Favipiravir

A Review of Pertinent Drug Information for SARS-CoV-2

Daniel B. Chastain, Pharm.D., BCIDP, AAHIVP
Clinical Assistant Professor, University of Georgia College of Pharmacy
Infectious Diseases Pharmacist, Phoebe Putney Memorial Hospital
Albany, Georgia
daniel.chastain@uga.edu

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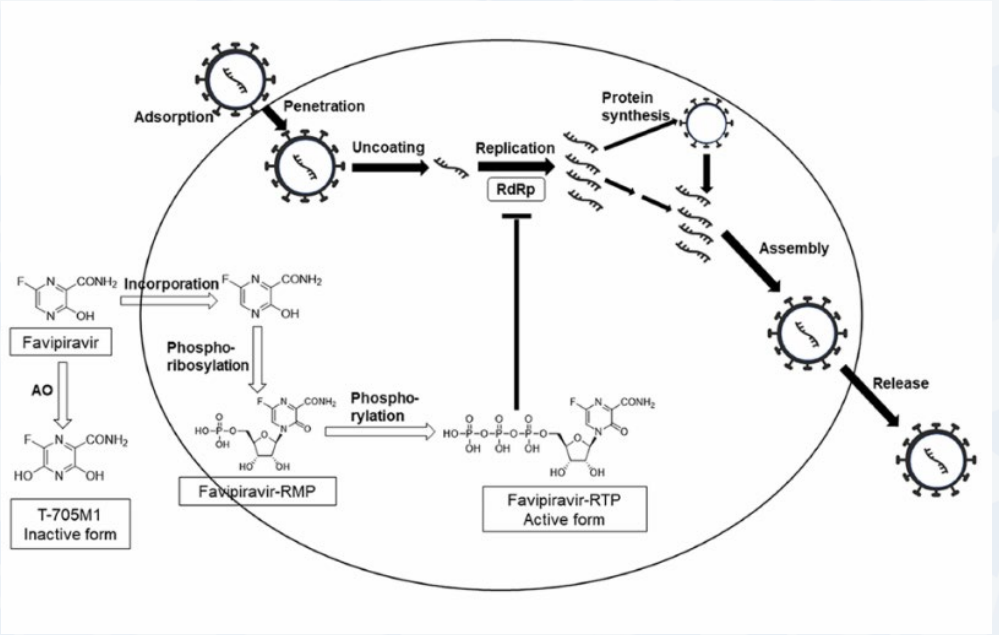
Data as of April 22, 2020

Favipiravir (Avigan®)

- Mechanism of action: nucleoside analog prodrug, RNA-dependent RNA polymerase (RdRp) inhibitor

- Status: approved in Japan for treatment of influenza viruses A, B, and C
  - Currently under investigation for use vs SARS-CoV-2



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Shiraki K, Daikoku T. Pharmacol Ther. 2020 Feb 22 : 107512.
Du YX, et al. Clin Pharmacol Ther. 2020 Apr 4. doi: 10.1002/cpt.1844.

Adverse Drug Reactions and Safety

- GI disturbances
- Transaminitis
- Neutropenia
- Dose-related, asymptomatic hyperuricemia
- Risk for teratogenicity and embryotoxicity

Madelain V, et al. Clin Pharmacokinet . 2016 Aug;55(8):907-23.
Furuta Y, et al. Proc Jpn Acad Ser B Phys Biol Sci. 2017 Aug 2; 93(7): 449–463.

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Table 4. Comparison of antiviral-associated adverse effects.

Adverse effects	Favipiravir group (N = 116)		Arbidol group (N = 120)		P value
	Frequency	Cases, n (%)	Frequency	Cases, n (%)	
Total	43	37 (31.90)	33	28 (23.33)	0.1410
Abnormal LFT	10	10 (8.62)	12	12 (10.00)	0.7156
Raised serum uric acid	16	16 (13.79)	3	3 (2.50)	0.0014
Psychiatric symptom reactions	5	5 (4.31)	1	1 (0.83)	0.1149*
Digestive tract reactions	16	16 (13.79)	17	14 (11.67)	0.6239

Chen C, et al. medRxiv 2020.03.17.20037432. doi.org/10.1101/2020.03.17.20037432.

