Favipiravir alone (N = 231), n (%)	212 (91.8%)	19 (8.2%)	0.1
Favipiravir + hq (N = 126), n (%)	108 (85.7%)	18 (14.3%)	

	No side effects (n = 320)	With side effects (n = 37)	P-value
BMI, kg/m^2 ± SD	28.73 ± 4.51	30.39 ± 4.76	**0.036**
Comorbidities, n (%)			
Hypertension	141 (44.1%)	8 (21.6%)	0.014
DM	96 (30%)	7 (18.9%)	0.224
CAD	57 (17.8%)	4 (10.8%)	0.401
CHF	19 (6%)	1 (2.7%)	0.707
COPD	49 (15.3%)	2 (5.4%)	0.167
Asthma	22 (6.9%)	3 (8.1%)	0.734

Table no-02

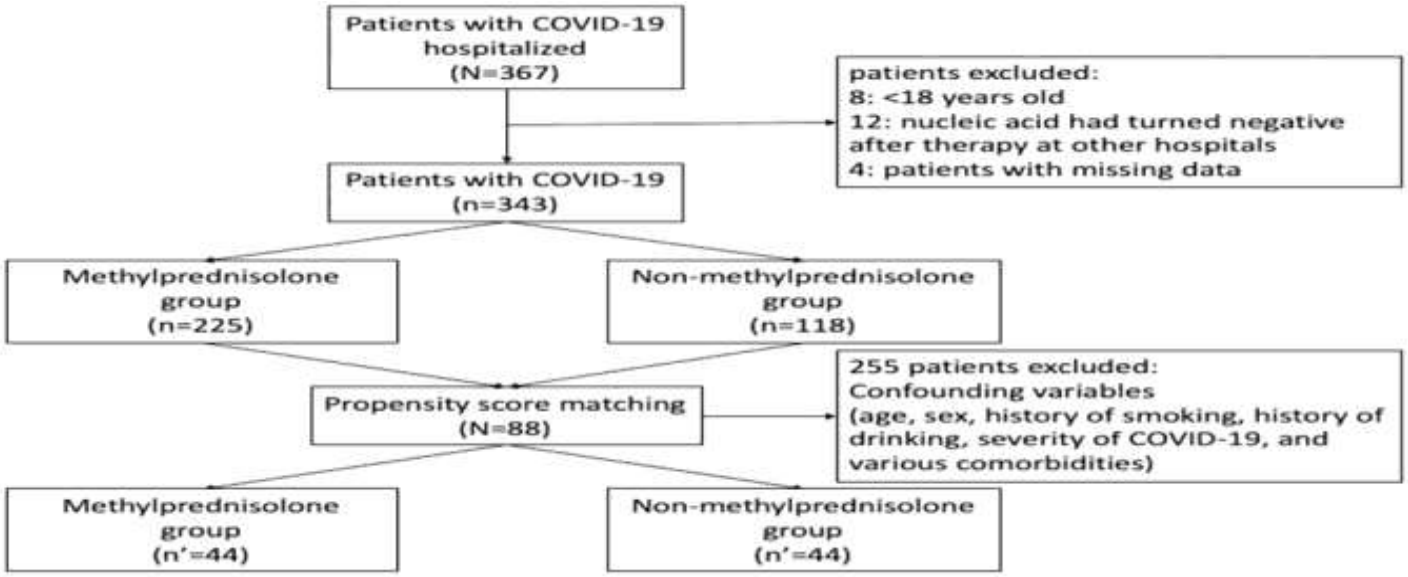
Side effects seen with favipiravir

Patients using favipiravir	**357**
Patients with drug side effects, n (%)	37 (10.4%)
Side effects, n (%)	
Elevated transaminases	25 (7%)
Diarrhea	5 (1.4%)
Nausea	2 (0.56%)
High blood sugar	2 (0.56%)
Abdominal pain	1 (0.28%)
Thrombocytopenia	1 (0.28%)
Nausea + elevated transaminases	1 (0.28%)

“ WHILE IN TREATMENT OF PATEINTS CORTICODTEROIDS LIKE METHYLPREDNISOLONE & DEXAMETHASONE ALSO USED IN COMBINATION TREATMENT WITH FAVIPIRAVIR.”

In thE study, total of 367 patients with COVID-19 being hospitalized at the Yichang Third People’s Hospital were identified. And after excluding 8 patients who were < 18 years old, 12 patients whose nucleic acid test had turned negative after therapy at other hospitals, and 4 patients with missing data, finally a total of 343 patients were included in our final analysis, as shown in Fig.

