Updated favipiravir and remdesivir: What is the pharmacist's role?

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11 Feb 2021

King Chulalongkorn Memorial Hospital
The Thai Red Cross Society

TRC EIDCC
Thai Red Cross Emerging Infectious Diseases Clinical Center

ศูนย์ความเป็นเลิศทางการแพทย์ โรคอุบัติใหม่ด้านคลินิก

ที่มา : อ. พญ.ปัทมา ต.วรพานิช

Outline

- Intro to case discussion
- Update GUIDELINE COVID-19
- Mechanism of action of COVID-19 therapeutic drug
- REMDESIVIR
- FAVIPIRAVIR
- Case discussion

Case: A 70 year-old Thai Female

- ผู้ป่วยหญิงไทยคู่ อายุ 70 ปี (สามารถใช้ชีวิตประจำวันได้ตามปกติ)
- TBW 94.5 kg , Ht 146 cm BMI 44.3 kg/m^2
- โรงพยาบาล 1 (9-15/1/64)
- CC: รู้สึกมีไข้เป็นๆ หายๆ ไอ มีเสมหะ มีน้ำมูก
- HPI:
  - 9 days PTA สัมผัสญาติที่เป็น confirmed case COVID-19
  - 1 day PTA กินได้ลดลง
- Underlying disease
  - T2DM (Last HbA1C 6.8%)
  - DLP
  - HT
  - ESRD (urine output 200-300 ml/day)

Case: A 70 year-old Thai female

- 9/1/64
- Lab
- DTX 27%, BUN 58, Scr 6.4 (baseline 3.6), Na 135, Cl 110, K 4.86, Ca 6.3, PO4 4.6, Alb 4.3, TB 0.2, DB 0.1, SGOT 30, SGPT 15, ALP 82
- Hb 10.2, Hct 30, WBC 7600 N 50%, L 6.4%, plt 221,000, INR 1.14
- Nasopharyngeal swab for SARS-Co-V_2 PCR positive
- 10/1/64
- CXR: reticular infiltration, cardiomegaly
- Echo EF 70%

Updated guideline for COVID-19

Lasted review 9 Feb 2021

Thai Guideline for COVID-19 28 Jan 2021

Adult

Confirmed case : asymptomatic COVID-19

Symptomatic COVID-19 without pneumonia and no risk factors for severe disease

Symptomatic COVID-19 with risk factors for severe disease or having co-morbidity or mild pneumonia

Pneumonia with hypoxia (resting O2 saturation <96 % or exercise-induced hypoxemia positive (decreasing of SpO2 ≥3%) or progression of pulmonary infiltrates

Risk factor

1. Age >60 yo, or < 1 yo
2. COPD, chronic lung disease
3. CKD
4. Cardiovascular disease, congenital heart disease
5. Cerebrovascular disease
6. Uncontrolled DM
7. Obesity BW > 90 kg
8. Cirrhosis
9. Immunocompromised patient
10. Lymphocyte <1,000 cells/mm^3

7 DEC 2020

7. Obesity BMI ≥ 35 kg/m^2

Children <15 years

Confirmed case : asymptomatic COVID-19

Symptomatic COVID-19 without pneumonia and no risk factors for severe disease

Symptomatic COVID-19 with risk factors for severe disease or having co-morbidity or mild pneumonia

Pneumonia with tachypnia (< 2 mo >60 bpm, 2-12 mo > 50 bpm, 1-5 years >40 bpm, >5 years >30 bpm)

Thai Guideline for COVID-19 28 Jan 2021

Adult

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- SpO2 <94% on room air
- non-invasive หรือ invasive ventilation
- ECMO

FPV 5 d

- การให้ FPV ภายใน 4 วัน เป็นปัจจัยที่ลด high flow oxygenation, invasive ventilator, ICU admission, death
- ลดปริมาณไวรัสได้ดี
- ควรเริ่มยาก่อนที่ผู้ป่วยมีอาการหนัก **พิจารณาให้ FPV ในผู้ที่ มีอาการมากหรือมีไข้ทุกคน**

FPV
5-10 d

FPV
5-10 d

LPV/r
5-10 d

Corticosteroid

RDV

ข้อพิจารณาอื่น

- มีข้อห้ามในการบริหารยาทางปาก หรือมีปัญหาการดูดซึม
- ไม่ตอบสนองต่อยาอื่นภายใน 72 ชั่วโมง
- เลือกใช้ FPV หรือ RDV อย่างใดอย่างหนึ่ง

Children <15 years

Symptomatic COVID-19
without pneumonia and
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Symptomatic COVID-19
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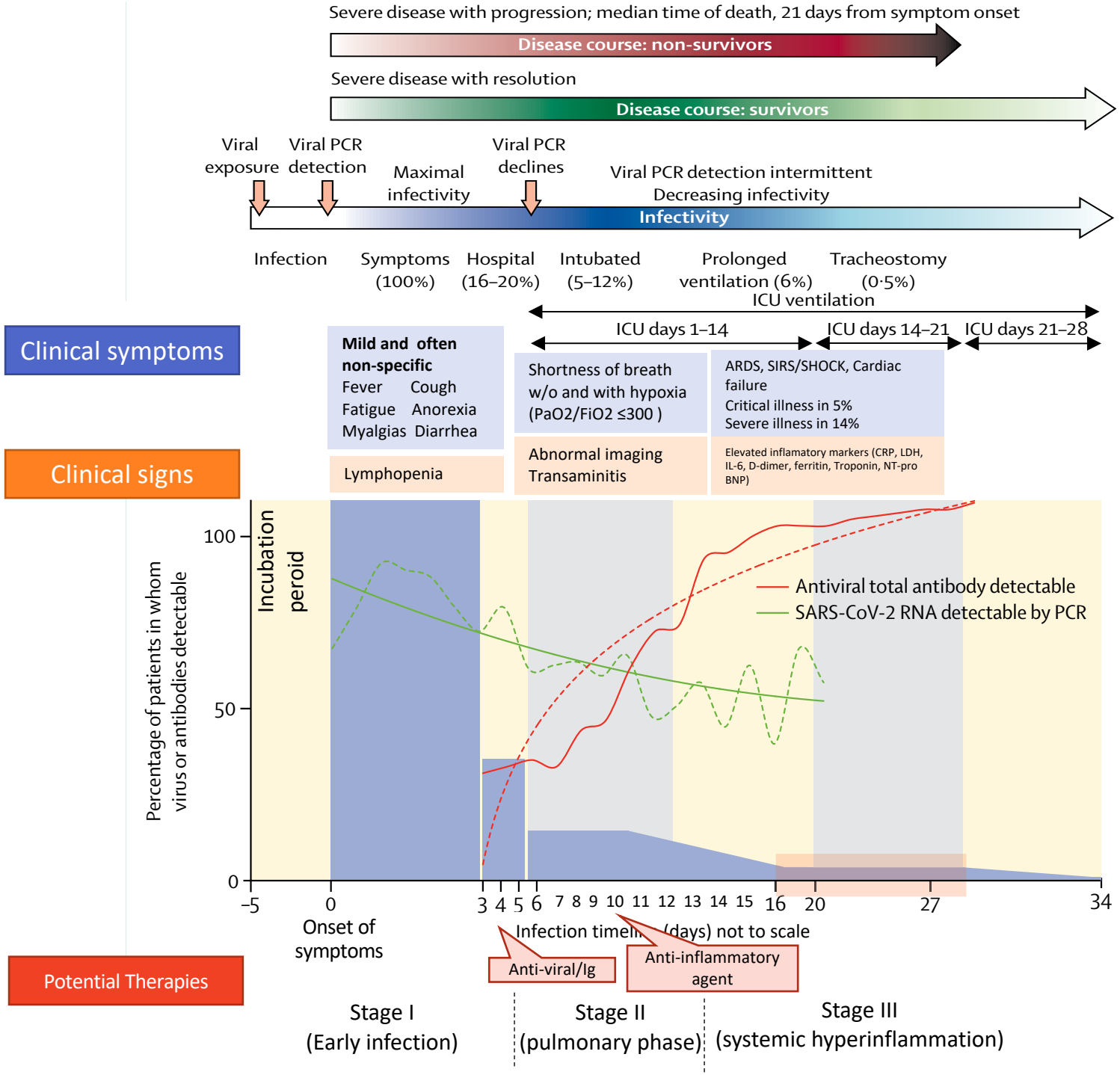
Pneumonia with tachypnia (< 2 mo >60 bpm, 2-12 mo > 50 bpm, 1-5 years >40 bpm, >5 years >30 bpm)



Time to start antiviral

Stage I (mild)—early infection

- Early intervention
- Targeting the viral replication
  - Achieve viral clearance
  - Reduced duration of symptoms
  - Minimize contagiousness (shortening the period of infectiousness)
  - Prevent progression to severity

Modified from

1. McGrath BA, et al. Lancet Respir Med. 2020;8(7):717-725.
2. Siddiqi HK, Mehra MR. J Heart Lung Transplant. 2020;39(5):405-407.
3. Berlin DA, Gulick RM, Martinez FJ. N Engl J Med. 2020;383(25):2451-2460.

Thai CPG 28 Jan 2021

Symptomatic COVID-19
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- SpO2 <94% on room air
- non-invasive หรือ invasive ventilation
- ECMO

IDSA GL 5 Feb 2021

Non-severe
- not requiring supplement oxygen or
- SpO2 >94% on room air

Severe
- SpO2 ≤94% on room air
- on supplemental oxygen

Critical illness
- Mechanical ventilation
- ECMO
- ARDS
- EOD - sepsis/septic shock

WHO 2020

Non-severe
Absence of signs of severe or critical disease

Severe
- SpO2 <90% on room air
- RR > 30 in adult
- Raised respiratory rate in children
- Signs of severe respiratory distress

Critical illness
- Requires life sustaining treatment
- ARDS
- Sepsis
- Septic shock

	Thai CPG 28 Jan 2021	IDSA GL 5 Feb 2021	WHO 2020
HCQ/CQ HCQ+Azit	✗	✗ ⊕⊕⊕◯/ ⊕⊕◯◯	✗
LPV/r	✓ Severe	✗ ⊕⊕⊕◯	✗
RDV Non-severe	✗	✗ ⊕◯◯◯	✗
RDV Severe	✗	✓ ⊕⊕◯◯	Duration- 5 days rather than 10 days ✗
RDV Critical illness	✓	✓ ⊕⊕⊕◯	✗
Corticosteroid non-severe	✗	✗ ⊕◯◯◯	✗
Corticosteroid severe	✓	✓ ⊕⊕⊕◯	✓
Corticosteroid critical	✓	✓ ⊕⊕⊕◯	✓

	Thai CPG 28 Jan 2021	IDSA GL 5 Feb 2021	WHO 2020
tocilizumab	✗	✗ ⊕⊕◯◯	
convalescent plasma		✓ Only in clinical trial, knowledge gap	
bamlanivimab casirivimab/imdevimab		✗ conditional	mild-to-moderate who are at high risk for progressing to severe these are reasonable option after informed decision-making
baricitinib + RDV		✓ Severe group or who non-invasive ventilation who has C/I for corticosteroid, conditional	
Ivermectin		✗ Severe, conditional ✓ Outpatient only in clinical trial, conditional	
Famotidine		✗ conditional	

IDSA GL 5 Feb 2021

darunavir/cobicistat	• not effective in achieving viral clearance at day seven post randomization, compared to conventional treatments • rate of critical illness and mortality 14 days after randomization, have not been reported to date
LPV/r+RBV+IFN β-1b	• compared with LPV/r for 14 days, in non-critically ill • significantly shorter median time to suppress the viral load in nasopharyngeal specimen • significantly shorter time to alleviate symptoms • resulted in shorter hospital stay • IFN β-1b: no significant improvement in time to clinical response, the overall mortality at 28 days was reduced (19% vs. 43.6%, p= 0.015)
Ribavirin	• less potent in vitro compared to CQ, RDV. • limited clinical studies in SARS-CoV-1 and MERS-CoV infections
Intravenous immunoglobulin	• From individuals who have recovered from SARS-CoV-2 • Open-label RCT patient with SPO2 ≤96% on ≥4 liters O2 by nasal cannula but not on mechanical ventilation • three days of IVIg (n=16) or no IVIg (n=17); methylprednisolone was provided with each IVIg dose, unbalanced interventions • Result : Mechanical ventilation 2 vs 7, died 1 vs 3
NSAIDS be stopped?	• NSAIDs, due to upregulation in ACE2 in human target cells • In the setting of bacterial pneumonia, NSAIDs may impair recruitment of polymorphonuclear cells • case-control study from Italy did not demonstrate an increased risk of SARS-CoV-2 infection in those taking NSAIDs chronically • Ongoing RCT
ACEI, ARBs be stopped?	• two contrasting hypotheses • ACEIs and ARBs may increase the risk of infection and severity of COVID-19 via increased ACE2 expression • infection with other coronaviruses have been shown to decrease ACE2 levels in vitro, which may lead to increased angiotensin II activity resulting in pulmonary, cardiovascular and other end organ damage in patients with COVID-19. • Observational study: ACEI and ARBs do not increase the risk of acquiring COVID-19, developing severe, disease or death; increase risk of renal dysfunction in severe COVID-19 • Most professional scientific and medical societies have recommended that ACEI or ARBs be continued in people who have an indication for these medications