Table 5
Statistics of adverse reactions after medication.

Characteristic	Treatment		
	FPV (*N* = 35)	LPV/RTV (*N* = 45)	*P* value
Total number of adverse reactions	4 (11.43%)	25 (55.56%)	<0.001
Diarrhea	2 (5.71%)	5 (11.11%)	0.46
Vomiting	0 (0%)	5 (11.11%)	0.06
Nausea	0 (0%)	6 (13.33%)	0.03
Rash	0 (0%)	4 (8.89%)	0.13
Liver and kidney injury	1 (2.86%)	3 (6.67%)	0.63
Others	1 (2.86%)	2 (4.44%)	1.00

Cai Q, et al. Engineering. doi: 10.1016/j.eng.2020.03.007.

Drug-Drug Interactions

- Hepatic metabolism via aldehyde oxidase and xanthine oxidase, but limited data on CYP interactions
  - Weak CYP2C8 inhibitor
  - Potent aldehyde oxidase inhibitors: selective estrogen receptor modulators, cimetidine, calcium channel blockers, propafenone, amitriptyline
  - Metabolized by aldehyde oxidase: citalopram, zaleplon, famciclovir, sulindac

Clinical significance remains unknown

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Du YX, et al. Clin Pharmacol Ther. 2020 Apr 4. doi: 10.1002/cpt.1844.

Data vs other pathogenic RNA viruses

- 'Broad-spectrum' activity against RNA viruses[1]
  - Suppressed Ebola virus replication in Vero E6 cells, EC50 of 67 µM[2]
  - Prevented death in mice infected with Ebola virus[2]
  - Case-fatality lower in patients with Ebola treated with favipiravir vs SOC[3]
  - Decreased mortality in mice infected with influenza vs oseltamivir[4]

- Potential activity vs SARS-CoV-2?

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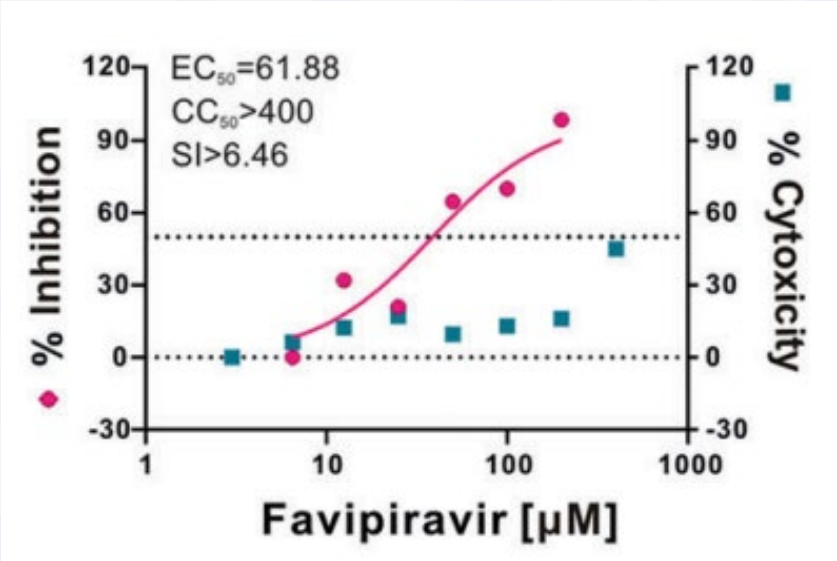
1. De Clercq E, Li G. Clin Microbiol Rev. 2016 Jul;29(3):695-747.
2. Oestereich L, et al. Antiviral Res. 2014 May;105:17-21.
3. Kerber R, et al. J Infect Dis. 2019 Jun 19;220(2):195-202.
4. Takahashi K, et al. Antivir Chem Chemother. 2003 Sep;14(5):235-41.

In Vitro Data vs SARS-CoV-2



Wang M, et al. Cell Res. 2020 Mar; 30(3): 269–271.