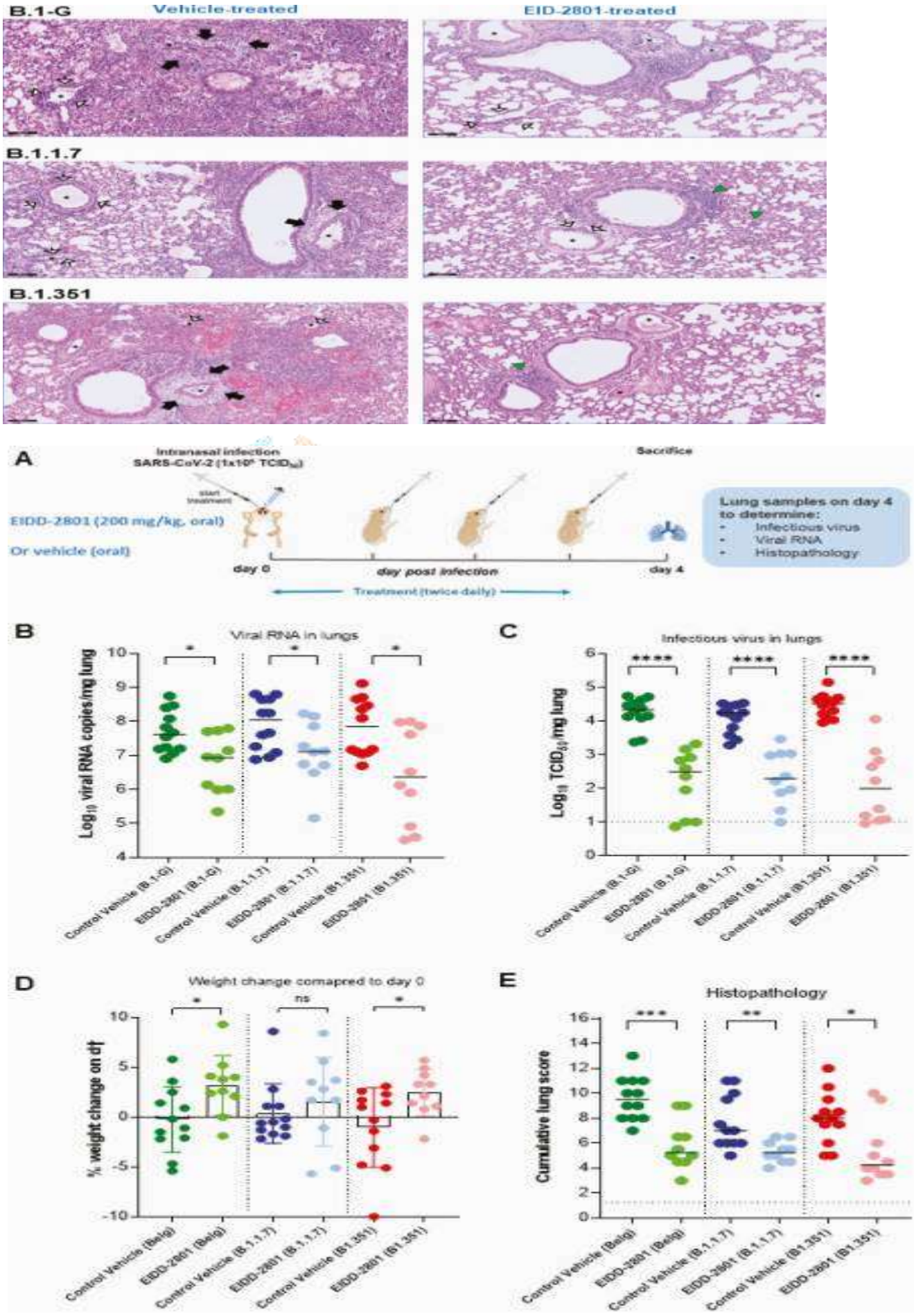
Among the 343 patients, 276 of them were classified as mild or stable COVID-19, while 67 were designated as serious or critically ill COVID-19. Moreover, 255 of them were treated using methylprednisolone and 188 did not receive any corticosteroid-related treatment and underwent usual care alone.



Methylprednisolone did not shorten a patient’s hospital stay or reduce their disease would worsen, and this was especially true for patients greater than 65 years old. Patients treated with methylprednisolone were more likely to require oxygen inhalation. The efficacy and safety of the use of methylprednisolone in patients with COVID-19 still remain uncertain.