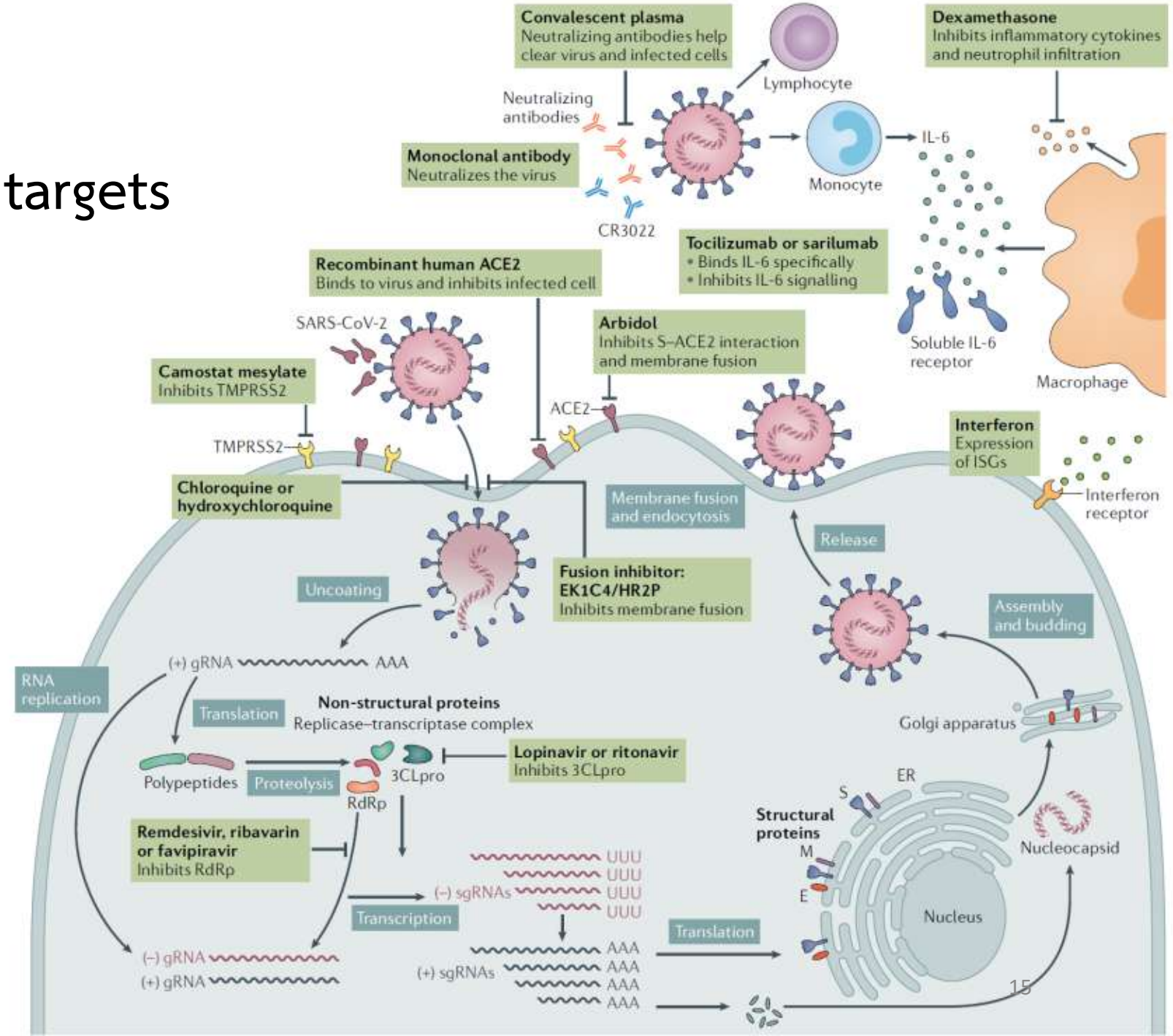
Thai GL 28 Jan 2021

FPV 200 mg/tab	วันที่ 1: 1800 mg (9 เม็ด) วันละ 2 ครั้ง วันต่อมา: 800mg(4เม็ด)วันละ2 ครั้ง ถ้าน้ำหนักตัว >90 กิโลกรัม วันที่ 1: 2,400 mg (12 เม็ด) วันละ 2 ครั้ง วันต่อมา: 1,000mg(5เม็ด)วันละ 2ครั้ง	วันที่ 1: 60 mg/kg/day วันละ 2 ครั้ง วันต่อมา: 20mg/kg/day วันละ2ครั้ง
LPV/r (เม็ด 200/50 mg/tab, น้ำ 80/20 mg/mL)	2 เม็ด ทุก 12 ชั่วโมง	อายุ 2 สัปดาห์-1 ปี 300/75 mg/m2/dose วันละ 2 ครั้ง อายุ 1-18 ปี 230/57.5 mg/m2/dose วันละ 2 ครั้ง ขนาดยาชนิดเม็ดตามน้ำหนักตัว 15-25 กิโลกรัม 25-35 กิโลกรัม 35 กิโลกรัมขึ้นไป 200/50 mg วันละ 2 ครั้ง 300/75 mg วันละ 2 ครั้ง 400/100 mg วันละ 2 ครั้ง
RDV	Remdesivir วันที่ 1: 200 mg IV วันที่ 2-5: 100 mg IV วันละครั้ง (US-NIH แนะนำให้ 5 วันในกรณีที่อาการไม่รุนแรง มาก แต่ถ้ามีอาการรุนแรงมากต้องใช้ ECMO แนะนำให้ 10 วัน)	วันที่ 1: 5 mg/kg IV วันละครั้ง วันต่อมา : 2.5 mg IV วันละครั้ง
Corticosteroid	Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid • methylprednisolone 32 mg • prednisone 40 mg	ให้ปรึกษาแพทย์ผู้เชี่ยวชาญ

Mechanism of action of potential therapeutic targets

- CQ/HCQ
- Favipiravir
- Lopinavir/ritonavir
- Remdesivir

- Tocilizumab
- Dexamethasone



Nat Rev Microbiol. 2020 Oct 6;1-14.

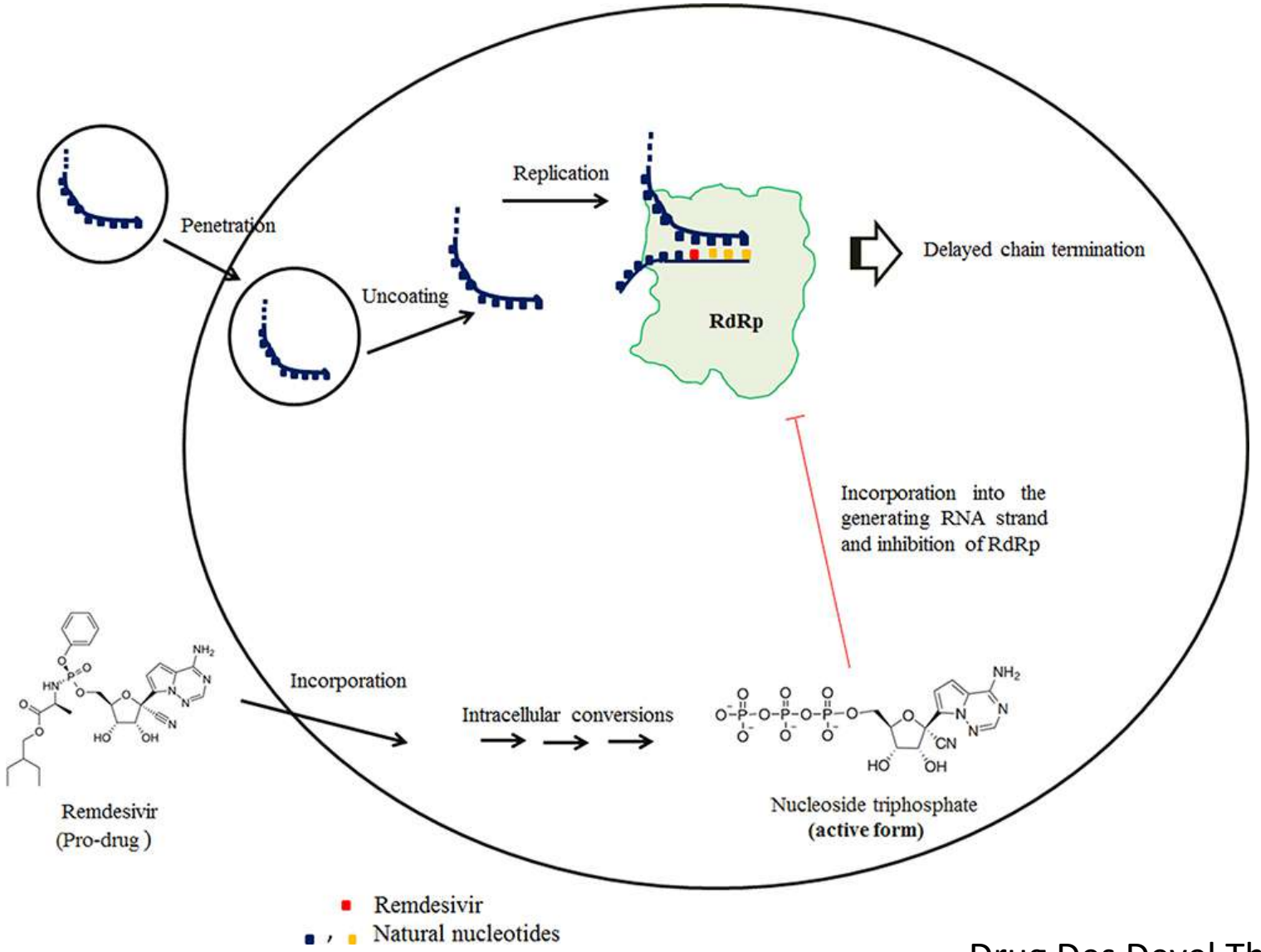
REMDESIVIR

Remdesivir: formulation

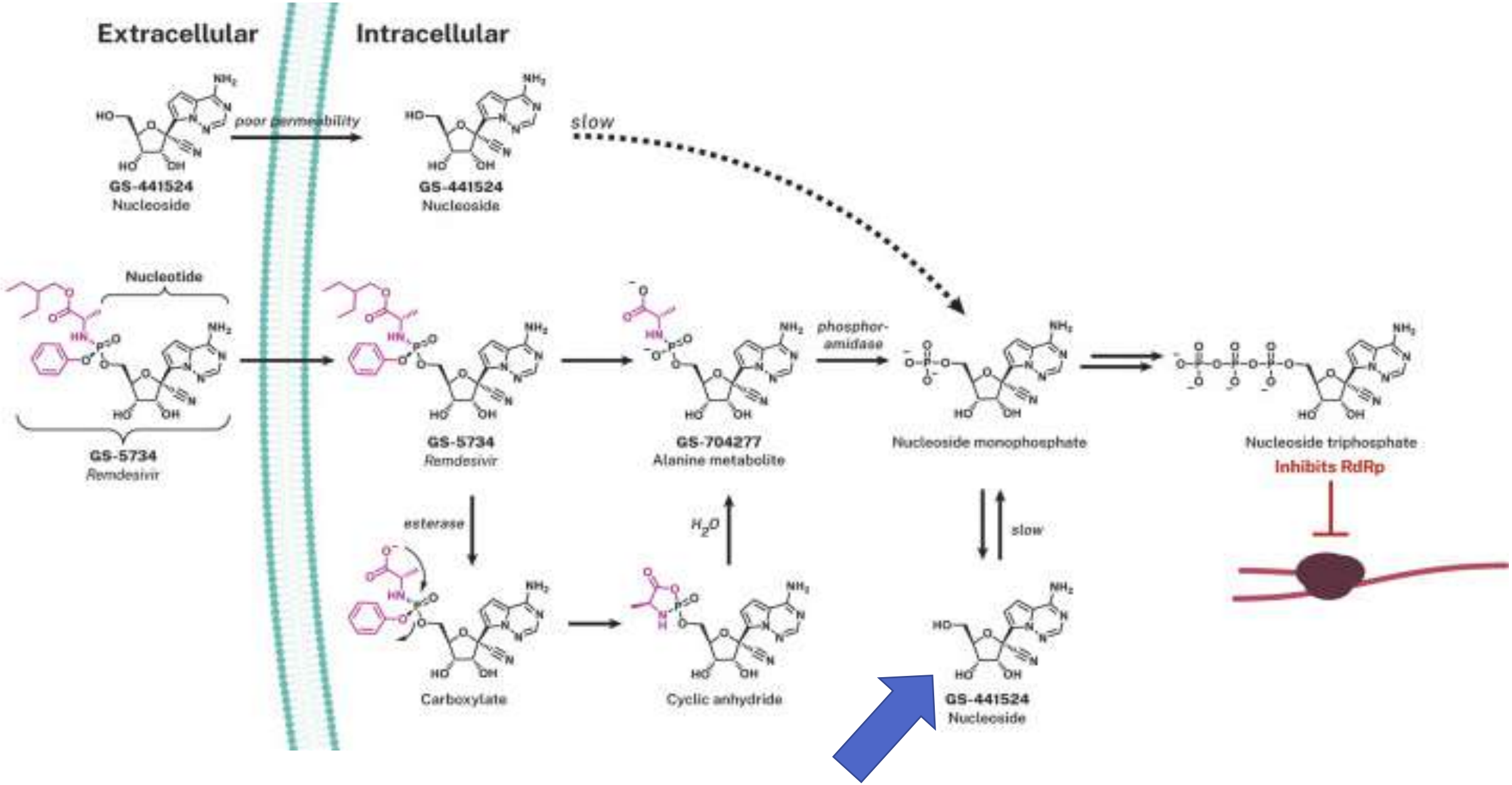
- Veklury (Remdesivir for injection 100 mg/vial)
- Formulation : injection solution, single use
- Sulfobutylether-β-cyclodextrin sodium salt (SBECD) 6 g

- COVIFOR (Remdesivir for injection 100 mg/vial)
- Formulation : Lyophilized powder white-yellow, single use
- Sulfobutylether-β-cyclodextrin sodium salt (SBECD) 3 g

Remdesivir: Pharmacodynamics



Drug Des Devel Ther. 2020; 14: 3215–3222.



Drug Des Devel Ther. 2020; 14: 3215–3222.