Antiviral activity	μM
CC_{50}	> 100
Cytopathic effect (CPE) inhibition	> 100
Reduction in infectious virus (EC_{50})	> 100
Reduction in viral RNA copy (EC_{50})	> 100

Choy KT, et al. Antiviral Res. 2020 Jun; 178: 104786.

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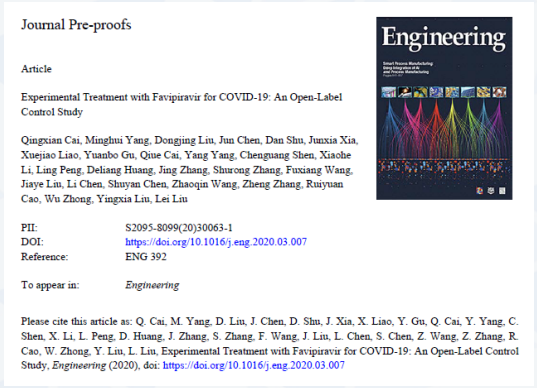
In Vivo Data vs SARS-CoV-2



Journal Pre-proofs

Article

Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study

Qingxian Cai, Minghui Yang, Dongjing Liu, Jun Chen, Dan Shu, Junxia Xia, Xuejiao Liao, Yuanbo Gu, Qiue Cai, Yang Yang, Chenguang Shen, Xiaohe Li, Ling Peng, Deliang Huang, Jing Zhang, Shurong Zhang, Fuxiang Wang, Jiaye Liu, Li Chen, Shuyan Chen, Zhaoqin Wang, Zheng Zhang, Ruiyuan Cao, Wu Zhong, Yingxia Liu, Lei Liu

PII: S2095-8099(20)30063-1
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Reference: ENG 392

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Open-label, nonrandomized study in Shenzhen, China

Inclusion: 16-75 YOA, duration of symptoms < 7 days, able to tolerate PO

Exclusion: RR > 30, SpO2 < 93%, respiratory failure, shock ± organ failure, chronic hepatic or renal disease, pregnant or lactating females

Experimental group (n=35): favipiravir 1,600 mg PO BID on day 1, followed by 600 mg BID days 2-14 + inhaled INF-α1b + SOC

Control group (n=45): patients treated with LPV/r 400 mg/100 mg PO BID until viral clearance or 14 days + inhaled INF-α1b + SOC

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Cai Q, et al. Engineering. doi: 10.1016/j.eng.2020.03.007.

In Vivo Data vs SARS-CoV-2

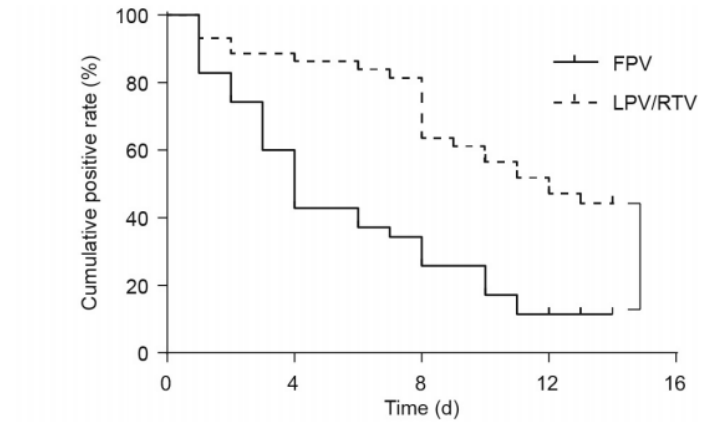

Fig 3. Kaplan-Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy ($P < 0.001$).

Table 2
Chest CT changes in patients with COVID-19 after treatment.

Chest CT changes	COVID-19 patients ($N = 80$)		
	FPV ($N = 35$)	LPV/RTV ($N = 45$)	P value
Day 4 after treatment			
Improve	8 (22.86%)	8 (17.78%)	
Worse	9 (25.71%)	15 (33.33%)	
Constant	18 (51.43%)	22 (48.89%)	0.42
Day 9 after treatment[a]			
Improve	18 (56.25%)	16 (35.55%)	
Worse	8 (25.00%)	16 (35.55%)	
Constant	6 (18.75%)	13 (28.90%)	0.11
Day 14 after treatment			
Improve	32 (91.43%)	28 (62.22%)	
Worse	1 (3.23%)	9 (20.00%)	
Constant	2 (6.45%)	8 (17.78%)	0.004

[a] For three patients in the FPV arm, the lung CT scan on Days 6–9 after medication was not carried out.