Emerging and currently circulating VoCs present new challenges to the coronavirus disease 2019 (COVID-19) pandemic. Mutations arising in these VoCs may result in variants having altered fitness in terms of virus replication and transmission, altered interactions with key host proteins, and evasion of host immune responses [2]. With extensive mutations in the spike protein, antibody resistance of VoCs B.1.1.7 and B.1.351 have been reported [13]. B.1.351, in particular, was demonstrated to be markedly resistant to multiple monoclonal antibodies generated against the N-terminal and receptor-binding domain, as well as convalescent plasma from vaccinated individuals [13]. VoCs therefore greatly threaten the efficacies of available monoclonal antibody therapies and vaccines, which have been developed to target the parent strain of SARS-CoV-2 [4, 14].

In contrast, by acting at the level of viral RNA replication, molnupiravir should be able to exert its antiviral SARS-CoV-2 activity in spite of the mutations present in the emerging VoCs. This hypothesis is confirmed in this study, whereby molnupiravir reduces viral RNA load and infectious virus titers in the lungs of hamsters infected with parent lineage B.1-G, and VoCs B.1.1.7 and B.1.351, all to a similar extent of about 2 to 2.5 $\log_{10}$ fold compared to nontreated, infected hamsters, with comparably significant improvements in lung pathology.



Molnupiravir has been the first oral antiviral authorized for COVID-19 outpatients, reporting extraordinary sales and preserved in vitro efficacy against Omicron sublineages so far. However, it has recently been

associated with very poor clinical efficacy, the risk of creating novel SARS-CoV-2 variants of concern, and long-term risk for mutagenicity in humans.

DISCUSSION

One major challenge with COVID-19 relates to the absence of reliable evidence regarding therapeutic options. Further, urgent therapeutic needs have resulted in the use of empirical treatments and other agents that were previously investigated for treatment of other viruses. Several drugs, such as chloroquine, umifenovir, remdesivir and favipiravir, are being used for COVID-19 treatments in many countries, including Iran, Japan, China , India & many more countries. [6,7,8,9]

Pharma companies sold emergency use drugs to treat COVID-19 worth more than Rs 2,600 crore in the past. Favipiravir, which was dropped from the treatment guidelines.

Favipiravir saw highest sales in year among COVID-19 drugs.

If you were wondering what kind of sales did COVID-19 drugs such as Remdesivir, Favipiravir did then here are some of the interesting data.

Antiviral medication Favipiravir saw the highest sales in the past one year. It is one of the cheapest COVID-19 drugs available in the market with at least 45 companies selling it. AWACS data indicates that nearly Rs 12,139 crore worth of Favipiravir was sold in the COVID time.

Since its emergency in all over the globe severe acute respiratory syndrome (SARS-CoV-2) has spread worldwide resulting in a global pandemic with more than 148 million cases and approximately 3.1 million deaths reported (www.covid19.who.int).

Variants of SARS-CoV-2 are emerging in different parts of the world, posing a new threat of increased virus spread and potential to escape from both vaccine-induced and natural infection-induced immunity. So far, 4 major circulating SARS-CoV-2 variants of concern (VoC) have been identified: lineages B.1.1.7 (UK), B.1.351 or 501Y.V2 (South Africa), B.1.1.28.1 or P.1 (Brazil), and B.429 (California) [2]. These VoC have been implicated in new, massive waves of infections and new spikes in excess mortality in regions that have been heavily affected by SARS-CoV-2 [3]. Moreover, several vaccine candidates showed lower efficacy in phase 3 clinical trials in regions of South Africa where the VoC B.1.351 is circulating [4]. Consequently, people vaccinated against SARS-CoV-2 may not all be efficiently protected from the disease following infection with one of these new variants.

Because the emergence of new SARS-CoV-2 variants will most probably continue to happen in the future, antiviral drugs that target conserved proteins of SARS-CoV-2 could solve this issue of reduced response of variants to vaccines. Such antivirals may be expected to reduce the chance of progress to severe disease when treatment is started sufficiently early and will also have a place in a prophylactic strategy.

The ribonucleoside analogue, N^4-hydroxycytidine (EIDD-1931), was initially developed as an influenza inhibitor, but also exerts broad-spectrum antiviral activity against multiple viruses belonging to different families of RNA viruses. The molecule exerts its antiviral activity via incorporation into viral RNA, resulting in the accumulation of deleterious transition mutations in the nascent viral RNA, leading to error catastrophe [5].

Molnupiravir (EIDD-2801, MK-4482), the orally bioavailable prodrug counterpart of N^4-hydroxycytidine [6], is effective against SARS-CoV-2 infections. Being the first bioavailable prodrug molnupiravir were gone through hopes to epic fail ,due to its poor to no clinical efficacy.

Till today it remains the question of Efficacy and Safety of use of Favipiravir , methylprednisolone & Molnupiravir in Treating COVID-19 Patients.

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