Remdesivir: Pharmacokinetics

A	Poor. The oral route will result in hydrolysis of the prodrug to Nucleoside-MP in the GI tract and will not be absorbed.
D	PB: Remdesivir: 88-93.6% GS-441524: 2%

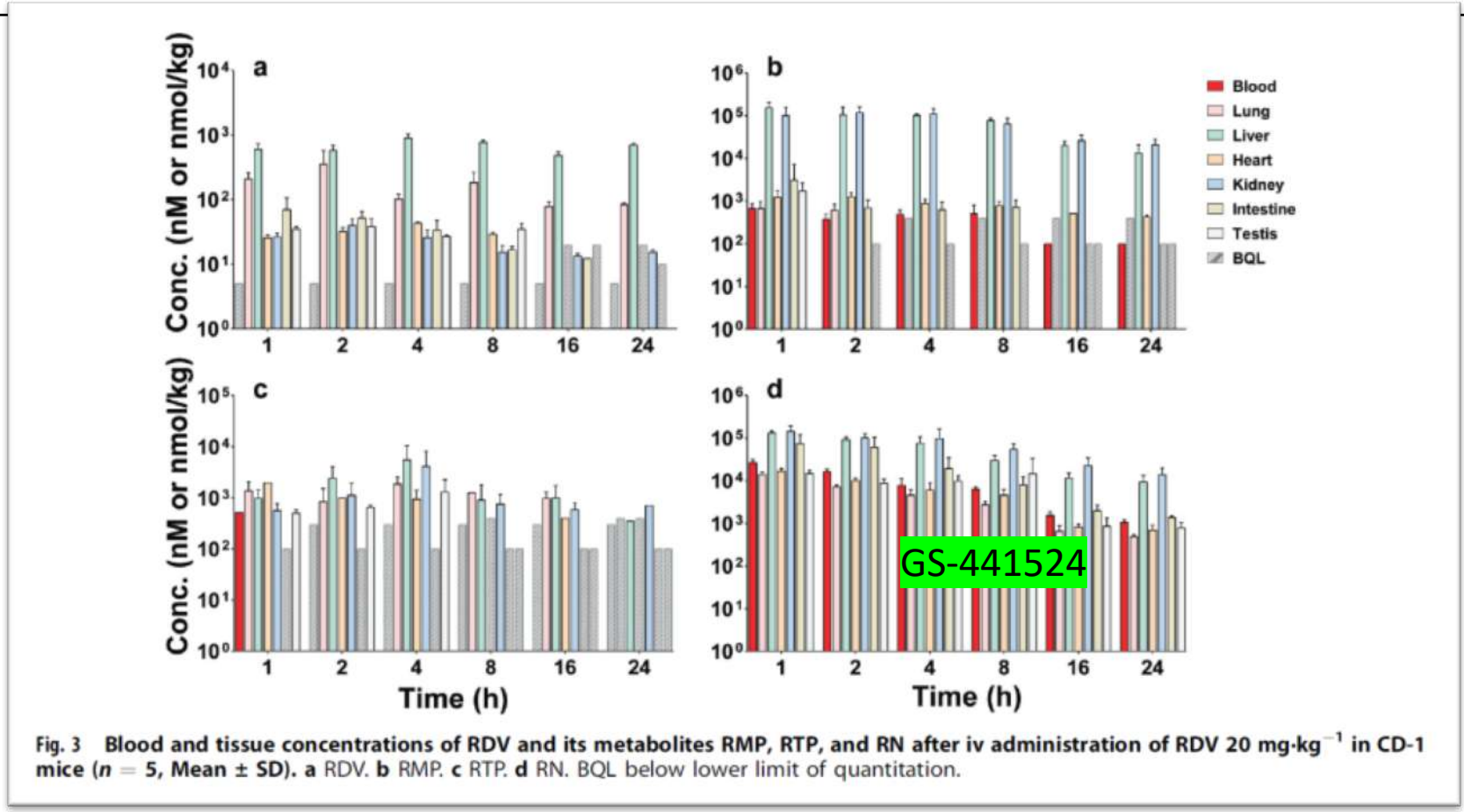
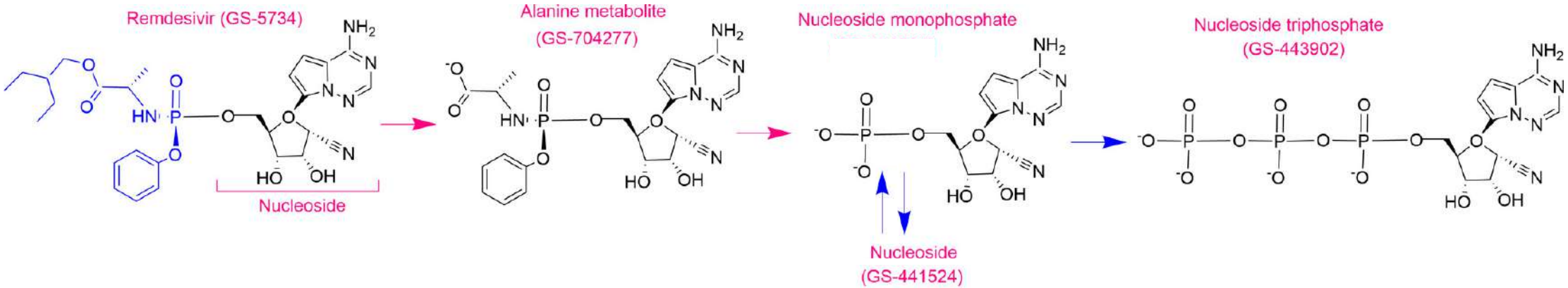


Fig. 3 **Blood and tissue concentrations of RDV and its metabolites RMP, RTP, and RN after iv administration of RDV 20 mg·kg^{-1} in CD-1 mice (n = 5, Mean ± SD). a** RDV. **b** RMP. **c** RTP. **d** RN. BQL below lower limit of quantitation.

Acta Pharmacol Sin. 2020 Oct 12;1-6.

Remdesivir: Pharmacokinetics

M	 Remdesivir: CES1 (80%); cathepsin A (10%); CYP3A (10%) GS-441524: Not significantly metabolized
E	Remdesivir: 1 hr GS-441524: 27 hr, excreted via glomerular filtration and active tubular secretion, 50% found in urine

Antimicrob Agents Chemother. 2020 Nov; 64(11): e01521-20.

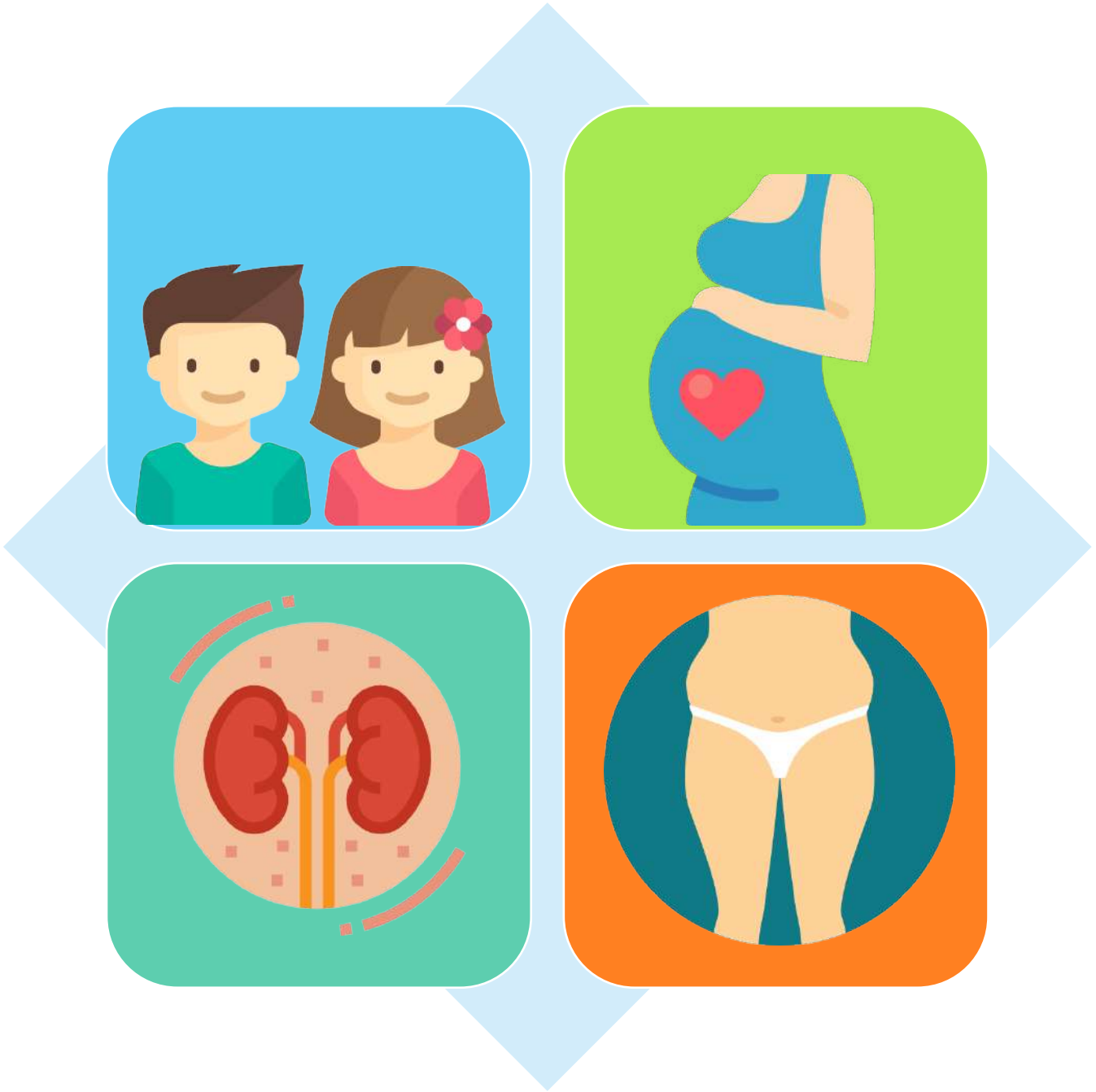
Remdesivir: dosing

- For 12 years & older with BW at least 40 kg) with pneumonia requiring supplemental oxygen
- Renal impairment: no dosage adjustment but caution use in e-GFR < 30 ml/min

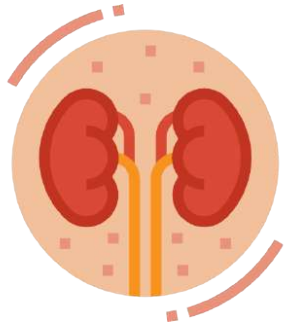
Body weight	LD (Day 1)	MD(Day 2 – 5)
3.5 kg to less than 40 kg 	5 mg/kg	2.5 mg/kg
40 kg and higher 	200 mg	100 mg

Remdesivir:

Special population



Remdesivir: special population

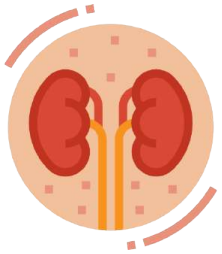


- SBECD containing 3 g/vial
- occurred in rats at the maximum dose of 3000 mg/kg, which is approximately 50-fold greater than the SBECD dose typically administered in man, as well as higher than exposure during a 5-10 days course of remdesivir.
- SBECD is dialyzable (46% removed by an ~4-hour dialysis session)
- CRRT: no dosage adjustment

Does **Remdesivir** induced-AKI ?

Does **Remdesivir** safe for renal impairment patient ?

Nephrol Dial Transplant. 2012 Mar;27(3):1207-12. Crit Care 2015; 19(1): 32. J Pharm Sci. 2010 Aug;99(8):3291-301.



Does it induced-AKI ?

Whether Remdesivir Increases the Risk of Acute Kidney Injury (AKI) in Patients with COVID-19: A Systematic Review and Meta-Analysis

Zhenjian Xu
Sun Yat-Sen University

Table 3
Results of meta-analysis of the incidence of AKI in COVID-19 patients

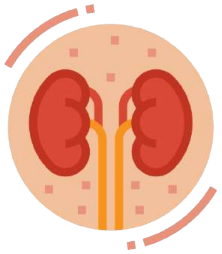
	Study	COVID-19 patients No	Proportion/OR	Study heterogeneity				
				Chi-square test	df	I^2	P value	Begger's test (P value)
The incidence of AKI in all hospitalization COVID-19 patients	18	15135	0.12 (0.09–0.15)	0.19	17	98%	< 0.01	0.73
The incidence of AKI in hospitalization COVID-19 patients using Remdesivir	5	981	0.06 (0.03–0.13)	0.70	4	86%	< 0.01	n < 10
						0%	0.44	n < 10

The pooled estimated incidence of AKI in all hospitalized COVID-19 patients was **12.0%** (95% CI 9.0%-15.0%)

The incidence of AKI in hospitalized COVID-19 patients using Remdesivir was **6%** (95% CI 3%-13%)

- The incidence of AKI was associated with the age, disease severity and race of patients.
- Remdesivir treatment do not increase the risk of AKI in COVID-19 patients showing OR 0.80 (95% CI 0.44-1.46, P>0.05).

Zhenjian X, Ying T, Qiuyan H, Sha F, Xiaomei L, Baojuan L, et al. BMC Nephrology. 2021.



Does it safe for renal impairment patient ?

Table 2. Renal function during remdesivir therapy in patients with AKI

Case	Serum creatinine at admission, mg/dl	KDIGO AKI stage	Serum creatinine before initiation of remdesivir, mg/dl	Peak serum creatinine on remdesivir therapy, mg/dl	Serum creatinine at completion/within 48 hrs of therapy, mg/dl
3	6.6	3	On dialysis	On dialysis	Death[a]
4	15.6	3	On dialysis	On dialysis	On dialysis
6	7.7	3	On dialysis	On dialysis	On dialysis[b]
7	8.0	3	On dialysis	On dialysis	Death[a]
8	7.9	3	On dialysis	Death[a]	Death[a]
10	6.1	3	On dialysis	Death[a]	Death[a]
11	3.5	3	4.5	3.7	2
12	7.3	3	2.9	2.7	2.5
14	5.5	3	4	3.7	3.2
15	8.2	3	On dialysis	On dialysis[c]	Death[a]
16	5.7	3	5.9	5.5	4
18	2.1	2	2.3	2.1	1.7
19	4.72	3	6.0	4	2.2
20	7.0	3	On dialysis	On dialysis	Death[a]
22	2.32	1	2.2	2.3	2.1
23	11.8	3	On dialysis	On dialysis	Death[a]
24	6.7	3	On dialysis	On dialysis	On dialysis
26	1.6	1	1.6	1.6	1.4
27	9.0	3	On dialysis	On dialysis	On dialysis
30	8.7	3	On dialysis	On dialysis	On dialysis
32	2.0	2	2.0	1.7	1.4
33	6.0	3	On dialysis	On dialysis	On dialysis
34	9.8	3	On dialysis	On dialysis	On dialysis
35	4.1	3	6.8[b]	6.6	6.1
38	11.0	3	On dialysis	On dialysis	On dialysis
39	9.8	3	On dialysis	On dialysis	On dialysis
41	7.3	3	On dialysis	On dialysis	On dialysis
42	1.4	1	1.79	1.9	1.5
44	4.7	3	On dialysis	On dialysis	On dialysis
45	11.5	3	On dialysis	On dialysis	On dialysis

Safety of Remdesivir in Patients With Acute Kidney Injury or CKD

Check for updates

Sayali Thakare[1], Chintan Gandhi[1], Tulsi Modi[1], Sreyashi Bose[1], Satarupa Deb[1], Nikhil Saxena[1], Abhinav Katyal[1], Ankita Patil[1], Sunil Patil[1], Atim Pajai[1], Divya Bajpai[1] and Tukaram Jamale[1]

[1]Department of Nephrology, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, India

Safety

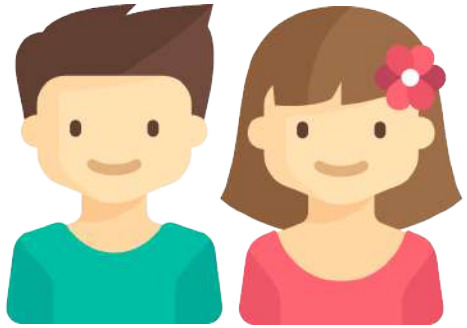
- Transient behavioral changes were noted in 5 cases
- Acute gout was observed in 1 patient
- Liver function remained stable in 28 (60.9%) cases. 3 (6.5%) patients were found to have newly occurring grade 1 elevations of AST/ALT during therapy.
- **No patient had a severe rise in AST/ALT >5 times the upper limit of normal**
- **No renal function abnormalities attributable to drug were observed**

From 46 Patients, Renal diagnoses were ESRD in 16 (34.7%) and AKI in 30 (65.2%%) patients.