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Authors' conclusion: Favipiravir was independently associated with faster viral clearance and a higher improvement rate in chest imaging.

Cai Q, et al. Engineering. doi: 10.1016/j.eng.2020.03.007.

In Vivo Data vs SARS-CoV-2

ELSEVIER

Engineering

Available online 18 March 2020

Withdrawn Article in Press

TEMPORARY REMOVAL: Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study

Qingxian Cai [a, 1], Minghui Yang [a, 1], Dongjing Liu [a, 1], Jun Chen [a, 1], Dan Shu [a], Junxia Xia [a], Xuejiao Liao [a], Yuanbo Gu [a], Qiue Cai [a], Yang Yang [a], Chenguang Shen [a], Xiaohe Li [a], Ling Peng [a], Deliang Huang [a], Jing Zhang [a], Shurong Zhang [a], Fuxiang Wang [a], Jiaye Liu [a] ... Lei Liu [a]

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https://doi.org/10.1016/j.eng.2020.03.007

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Cai Q, et al. Engineering. doi: 10.1016/j.eng.2020.03.007.

In Vivo Data vs SARS-CoV-2

Engineering
Available online 18 March 2020
In Press, Corrected Proof

Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study

Qingxian Cai [a, †], Minghui Yang [a, †], Dongjing Liu [a, †], Jun Chen [a, †], Dan Shu [a], Junxia Xia [a], Xuejiao Liao [a], Yuanbo Gu [a], Qiue Cai [a], Yang Yang [a], Chenguang Shen [a], Xiaohe Li [a], Ling Peng [a], Deliang Huang [a], Jing Zhang [a], Shurong Zhang [a], Fuxiang Wang [a], Jiaye Liu [a] ... Lei Liu [a]

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Cai Q, et al. Engineering. doi: 10.1016/j.eng.2020.03.007.

In Vivo Data vs SARS-CoV-2

Prospective, multicenter, open-label, randomized, superiority trial in China

Inclusion: ≥ 18 YOA, duration of symptoms ≤ 12 days, diagnosed with COVID-19 pneumonia

Exclusion: ALT/AST > 6x ULN, Child-Pugh C, pregnant female, HIV-infected, not expected to survive > 48 hrs

Favipiravir group (n=116): 1,600 mg PO BID on day 1, followed by 600 mg BID x 7-10 days

Umifenovir (Arbidol®) group (n=120): 200 mg PO TID x 7-10 days

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Chen C, et al. medRxiv 2020.03.17.20037432. doi.org/10.1101/2020.03.17.20037432.

What is umifenovir (Arbidol®)?

- ‘Broad-spectrum’ activity against numerous RNA and DNA viruses
- Mechanism of action: virucidal via direct acting antiviral/host-targeting agent

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Blaising J, et al. Antiviral Res. 2014 Jul; 107: 84–94.
https://www.drugbank.ca/drugs/DB13609

What is umifenovir (Arbidol®)?

- Dose: unknown, 200mg PO TID most often used
- Rapid absorption after oral administration
- Hepatic metabolism via CYP3A4, UGT1A9, and UGT2B7
- Well tolerated, large therapeutic window
- Limited viral resistance

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Blaising J, et al. Antiviral Res. 2014 Jul; 107: 84–94.
https://www.drugbank.ca/drugs/DB13609

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Moderate: fever, symptomatic, imaging

Severe: RR > 30, SpO2 < 93%, PaO2/FiO2 < 300, lesion progressed > 50% within 24-48 hrs

Clinical recovery: T ≤ 36.6°C, RR ≤ 24, SpO2 ≥ 98%, mild or no cough

Table 2. The comparison of clinical recovery rate of day 7 between two group.