- The median number of days from hospital admission to starting remdesivir was 5 days (range 1–26 days).
- The median duration of follow-up was 15.5 days (range 6–81 days).

Thakare S, Gandhi C, Modi T, Bose S, Deb S, Saxena N, et al. Kidney Int Rep. 2021;6(1):206-10.

Remdesivir: special population



Compassionate use of remdesivir in children with COVID-19

Ana Méndez-Echevarría[1] · Antonio Pérez-Martínez[2] · Luis Gonzalez del Valle[3] · María Fátima Ara[4] · Susana Melendo[5] · Marta Ruiz de Valbuena[6] · Jose Luis Vazquez-Martinez[7] · Antonio Morales-Martínez[8] · Agustín Remesal[9] · Kinga Amália Sándor-Bajusz[10] · Fernando Cabañas[11] · Cristina Calvo[1]

Received: 30 May 2020 / Revised: 5 November 2020 / Accepted: 11 November 2020

Abstract

Children represent a minority of total COVID-19 cases, but studies have reported severe disease and death in pediatric patients. Remdesivir (RDV) has recently demonstrated promising results in adults with COVID-19, but few data have been reported to date in children.

A nationwide multicenter observational study was conducted on children with confirmed SARS-CoV-2 receiving compassionate treatment with RDV in Spain. Eight patients were included in the study, four infants and four older children [median age 5 years old; IQR 4 months–11.6 years old]. Half of them had complex underlying medical conditions, and the rest were mostly infants (3/4). Six out of eight children needed Pediatric Intensive Care Unit Admission. No RDV-related adverse outcomes were observed in our patients. Seven have reached successful clinical outcome, but one patient with serious clinical status died due to complications. However, she received RDV very late after the first COVID-19 symptom.

Conclusions: In our cohort, most of the patients achieved successful clinical outcome, without observing adverse events. Clinical trials of RDV therapy for children with COVID-19 are urgently needed, to assess the safety, tolerability, efficacy, and pharmacokinetics of RDV in children, as this could be an effective treatment in severe cases.

- No RDV-related adverse outcomes were observed in our patients.
- 7 have reached successful clinical outcome
- but 1 patient with serious clinical status died due to complications. However, she received RDV very late after the first COVID-19 symptom

Eur J Pediatr. 2020 Nov 16;1-6.

Remdesivir: special population

Clinical Infectious Diseases

MAJOR ARTICLE

Compassionate Use of Remdesivir in Pregnant Women With Severe Coronavirus Disease 2019

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Background. Remdesivir is efficacious for severe coronavirus disease 2019 (COVID-19) in adults, but data in pregnant women are limited. We describe outcomes in the first 86 pregnant women with severe COVID-19 who were treated with remdesivir.

Methods. The reported data span 21 March to 16 June 2020 for hospitalized pregnant women with polymerase chain reaction–confirmed severe acute respiratory syndrome coronavirus 2 infection and room air oxygen saturation ≤94% whose clinicians requested remdesivir through the compassionate use program. The intended remdesivir treatment course was 10 days (200 mg on day 1, followed by 100 mg for days 2–10, given intravenously).

Results. Nineteen of 86 women delivered before their first dose and were reclassified as immediate "postpartum" (median postpartum day 1 [range, 0–3]). At baseline, 40% of pregnant women (median gestational age, 28 weeks) required invasive ventilation, in contrast to 95% of postpartum women (median gestational age at delivery 30 weeks). By day 28 of follow-up, the level of oxygen requirement decreased in 96% and 89% of pregnant and postpartum women, respectively. Among pregnant women, 93% of those on mechanical ventilation were extubated, 93% recovered, and 90% were discharged. Among postpartum women, 89% were extubated, 89% recovered, and 84% were discharged. Remdesivir was well tolerated, with a low incidence of serious adverse events (AEs) (16%). Most AEs were related to pregnancy and underlying disease; most laboratory abnormalities were grade 1 or 2. There was 1 maternal death attributed to underlying disease and no neonatal deaths.

Conclusions. Among 86 pregnant and postpartum women with severe COVID-19 who received compassionate-use remdesivir, recovery rates were high, with a low rate of serious AEs.

- At baseline, 40% of pregnant women (median gestational age, 28 weeks) required invasive ventilation, in contrast to 95% of postpartum women (median gestational age at delivery 30 weeks).
- By day 28 of follow-up, the level of oxygen requirement decreased in 96% and 89% of pregnant and postpartum women, respectively.
- Low incidence of serious adverse events (AEs) (16%)

Clin Infect Dis. 2020 Oct 8;ciaa1466.

Remdesivir: special population

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Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All (N=1062)	Remdesivir (N=541)	Placebo (N=521)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.4)	352 (65.1)	332 (63.7)
ic group — no. (%)†			
Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
	135 (12.7)	79 (14.6)	56 (10.7)
African American	226 (21.3)	109 (20.1)	117 (22.5)
	566 (53.3)	279 (51.6)	287 (55.1)
Latino — no. (%)	250 (23.5)	134 (24.8)	116 (22.3)
(IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
ting conditions — no. /total no. (%)‡			
	194/1048 (18.5)	97/531 (18.3)	97/517 (18.8)
One	275/1048 (26.2)	138/531 (26.0)	137/517 (26.5)
Two or more	579/1048 (55.2)	296/531 (55.7)	283/517 (54.7)
Coexisting conditions — no./total no. (%)			
Type 2 diabetes	322/1051 (30.6)	164/532 (30.8)	158/519 (30.4)
Hypertension	533/1051 (50.7)	269/532 (50.6)	264/519 (50.9)
Obesity	476/1049 (45.4)	242/531 (45.6)	234/518 (45.2)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	138 (13.0)	75 (13.9)	63 (12.1)
5. Hospitalized, requiring supplemental oxygen	435 (41.0)	232 (42.9)	203 (39.0)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	193 (18.2)	95 (17.6)	98 (18.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	285 (26.8)	131 (24.2)	154 (29.6)
Baseline score missing	11 (1.0)	8 (1.5)	3 (0.6)

Remdesivir: Administration

- IV only, not use IM
- reconstitution in SWFI 19 ml/vial
- Dilution: 0.9 % NSS 250 ml, IV infusion 30-120 min [Max conc. 2 mg/ml]
- After reconstitution, the total storage time before administration should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C)

Table 1: Recommended Dilution Instructions Using Reconstituted Remdesivir for Injection Lyophilized Powder

Remdesivir dose	0.9% sodium chloride infusion bag volume to be used	Volume of saline to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of reconstituted Remdesivir for injection
200 mg (2 vials)	250 mL	40 mL	40 mL (2 × 20 mL)
	100 mL	40 mL	40 mL (2 × 20 mL)
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

Remdesivir: DIs

Citation: Clin Transl Sci (2020) 13, 842–844; doi:10.1111/cts.12815

COMMENTARY

What Do We Know About Remdesivir Drug Interactions?

Katherine Yang[1,*]

Clin Transl Sci. 2020 Sep;13(5):842-844.

Table 1 Published guidance regarding remdesivir metabolism and drug-drug interactions

Source	Website	Date published or updated	Conclusions and recommendations
McCreary *et al.*[14] SIDP	https://doi.org/10.1093/ofid/ofaa105	March 23, 2020	"There is no reason to believe that any significant drug interactions between remdesivir and CYP3A4 inhibitors or inducers are likely"
Liverpool Drug Interaction Group[15]	https://www.covid19-druginteractions.org	April 9, 2020	Voriconazole: no clinically significant interaction expected. Rifampicin, carbamazepine, phenytoin: Potential decreased exposure of [remdesivir]. These drugs should not be co-administered.
Sanders *et al.*[16]	https://doi.org/10.1001/jama.2020.6019	April 13, 2020	Not a significant inducer/inhibitor of CYP enzymes, monitor with strong inducers/inhibitors
NIH COVID-19 Treatment Guidelines[18]	https://covid19treatmentguidelines.nih.gov	April 21, 2020	RDV levels are unlikely to be markedly altered by CYP2C8, CYP2D6, or CYP3A4 enzymes, or by P-gp or OATP drug transporters. It may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP, or P-gp. Strong induction of P-gp is expected to modestly reduce RDV levels. The clinical relevance of lower RDV levels is unknown. The use of RDV with known inducers of P-gp (e.g., rifampin) is not recommended.
Fact Sheet for Health Care Providers Emergency Use Authorization of Remdesivir (GS-5734)[19]	https://www.fda.gov/media/137566/download	May 3, 2020	Drug-drug interaction trials of remdesivir and other concomitant medications have not been conducted in humans. *In vitro*, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for OAPT1B1 and P-gp transporters. *In vitro*, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. The clinical relevance of these *in vitro* assessments has not been established.

Remdesivir: ADRs monitoring

- Anaphylaxis reaction
- nausea, anemia, AKI, pyrexia, hyperglycemia, elevated ALT, ASL
- Hepatitis: LFTs (discontinue when ALT ≥ 5 or ALT elevated + clinical)
- BUN, Serum creatinine (e-GFR)

Monitor LFTs and RFTs daily

Before and after start of tx.

FAVIPIRAVIR

Agrawal U, et al. Med J Armed Forces India. 2020 Oct; 76(4): 370–376.

Feb 3, 2014 — approved for influenza in Japan (stockpiling against influenza pandemics)

2014 - 2015 — Ebola virus outbreak initiated in West Africa

Feb 2020 — approved for treatment of novel influenza in China
available for use in Thailand (emergency)

Jun 19, 2020 — approved for treatment of mild and moderate COVID-19 in India (emergency)

Jun 2020 — approved for treatment of in-hospital COVID-19 in Russia (emergency)

- Approved for clinical trial
- Include in treatment guideline
- Comercial lunch

Timeline of approval and distribution of favipiravir use

Avigan® 200 mg
Film-coated tablet
Fujiflim, Japan

Favilavir® 200 mg
Zhejiang Hisun Pharmaceutical Co., Ltd. (HISUN), China

Favivir® 200 mg tablet
Hetero healthcare, India
FabiFlu® 200 mg tablet
Glenmark Pharmaceuticals, India

Avifavir ® 200 mg tablet
ChemRar, Russia

Chemical structure of favipiravir (T-705).

Formula : $C_5H_4FN_3O_2$

IUPAC name: 6-fluoro-3-hydroxy-2-pyrazinecarboxamide

Pyrazine analogue

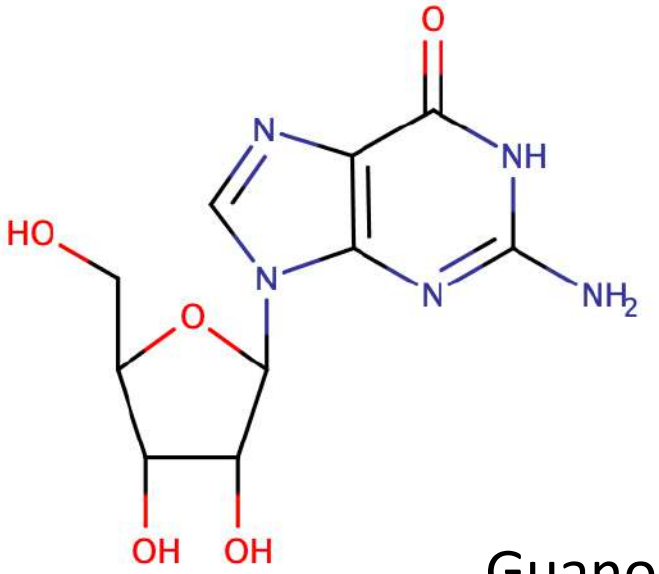
Purine analogue (Guanosine)

Fujifilm's Toyama Chemical Co., Ltd. 2014

favipiravir (T-705)

MW=157.1 g/mol

logP 0.25

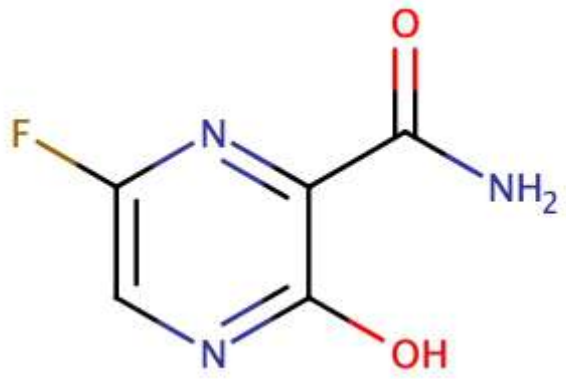


Guanosine

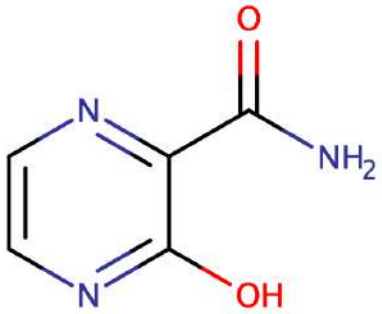
Hu B, Guo H, Zhou P, Shi Z-L. Nature Reviews Microbiology. 2020.

Mechanism of action

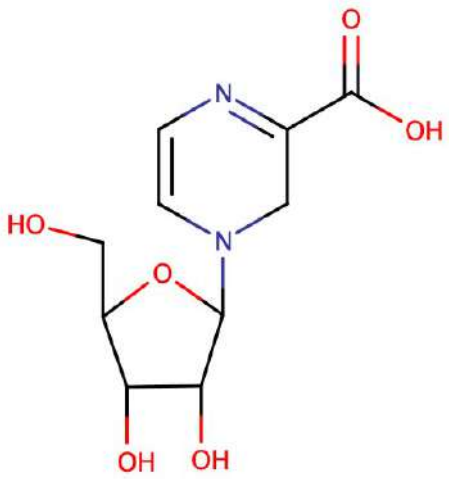
Once incorporated into host cells, favipiravir undergoes phosphoribosylation and further phosphorylation to become favipiravir-RTP, which blocks viral RNA-dependent RNA-polymerase (RdRp). Inhibit viral replication / transcription



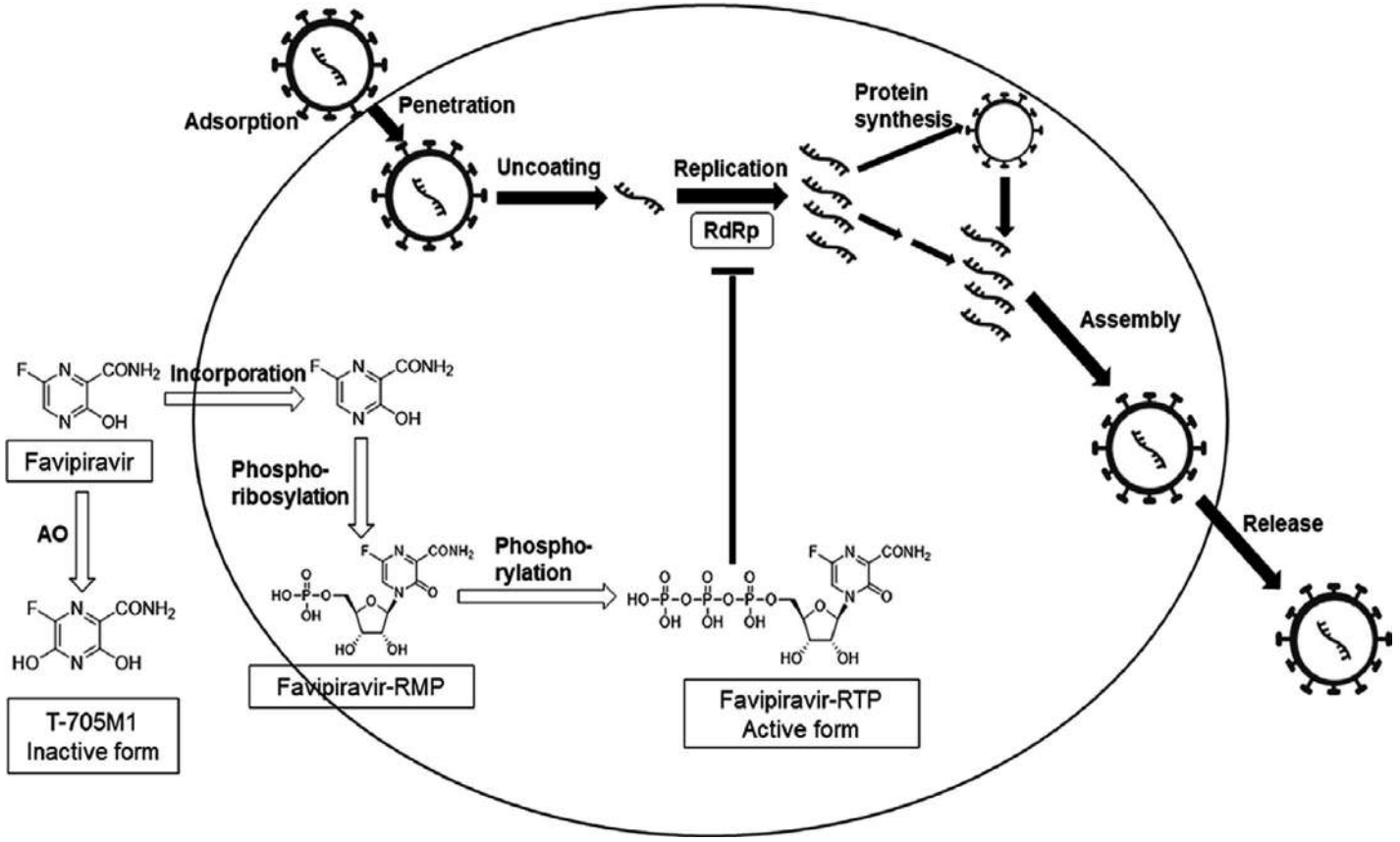
Favipiravir (Prodrug)



T-1105



T-1106



Favipiravir ribofuranosyl-5'-triphosphate

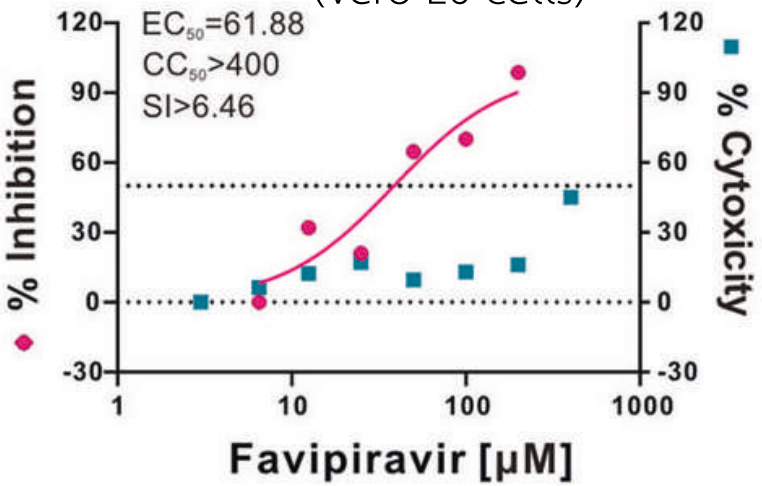
Furuta Y, et al. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(7):449-463.

Du, Y.-X. and Chen, X.-P. (2020), Clin. Pharmacol. Ther., 108: 242-247.

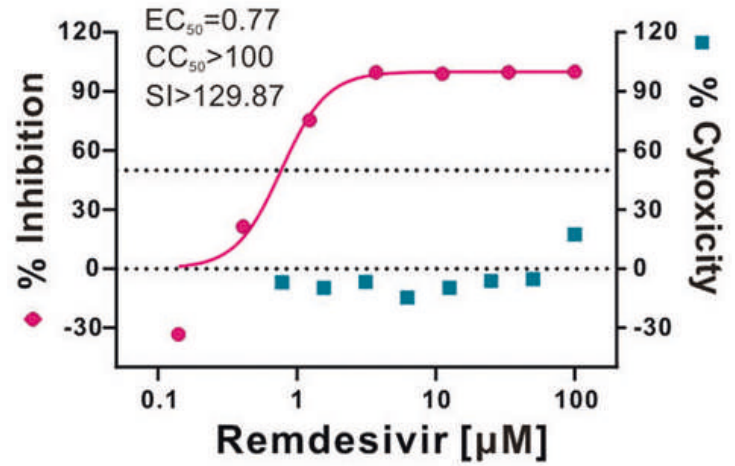
Pharmacodynamics

- Possible mechanism of the interaction of favipiravir- RTP with RdRp molecule
  - misincorporated in a nascent viral RNA, or it may act by binding to conserved polymerase domains
- virucidal drug. (uncertain for SARS-CoV2)
- Favipiravir inhibited proliferation of RNA viruses but not of DNA viruses
- Favipiravir-RTP (1000 μmol/L) no inhibitory effect on α human DNA polymerase, 9-13% inhibitory effect on β, 11-49% inhibitory effect on γ
- Broad spectrum antiviral of RNA viruses: Influenza, Ebola, bunyavirus, filovirus, West Nile virus, yellow fever virus, foot-and-mouth-disease virus etc.

In vitro activity to SARS-CoV-2 (Vero E6 cells)



61.88 μmol/L = 9.721 μg/ml



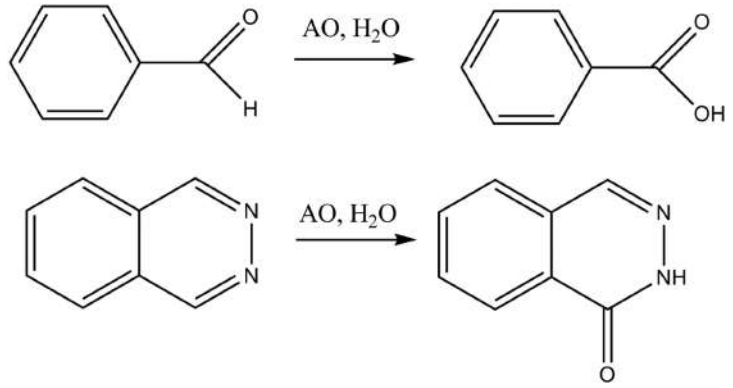
Furuta Y, et al. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(7):449-463.

Wang, M.. et al. Cell Res 30, 269–271 (2020) 11.

AVIGAN® (favipiravir) 200 mg [prescribing information]. Tokyo, Japan: Toyama Chemical Co Ltd; January 2017.

Pharmacokinetics

Bioavailability	94%
Cmax	2 hr (afer single dose)
t1/2	2-5.5 hours
Protein binding Albumin α1-acid glycoprotein	54% 65% 6.5%
Low volume distribution	10-20 L
Metabolism	• Aldehyde oxydase (AO), inhibit AO activity in concentration-dependent and time-dependent manners (self inhibitor) • Increasing in T-705/T-705M1 facilitate the cellular uptake and trapping of favipiravir in the tissue by gradient • repeated doses indicates obvious nonlinear pharmacokinetics over time and over a range of doses, continuous administration decrease in drug concentration • Xanthine oxydase • >>> inactive oxidative metabolite T-705M1 • rapid excretion of favipiravir by the liver in mice • It is not metabolized by the cytochrome P450 system, but inhibits one of its components (CYP2C8)
Excretion	Favipiravir is mainly renally excreted (90.5%), of which the majority exists as M1 (82.0–92.4%)



Agrawal U, et al. Med J Armed Forces India. 2020 Oct; 76(4): 370–376.

Du, Y.-X. and Chen, X.-P. (2020), Clin. Pharmacol. Ther., 108: 242-247.

Clinical trials

	P	I, C	O
China Chen, C., et al., *Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial.* medRxiv, 2020: p. 2020.03.17.20037432. prospective, open-label multi- centric trial RCT 1:1 (n=240)	clinically confirmed COVID-19 • aged 18 years or older • initial symptoms were within 12 days • Diagnosed as COVID-19 pneumonia. • (PCR pos 46% in favipiravir gr. , 38% in arbidol gr.) • (mostly mod clinical) • Exclude • ALT/AST (>6x upper limit of normal range) or with chronic liver disease (cirrhosis at grade Child-Pugh C) • pregnancy	• umifenovir (Arbidol) (200 mg thrice a day) • favipiravir (1600 mg twice daily followed by 600 mg twice daily) for 7 days (extendable to 10 days)	• clinical recovery rate at day 7 did not differ significantly (61.21% for favipiravir vs 51.67% for umifenovir, 95% CI: 0.0305 to 0.2213, p = 0.1396) • Post hoc: favipiravir-treated patients showed a trend toward clinical improvement at day 7 among those with moderate COVID-19 (71.43% vs 55.86%, 95% CI: 0.0271 to 0.2843, P 1/4 0.0199) and earlier resolution of fever and cough (p < 0.0001) • auxiliary oxygen therapy or noninvasive mechanical ventilation did not differ • Mild side effect

Clinical trials

	P	I, C	O
China Cai Q, et al. Engineering (Beijing) 2020;6(10):1192-1198. open-labeled nonrandomized study before-after controlled	• nasopharyngeal swabs positive for SARs-CoV-2 • disease onset <7 days • past 7 days and mild-moderate disease • (aged 16-74) • (normal LFT at baselinne)	• favipiravir (day 1: 1600 mg twice daily; days 2e14: 600 mg twice daily) • LPV/r (day 1-14: 400/100 twice daily) • Both groups received interferon-alpha (5 million units twice daily) by nasal inhalation.	• Significant viral clearance on Day 14 median time 4 d (IQR 2.5–9) vs 11 d (IQR: 8–13), P < 0.001 • Significant change in CT scan on Day 14 after treatment 91.43% versus 62.22% , P = 0.004

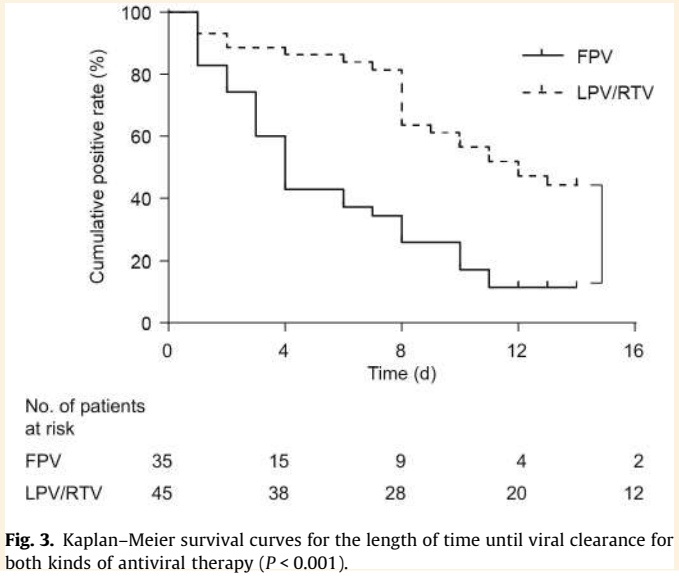


Fig. 3. Kaplan–Meier survival curves for the length of time until viral clearance for both kinds of antiviral therapy ($P < 0.001$).