Variables	Favipiravir group	Arbidol group	Rate ratio (95% CI)	P value
Total patients	**(N = 116)**	**(N = 120)**		0.1396
Recovered, n (%)	71 (61.21)	62 (51.67)	0.0954 (-0.0305, 0.2213)	
Moderate patients	**(N = 98)**	**(N = 111)**		
Recovered, n (%)	70 (71.43)	62 (55.86)	0.1557 (0.0271, 0.2843)	0.0199
Severe patients	**(N = 18)**	**(N = 9)**		
Recovered, n (%)	1 (5.56)	0 (0.00)	0.0556 (-0.0503, 0.1614)	0.4712
Patients with hypertension and/or diabetes	**(N = 42)**	**(N = 35)**		
Recovered, n (%)	23 (54.76)	18 (51.43)	0.0333 (-0.1904, 0.2571)	0.7704

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Chen C, et al. medRxiv 2020.03.17.20037432. doi.org/10.1101/2020.03.17.20037432.

In Vivo Data vs SARS-CoV-2

Table 1. Basic characteristics of the participants.

Variables	Favipiravir group (N = 116)	Arbidol group (N = 120)	P value
Nucleic acid tests			
Positive	54 (46.55)	46 (38.33)	0.4202
Suspected	6 (5.17)	6 (5.00)	
CT (N = 235 with data)	N = 116	N = 119	0.7635
COVID-19 pneumonia	112 (96.55)	114 (95.80)	

Authors' conclusion: In moderate patients, favipiravir has higher clinical recovery rate of day 7 (71.43%) than arbidol (55.86%), and the time of cough relief and fever reduction of favipiravir was significantly shorter than that of arbidol.

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Chen C, et al. medRxiv 2020.03.17.20037432. doi.org/10.1101/2020.03.17.20037432.

Favipiravir dosing

- Supplied as 200 mg tablets, but unavailable in the US

1,600 mg by mouth twice daily on day 1, followed by 600 mg twice daily for a total duration of 7 to 14 days

(*Cai et al 2020.; Chen et al, 2020.; NCT04310228*)

2.4 g by mouth every 8 hours for 2 doses, followed by a dose of 1.2 g 8 hours later on day 1, followed by 1.2 g twice daily for a total duration of 7 to 10 days

(*NCT04303299*)

- Optimal dose and duration are unknown

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Chen C, et al. medRxiv 2020.03.17.20037432. doi.org/10.1101/2020.03.17.20037432.
NCT04310228, NCT04303299

Relevant Clinical Trials

Study identifier (Location)	Study type	Intervention	Comparator(s)	Primary outcome	Estimated date of completion
NCT04310228 (China)	Randomized, multicenter, open-label	• Tocilizumab + favipiravir	• Tocilizumab • Favipiravir	Clinical cure (negative SARS-CoV-2 RT-PCR)	May 2020
NCT04333589 (China)	Randomized, multicenter, open-label	• Favipiravir	• SOC (excluding LPV/r, CQ, HCQ, arbidol)	Negative SARS-CoV-2 RT-PCR	September 2020
NCT04336904 (Italy)	Randomized, multicenter, double-blind, placebo-controlled	• Favipiravir	• Placebo	Clinical recovery	July 2020
ChiCTR2000030987 (China)	Randomized, controlled	• Favipiravir + CQ	• Favipiravir • Placebo	Clinical improvement	June 2020
ChiCTR2000030254 (China)	Randomized, multicenter, open, positive, parallel-controlled	• Favipiravir	• Arbidol	Clinical recovery at day 7	March 2020
ChiCTR2000029600 (China)	Non-randomized, controlled	• Favipiravir + α-INF atomization	• α-INF atomization • LPV/r + α-INF atomization	Negative SARS-CoV-2 RT-PCR	May 2020
JPRN-jRCTs041190120 (Japan)	Randomized, multicenter, open-label (asymptomatic, mildly ill)	• Favipiravir, immediate (d1-10)	• Favipiravir, delayed (d6-15)	Negative SARS-CoV-2 RT-PCR	August 2020

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**not all inclusive*

Summary

- Efficacy and safety of favipiravir for treatment of patients with COVID-19 not established
- Additional data needed to verify initial efficacy data for treatment of COVID-19 and identify optimal dose and duration

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Data as of April 22, 2020