Clinical trials

	P	I, C	O
Japan Investigator-initiated, individually randomized, open-label trial Doi, Y., et al., A Prospective, Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with COVID-19. Antimicrobial Agents and Chemotherapy, 2020. 64(12): p. e01897-20. 55 hospitals 89 patient	• age of 16 years or older, • inpatient status, • positive RT-PCR for SARS-CoV-2 collected within 14 days • ECOG performance status of 0 or 1 • Exclude severe hepatic disease, **need for dialysis, pregnancy**	• Early FPV use (within 6 days)	• Viral clearance by day 6 was achieved in 66.7% vs 56.1% aHR 1.42; 95% CI 0.76 to 2.62 • 30 patient who has fever on day1. Defervescence 2.1 days (95% CI, 1.421 to 2.846) in the early treatment group and 3.2 days (95% CI, 2.390 to 3.918)

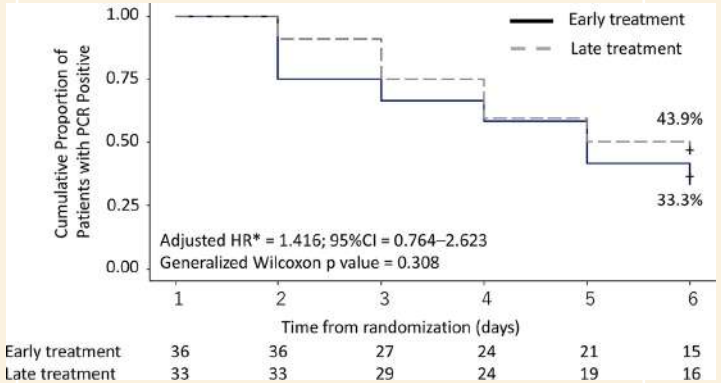


FIG 2 Viral clearance by day 6 among the infected intention-to-treat population. *, HR is adjusted for age and days between collection of the SARS-CoV-2-positive specimen and enrollment.

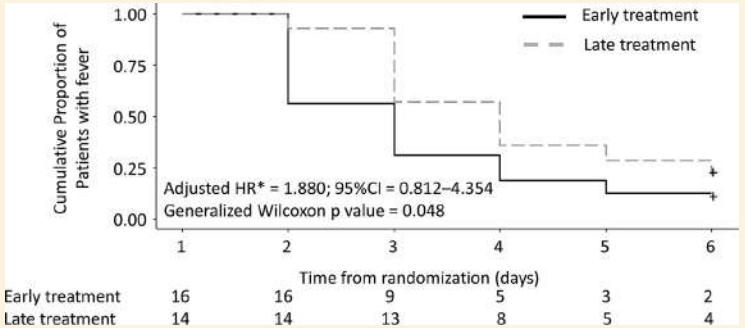


FIG 3 Time to defervescence (<37.5°C) among the intention-to-treat population. Only those with temperatures of ≥37.5°C on day 1 are included. *, HR is adjusted for age and days between collection of the SARS-CoV-2-positive specimen and enrollment.

Clinical trials

	P	I, C	O
Russia Phase II/III clinical trial Ivashchenko, A.A., et al., AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. Clin Infect Dis, 2020. 1:1:1	• PCR-confirmed COVID-19 • >18 yo • Non-pregnant woman	• AVIFAVIR 1600 mg BID on Day 1 followed by 600 mg BID on Days 2-14 (1600/600 mg) • AVIFAVIR 1800 mg BID on Day 1 followed by 800 mg BID on Days 2-14 (1800/800 mg) • Standardof care : HCQ or CQ 75%, LPV/r 5%	• viral clearance in 62.5% within 4 days similar in both dosing regimens

Clinical trials

	P	I, C	O
Japan Japanese observational study group	• All severity COVID-19	• more than 90 percent of cases, favipiravir was administered at a dose of 1800 mg orally on day 1 followed by 800 mg twice daily on subsequent days • median duration of therapy was 11 days • no control arm	• Rates of clinical improvement at 7 and 14 days/ mortality rate • Mild 73.8% and 87.8% / 5.1% • Moderate 66.6% and 84.5%/ 12.7% • Severe 40.1% and 60.3% /31.7%

Clinical trials

	P	I, C	O
Retrospective observational study Rattanaumpawan, P., et al., Real-world Experience with Favipiravir for Treatment of COVID-19 in Thailand: Results from a Multicenter Observational Study. medRxiv, 2020: p. 2020.06.24.20133249.	• hospitalized adult patients 247 COVID-19 patients, 63 (23.0%) received 1 dose of favipiravir • 27.0% required an O2-nasal cannula • 9.5% required non-invasive ventilation and/or high-flow O2-therapy • 6.4% required invasive mechanical ventilation and/or ECMO • Median baseline NEWS2 score was 5(0–16) • Age 22-85 • CKD 6.4% • Chronic liver disease 4.8%	• Thai CPG March-May 2020 • 1600 mg twice daily on Day 1, followed by 600 mg twice daily on Days 2–5 • ถ้า BMI ≥ 35 kg/m2 วันที่ 1: 60 mg/kg/day แบ่งให้วันละ 2 ครั้ง • วันต่อมา: 20 mg/kg/day แบ่งให้วันละ 2 ครั้ง • maximal loading dose of 3000 mg twice daily on Day 1 and a maintenance dose of 1200 mg twice daily on Days 2–9 were safely used in a previous Ebola study • chloroquine-based agent (98.4%) , a protease inhibitor (96.8%), azithromycin (49.2%), steroid (12.7%) or tocilizumab (6.4%)	• The Day-7 clinical improvement rate • 66.7%[53.7–78.0%] in all patients • 92.5%[75.7%–99.1%] in patients who did not require O2-supplementation • 47.2%[0.4%–64.5%] in patients who required O2-supplementation • No life-threatening adverse events were identified • The 28-day mortality rate was 4.8%. • Multivariate analysis revealed three poor prognostic factors for Day-7 clinical improvement 1. older age [0.94 (0.89–0.99); p=0.04], 2. higher baseline NEWS2 score [0.64 (0.47–0.88); p=0.006], 3. lower favipiravir loading dose (45 mg/kg/day) [0.04 (0.005–0.4); p=0.006].

Overview of IDSA COVID-19 Treatment Guidelines

Version 3.5.1 – December 2, 2020

		Setting and severity of illness			
		Ambulatory care: *mild-to-moderate disease*	***Hospitalized:*** *mild-to-moderate disease without need for suppl. oxygen*	***Hospitalized:*** *severe but non-critical disease (spO_2 <94% on room air)*	***Hospitalized:*** *critical disease (e.g., in ICU needing MV, or septic shock, ECMO)*
1	*Hydroxy-chloroquine (HCQ)**	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
2	*HCQ* + azithromycin*	NA	**Recommend against use** ⊕⊕◯◯	**Recommend against use** ⊕⊕◯◯	**Recommend against use** ⊕⊕◯◯
3	*Lopinavir + ritonavir*	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
4-6	*Corticosteroids*	NA	**Suggest against use** ⊕◯◯◯	**Suggest use** ⊕⊕⊕◯ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**	**Recommend use** ⊕⊕⊕◯ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**
7	*Tocilizumab*	NA	**Suggest against routine use** ⊕⊕◯◯	**Suggest against routine use** ⊕⊕◯◯	**Suggest against routine use** ⊕⊕◯◯
8	*Convalescent plasma*	NA	Recommended only in the context of a clinical trial (knowledge gap)	Recommended only in the context of a clinical trial (knowledge gap)	Recommended only in the context of a clinical trial (knowledge gap)
9-11	*Remdesivir*	NA	**Suggest against routine use** ⊕◯◯◯	**Suggest use** ⊕⊕◯◯ R: In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.	**Suggest use** ⊕⊕⊕◯ R: For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.
12	*Famotidine*	NA	**Suggests against use except in a clinical trial** ⊕◯◯◯	**Suggests against use except in a clinical trial** ⊕◯◯◯	**Suggests against use except in a clinical trial** ⊕◯◯◯
13	*Bamlanivimab*	**Suggest against routine use** ⊕◯◯◯ R: In patients at increased risk*** bamlanivimab is a reasonable treatment option if, after informed decision-making, the patient puts a high value on the uncertain benefits and a low value on uncertain adverse events.	NA	NA	NA

NA: not applicable/not reviewed; **MV**: mechanical ventilation; **ECMO**: extracorporeal membrane oxygenation; **R**: remark; **AE**: adverse events

*Chloroquine is considered to be class equivalent to hydroxychloroquine.

**Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

***Patients at increased risk, see EUA at https://www.fda.gov/media/143603/download

Ongoing Clinical trials

			outcome
double-blind, placebo-controlled trial Researchers at Stanford Medicine in the US	outpatients	Favipiravir for 2 weeks	reducing symptoms and viral shedding
Italian Pharmaceuticals Agency AIFA			

VIEWPOINT

Outpatient treatments for COVID-19, coupled with an effective vaccine, would have significant implications for the ability to end this pandemic.

Benefit of early effective treatment

- improvement of patient outcomes
- prevention of hospitalizations
- prevention of the chronic sequelae of infection
- prevention of transmission by shortening the period of infectiousness.

Kim, P.S., S.W. Read, and A.S. Fauci, Therapy for Early COVID-19: A Critical Need. JAMA, 2020. 324(21): p. 2149-2150.

Dosage regimen

Thai GI 7 Dec 2020	Thai GI 28 Jan 2021
ผู้ใหญ่ วันที่ 1: 1600 mg (8 เม็ด) วันละ 2 ครั้ง วันต่อมา: 600 mg (3 เม็ด) วันละ 2 ครั้ง ถ้า BMI ≥ 35 kg/m^2 วันที่ 1: 60 mg/kg/day แบ่งให้วันละ 2 ครั้ง วันต่อมา: 20 mg/kg/day แบ่งให้วันละ 2 ครั้ง	ผู้ใหญ่ วันที่ 1: 1800 mg (9 เม็ด) วันละ 2 ครั้ง วันต่อมา: 800 mg (4 เม็ด) วันละ 2 ครั้ง ถ้าน้ำหนักตัว >90 กิโลกรัม วันที่ 1: 2,400 mg (12 เม็ด) วันละ 2 ครั้ง วันต่อมา: 1,000 mg (5 เม็ด) วันละ 2 ครั้ง
เด็ก วันที่ 1: 30 mg/kg/dose วันละ 2 ครั้ง วันต่อมา: 10 mg/kg/dose วันละ 2 ครั้ง	เด็ก วันที่ 1: 60 mg/kg/dose วันละ 2 ครั้ง วันต่อมา: 20 mg/kg/dose วันละ 2 ครั้ง

Agrawal U, et al. Med J Armed Forces India. 2020 Oct; 76(4): 370–376.
Łagocka R, et al. J Clin Med. 2021 Jan 13;10(2):273.

Dosage regimen

- Ebola dose based on preclinical studies showing the target concentrations needed to inhibit the Ebola virus EC50: 67 mM (JIKI trial the predicted target concentrations could not be achieved when PK studies)
- Influenza EC50: 0.48 mM
- SARS-CoV-2 EC50: 61.88
- it is difficult to ascertain the basis on which the current dose

Table 1. Favipiravir (FPV) dosing regimens used in various viral infections in humans presented in the best documented clinical trials.

Type of Viral Diseases	FPV Dosage	References
Treatment of uncomplicated influenza Studies before drug registration	Low-dose regimen: Day 1: 2000 mg (1000 mg twice a day) Day 2–5: 800 mg (400 mg twice a day) High-dose regimen: Day 1: 2400 mg (1200 mg twice a day) Day 2–5: 1600 mg (800 mg twice a day)	[20]
	Day 1: 3600 mg (1800 mg twice a day) Day 2–5: 1600 mg (800 mg twice a day)	[21]
	Day 1: 3600 mg (1800 mg twice a day) Day 2–5: 1600 mg (800 mg twice a day)	[22]
The approved FPV dose for influenza in Japan	Day 1: 3200 mg (1600 mg twice a day) Day 2–5: 1200 mg (600 mg twice a day)	[19]
Treatment of severe influenza patients (combination therapy FPV and oseltamivir)	Day 1: 3200 mg (1600 mg twice a day) Day 2–5: 1200 mg (600 mg twice a day)	[23]
Treatment of Ebola virus disease (EVD)	Adults: Day 1: 6000 mg ((first dose: 2400 mg; second dose (8 h after the first dose): 2400 mg; third dose (8 h after the second dose) 1200 mg. Day 2–10: 2400 mg (1200 mg twice a day) Children: The dose was adapted according to body weight	[24]
	Day 1: 1600 mg (800 mg twice a day) Subsequent days, ranging from 3 to 11 days: 1200 mg (600 mg twice a day) until discharge, transfer, or death	[25]

Agrawal U, et al. Med J Armed Forces India. 2020 Oct; 76(4): 370–376.
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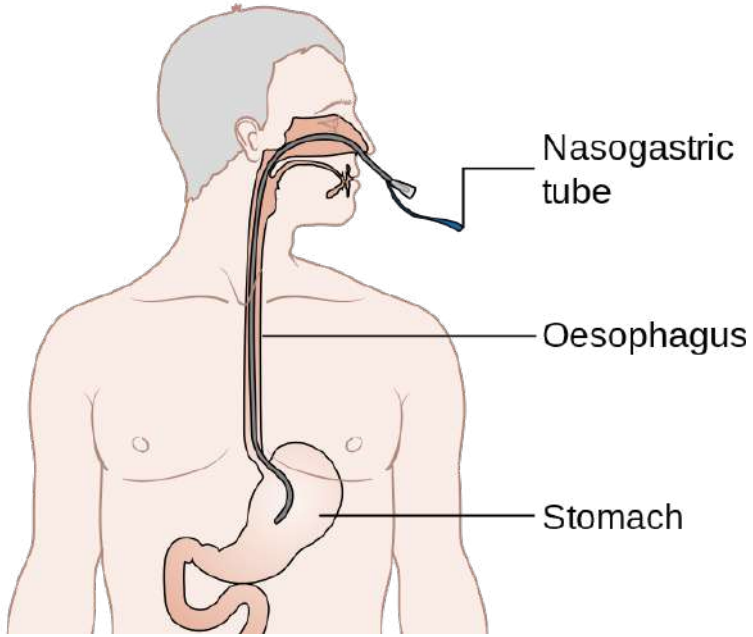
Table 1. Favipiravir (FPV) dosing regimens used in various viral infections in humans presented in the best documented clinical trials.

Type of Viral Diseases	FPV Dosage	References
Treatment of COVID-19 patients	Day 1: 3200 mg (1600 mg twice a day) Day 2–10: 1200 mg (600 mg twice a day)	[26]
	Day 1: 3200 mg (1600 mg twice a day) Day 2–14: 1200 mg (600 mg twice a day) plus interferon (IFN)-α by aerosol inhalation twice daily	[27]
	Day 1: 3600 mg (1800 mg twice a day) Day 2–14: 1600 mg (800 mg twice a day) plus standard supportive care	[28]
	Day 1: 3600 mg (1800 mg twice a day) Day 2 for a total of up to 19 doses over 10 days; 1600 mg (800 mg twice a day)	[29]
	The first dose was 1600 mg or 2200 mg orally, followed by 600 mg each time, three times a day, and the duration of administration was not more than 14 days.	[30]
	Day 1: 3200 mg (1600 mg twice a day) Day 2–14: 1200 mg (600 mg twice a day) or Day 1: 3600 mg (1800 mg twice a day) Day 2–14: 1600 mg (800 mg twice a day)	[31]



- Favipiravir (Toyama Chemical, 200-mg tablets that can be crushed and mixed with liquid) was given orally.

Critically Ill Patients

- P : Critically ill patients with PCR confirmed COVID-19 who were admitted to the ICU on mechanical ventilation and administered FPV tablets
- 1,600 mg of FPV twice on day 1, followed by 600 mg twice daily from day 2 to day 5
- The suspensions were prepared by dissolving FPV tablets in water at 55°C. The administration procedure was followed as instructed by the manufacturer and stability was confirmed.

Irie K, et al. Clin Transl Sci. 2020 Sep;13(5):880-885.

	Age	Sex	BMI	Clinical status after starting FPV with body temperature and PaO_2/FiO_2						
				Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14
Patient 1	78	Female	25.1	6 (37.4°C, 150)[b]	6 (37.7°C, 169)	6 (37.1°C, 193)	6 (37.7°C, 231)	4 (37.7°C, 299)	4 (36.9°C, 254)	3 (36.7°C, NE)
Patient 2	75	Male	NE	6 (38.0°C, 171)	6 (37.9°C, 166)	6 (37.0°C, 164)	6 (37.4°C, 175)	6 (38.4°C, 210)	6 (38.5°C, 201)	6 (37.6°C, 277)
Patient 3	75	Female	NE	6 (39.0°C, 134)	6 (38.7°C, 156)	6 (39.2°C, 178)	6 (38.9°C, 169)	6 (38.1°C, 154)	6 (37.7°C, 150)	6 (36.8°C, 150)
Patient 4	76	Male	19.0	4 (39.5°C, 143)	6 (38.9°C, 190)	6 (38.5°C, 227)	6 (38.6°C, 214)	6 (39.2°C, 196)	6 (38.5°C, 264)	3 (36.6°C, NE)
Patient 5	66	Male	27.6	4 (39.2°C, 115)	6 (39.3°C, 152)	6 (39.7°C, 140)	6 (38.7°C, 178)	6 (39.0°C, 235)	6 (39.7°C, 113)	6 (38.4°C, 198)
Patient 6	41	Male	29.9	6 (38.6°C, 89)	6 (38.2°C, 210)	6 (38.9°C, 134)	6 (39.5°C, 74)	6 (39.8°C, 77)	6 (38.6°C, 124)	4 (37.4°C, 214)
Patient 7	66	Male	NE	6 (38.8°C, 113)	6 (39.8°C, 130)	6 (39.2°C, 99)	6 (38.2°C, 124)	6 (38.3°C, 109)	6 (38.0°C, 106)	6 (40.0°C, 232)

Clinical status (seven-category ordinal scale); (1) non-hospitalization, no limitation of activities; (2) non-hospitalization, limitation of activities; (3) hospitalization, not-required oxygen; (4) hospitalization, required oxygen by mask or nasal prongs; (5) hospitalization, required noninvasive ventilation and/or high-flow oxygen; (6) hospitalization, required oxygen (invasive) and/or extracorporeal membrane oxygenation; and (7) death.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; FPV, favipiravir; NE, not evaluated; SCr, serum creatinine.

[a]Days from COVID-19 diagnosis, Hospitalization, or admission to intensive care unit up to FPV initiation.

[b]Best score of clinical status (highest body temperature, lowest PaO_2/FiO_2) at each day.

Irie K, et al. Clin Transl Sci. 2020 Sep;13(5):880-885.

- FPV trough (after 12 hours) concentration in healthy subjects was 20–60 μg/mL

Table 2 Favipiravir serum concentration in severely ill patients with COVID-19

	FPV concentration, μg/mL																	
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9		Day 10	
	1,600 mg	1,600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg
Patient 1	< 1.0 (8 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (12 hours)		< 1.0 (10 hours)		< 1.0 (11 hours)		2.7 (10 hours)		NA		NA		NA	
Patient 2	2.5 (8 hours)		1.2 (12 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (9 hours)		NA		NA		NA		NA		NA	
Patient 3	3.9 (10 hours)		5.5 (12 hours)		1.7 (11 hours)		2.4 (10 hours)		3 (9 hours)		NA		NA		NA		NA		NA	
Patient 4[a]		45.6, 38.8, 34.0 (8, 9, 10 hours)		17.4, 16.8 (10, 10.3 hours)		8.8 (13 hours)		5.3 (9 hours)		2.4 (11 hours)	NA		NA		NA		NA		NA	
Patient 5[a]		41.6 (6 hours)	25.8 (6 hours)	5.6 (11 hours)		< 1.0 (11 hours)		2.8, < 1.0 (5, 11 hours)		< 1.0 (10 hours)	NA		NA		NA		NA		NA	
Patient 6	< 1.0 (12 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (11 hours)		< 1.0 (12 hours)		< 1.0 (10 hours)		< 1.0 (12 hours)		< 1.0 (12 hours)	
Patient 7	< 1.0 (1 hours)	23 (9 hours)		3 (12 hours)		< 1.0 (10 hours)		< 1.0, < 1.0 (10, 12 hours)		< 1.0 (11 hours)	NA		NA		NA		NA		NA	

() indicates blood sampling time after administration.
COVID-19, coronavirus disease 2019; FPV, favipiravir; NA, not applicable.
[a]FPV (1,600 mg) was taken twice orally on day 1.

half-maximal effective concentration (9.7 μg/mL)

Irie K, et al. Clin Transl Sci. 2020 Sep;13(5):880-885.

Critically Ill Patients

- Outcome
- 1 of 7 patients (14.3%) showed improvement and was weaned from mechanical ventilation 7 days after starting FPV.
- 3 of 7 patients (42.9%) improved and were weaned from mechanical ventilation after 14 days
- 2 patients (28.6%) did not require oxygenation after 14 days.
- Mild aspartate aminotransferase increase was observed in patient 5 as an adverse event related to FPV, but multiple other drugs were suspected to cause this event.

Irie K, et al. Clin Transl Sci. 2020 Sep;13(5):880-885.

Renal dysfunction

- In the global phase III study, no patients with eGFR < 30 mL/min were included
- No PK data about the group of patients with eGFR 50–80 mL/ min
- CKD : no data , Plasma concentrations are increased around 1.3-2.5 fold in patients with renal insufficiency
  - Phase III trial (not COVID-19) rate of ADR 43.4% in mild renal impairment, 30.3% normal renal function
- ESRD : no data possibility of adverse events caused by accumulation of M1 should be considered, favipiravir increases uric acid levels in urine, which should be further investigated in patients with renal impairment
- PD : no data

Marra, F., Smolders, E.J., El-Sherif, O. *et al.* Recommendations for Dosing of Repurposed COVID-19 Medications in Patients with Renal and Hepatic Impairment. *Drugs R D* (2020).

Kodhi E, et al. CEN Case Rep. 2021 Feb; 10(1): 126–131

Renal dysfunction

- IHD : clinical data is lacking regarding clearance by dialysis.
- molecular weight 157 Da
- PB 54%
- Vd ~20 L
- >>>suggesting that dialysis would eliminate
- case report 1 : 3600 mg loading dose followed by 1600 mg administered orally daily in two divided doses >> effective, no documented side effect

Kodhi E, et al. CEN Case Rep. 2021 Feb; 10(1): 126-131

Renal dysfunction

- Case report 2
- A 72-year-old man, IHD 2-3
- half-maximal effective concentration of favipiravir against SARS-CoV-2 infection is 9.7 μg/mL, but blood concentrations after day 9 were all below this level
- sudden clinical deterioration and died

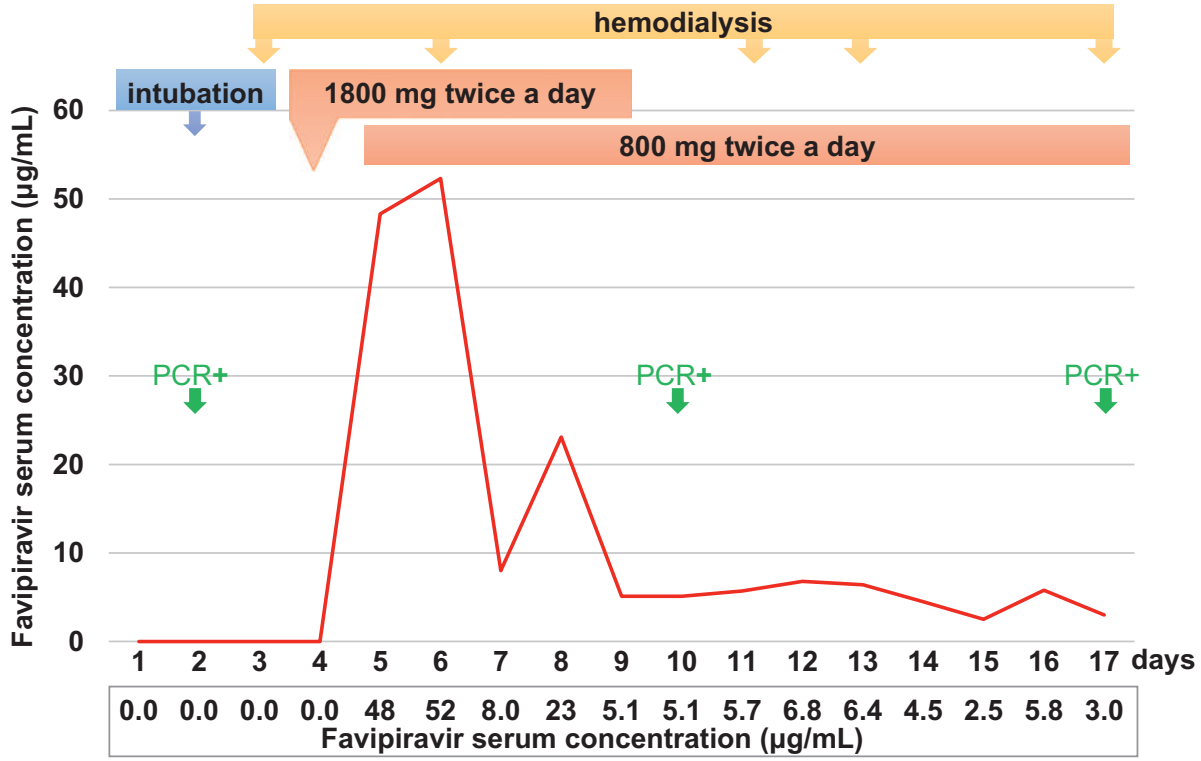


Figure 1. Blood concentrations of favipiravir. Hemodialysis was performed on days 3, 6, 11, 13, and 17. Abbreviation: PCR, polymerase chain reaction.

Hiral D, et al AJKD Vol 77 2021

CRRT ECMO

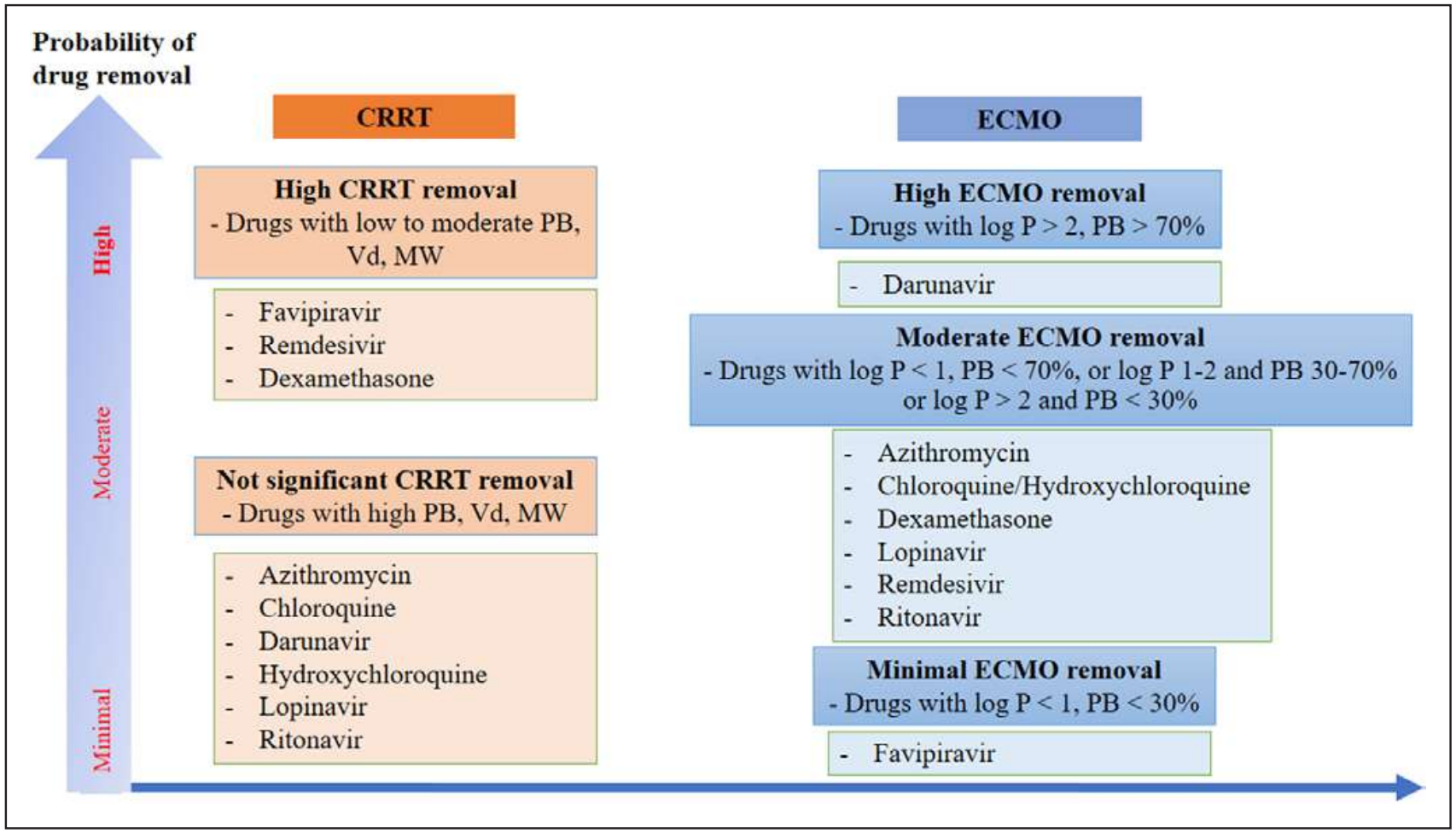


Figure 1. Probability of drug removal via extracorporeal therapy based on physicochemical properties and pharmacokinetic variables. CRRT = continuous renal replacement therapy, ECMO = extracorporeal membrane oxygenation, MW = molecular weight, PB = protein binding, Vd = volume of distribution.

Chaijamorn, W., et al., Antiviral Dosing Modification for Coronavirus Disease 2019–Infected Patients Receiving Extracorporeal Therapy. Critical Care Explorations, 2020. 2(10): p. e0242.

Favipiravir dose for CRRT

Case report 62-year-old man BW 67 kg
Diagnosis influenza virus type A pneumonia
Multi-organ failure with ARDS and cardiomyopathy

4th day of ICU admission the patient developed AKI (eGFR <20 ml/min/1.73 m2) necessitating CVVH
Favipiravir 1,800 mg orally twice daily on day 1 followed by 400 mg orally twice daily for 4 days

Table 1. Pharmacokinetic parameters of favipiravir

Route	Time	D, mg	C_{max}, µg/ml	AUC, µg•h/ml	t_{max}, h	$t_{1/2}$, h	CL/F, l/h	V_d/F, l
Healthy volunteers [2]								
Oral	First day	400	16.59	39.41	0.25–0.75	1.6	10.15	23.4
Oral	First day	1,600	59.43	397.79	0.5–1.5	4.6	4.02	26.7
Oral	First day	2,400	92.17	1,297.56	0.75–3	4.5	1.85	12.0
Oral	Steady state	400 BID	30.56	193.69	0.5–2	4.5	2.07	13.4
Oral	Steady state	600 BID	61.50	470.53	0.5–1.5	5.8	1.28	10.7
Patient case								
Oral	Steady state	400 BID	4.43	8.90	0.21	1.28	44.95	83.17

Healthy volunteers t_{max} data presented as lowest and highest value within the group. AUC, area under the curve; BID, twice daily, C_{max}, maximum plasma concentration; D, dose; t_{max}, time to maximum plasma concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total clearance after oral administration; V_d/F, apparent volume of distribution.

Favié LM, et al. Pharmacokinetics of favipiravir during continuous venovenous haemofiltration in a critically ill patient with influenza. Antivir Ther. 2018;23(5):457-461.

TABLE 2. Drug Dosing Suggestions of Selected Antiviral Agents of Coronavirus Disease 2019 Infection Treatment for Critically Ill Patients Receiving Continuous Renal Replacement Therapy and Extracorporeal Membrane Oxygenation

Drugs	Literature-Based Dosing Regimens (2, 20, 21)	CRRT	Extracorporeal Membrane Oxygenation
Azithromycin	500 mg on day 1 followed by 250 mg/d for the next 4 d	No dosage adjustment necessary	No dosage adjustment necessary
Chloroquine	500 mg q 12 hr × 7 d	No dosage adjustment necessary	Increased dosage may be required
Darunavir	600 mg q 12 hr with ritonavir	No dosage adjustment necessary	Increased dosage may be required and may increase up to 800 mg q 12 hr
Dexamethasone	6 mg daily × 10 d	May increase daily dose by 110%	Increased dosage may be required
Favipiravir	1,600 mg q 12 hr on day 1 followed by 600 mg q 12 hr × 7–10 d	No dosage adjustment necessary and may increase when high volume CRRT is required	No dosage adjustment necessary
Hydroxychloroquine	400 mg q 12 hr on day 1 followed by 200 mg q 12 hr × 5 d or 200 mg q 8 hr × 10 d	No dosage adjustment necessary	Increased dosage may be required
Lopinavir	400 mg q 12 hr × 14 d with ritonavir	No dosage adjustment necessary	Increased dosage may be required
Remdesivir	200 mg IV loading dose, then 100 mg IV daily for 5–10 d	No dosage adjustment necessary and may increase when high volume CRRT is required	Increased dosage may be required
Ritonavir	100 mg q 12 hr × 14 d	No dosage adjustment necessary	Increased dosage may be required

CRRT = continuous renal replacement therapy.

Chaijamorn, W., et al., Antiviral Dosing Modification for Coronavirus Disease 2019–Infected Patients Receiving Extracorporeal Therapy. Critical Care Explorations, 2020. 2(10): p. e0242.

Liver dysfunction

- There was a roughly 2.1 fold rise and 6.3 fold rise in the Cmax and AUC, respectively, when favipiravir was given to patients with severe liver dysfunction (Child-Pugh classification C) compared to healthy participants, which warrants a cautious use of favipiravir in patients with liver dysfunction.

Children

Neonate

0-1 mo

Infant

1 mo -1 yr

- ควรระวังการใช้ยา favipiravir ในผู้ป่วยเด็กอายุน้อยกว่า 12 เดือน เนื่องจากการพัฒนาเอนไซม์ aldehyde oxidase ที่ใช้ในการ metabolize favipiravir ยังไม่สมบูรณ์ หากมีความจำเป็นต้องใช้ยา favipiravir ในผู้ป่วยกลุ่มนี้ บุคลากรทางการแพทย์ต้องคุยความเสี่ยงและประโยชน์ที่จะได้รับกับผู้ปกครอง

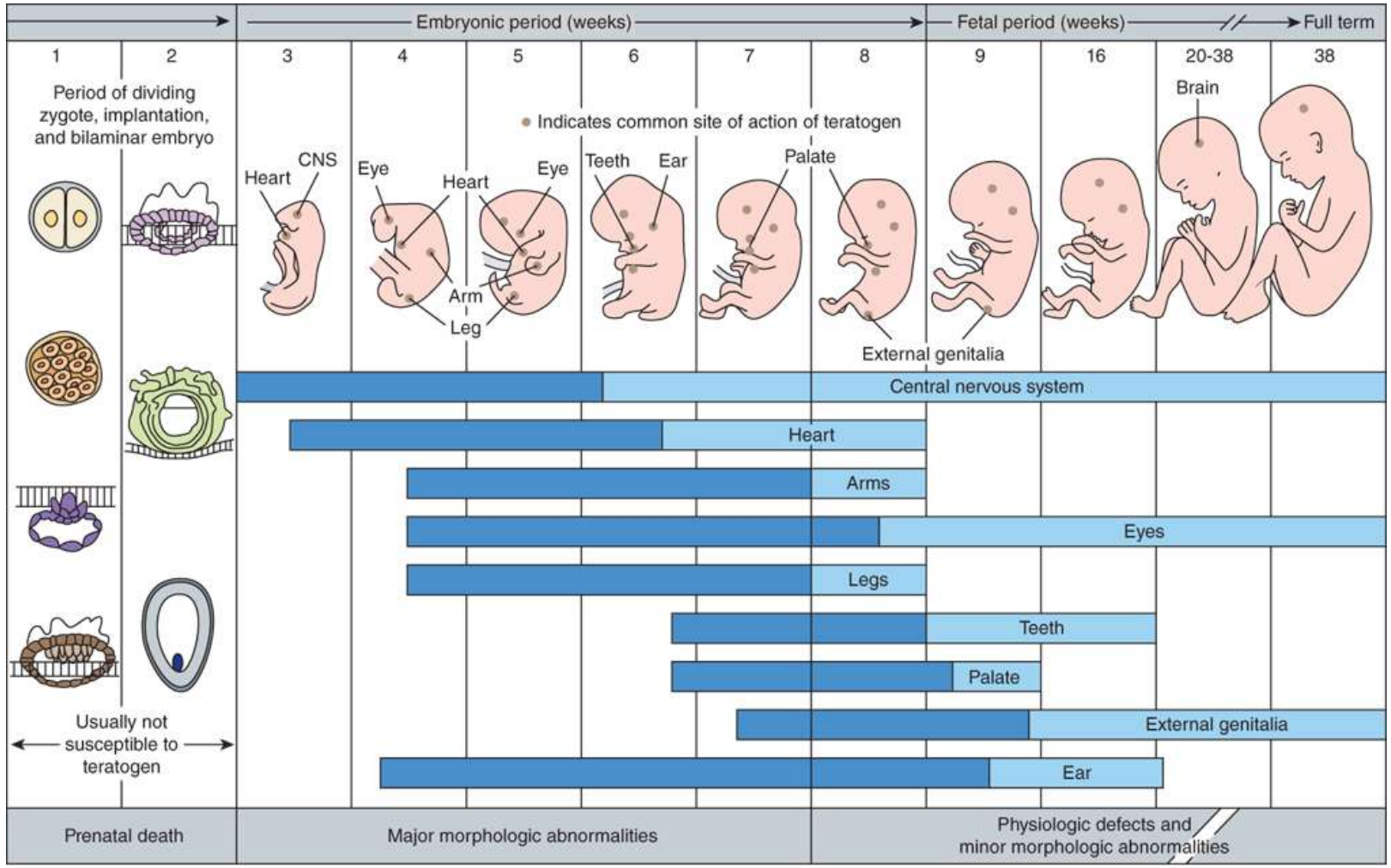
Bouazza N, et al. Favipiravir for children with Ebola. Lancet. 2015;385(9968):603–604.

Pregnancy

- Early embryonic deaths [rats] and teratogenicity [monkeys, mice, rats and rabbits] have been observed in animal studies with exposure levels similar to or lower than the clinical exposure.
  - When administering AVIGAN to women of child-bearing potential, confirm a negative pregnancy test result before starting the treatment. Explain fully the risks and instruct thoroughly to use most effective contraceptive methods with her partner during and for 7 days after the end of the treatment
  - AVIGAN is distributed in sperm the drug to male patients, explain fully the risks and instruct thoroughly to use most effective contraceptive methods in sexual intercourse during and for 7 days after the end of the treatment (men must wear a condom). In addition, instruct not to have sexual intercourse with pregnant women
- งานวิจัยแบบ Randomized controlled trial ส่วนใหญ่ได้คัดกลุ่มประชากรกลุ่มเด็กและหญิงตั้งครรภ์ออกทำให้มีข้อมูลการใช้ยาในการรักษาสำหรับประชากรกลุ่มดังกล่าวจำกัด

AVIGAN® (favipiravir) 200 mg [prescribing information]. Tokyo, Japan: Toyama Chemical Co Ltd; January 2017.

การใช้ favipiravir ในหญิงตั้งครรภ์ตามคำแนะนำ Thai CGP 28 Jan 2021



- หญิงตั้งครรภ์ตั้งแต่ไตรมาสที่ 1 ที่อาการไม่รุนแรง ไม่มีปอดอักเสบ ให้รักษาตามอาการ
- หญิงตั้งครรภ์ตั้งแต่ไตรมาสที่ 2 ขึ้นไป ถ้าแพทย์พิจารณาแล้วว่าจะได้ประโยชน์จาก favipiravir มากกว่าความเสี่ยง อาจจะพิจารณาใช้favipiravir โดยมีการตัดสินใจร่วมกับป่วยและญาติ
- หญิงตั้งครรภ์ทุกไตรมาสที่มีปอดอักเสบ อาจพิจารณาใช้ remdesivir เนื่องจากมีข้อมูลความปลอดภัยของการใช้ remdesivir ในหญิงตั้งครรภ์จานวนหนึ่งและไม่มีรายงานผลรายในทารก ทั้งนี้เพื่อให้สอดคล้องกับข้อบ่งชี้ที่ว่า remdesivir จะให้ประโยชน์เฉพาะในผู้ที่มีปอดอักเสบและต้องใช้ออกเจนรักษาเท่านั้น

Lactation

- stop lactating while administering AVIGAN
- (The major metabolite of AVIGAN, a hydroxylated form, was found to be distributed in breast milk.)

Adverse drug reaction

	≥ 1%	0.5 - < 1%	< 0.5%
Hypersensitivity		Rash	Eczema, pruritus
Hepatic	AST (GOT) increased, ALT (GPT) increased, γ-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal	Diarrhoea	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hematologic	Neutrophil count decreased, white blood cell count decreased	Glucose urine present	White blood cell count increased reticulocyte count decreased, monocyte increased
Metabolic disorders	Blood uric acid increased 4.79%), Blood triglycerides increased		Blood potassium decreased
Respiratory			Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Others			CPK increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo,

Fig. 3 – Figure depicting adverse effects of favipiravir (source: Fabiflu monograph).

Table 2 Adverse Drug Events Suspected to Be Caused by Favipiravir, as Reported in the WHO Database (N=93)

Adverse Drug Events	Frequency
Intentional product use issue	65 (69.89)
Hepatic enzyme increased	22 (23.66)
Nausea and Vomiting	13 (13.98)
Tachycardia	9 (9.68)
Diarrhoea	7 (7.52)
Electrocardiogram QT prolonged	5 (5.37)
Headache	5 (5.37)
Pruritus	5 (5.37)
Rash	5 (5.37)
Erythema	4 (4.30)
Hepatotoxicity	4 (4.30)
Thrombocytopenia	4 (4.30)
Bradycardia	3 (3.22)
Abdominal pain	2 (2.15)
Abdominal pain upper	2 (2.15)
Constipation	2 (2.15)
Hypotension	2 (2.15)
Rash maculopapular	2 (2.15)
Anemia	2 (2.15)
Acute kidney injury	1 (1.07)
Arthritis	1 (1.07)
Asthenia	1 (1.07)
Atrial fibrillation	1 (1.07)
Bronchospasm	1 (1.07)
Colitis	1 (1.07)
Cough	1 (1.07)
Cystic fibrosis	1 (1.07)
Death	1 (1.07)
Dizziness	1 (1.07)
Dyspnoea	1 (1.07)
Hemorrhage	1 (1.07)
Hair color changes	1 (1.07)
Hepatic function abnormal	1 (1.07)
Hyperglycaemia	1 (1.07)
Hypersensitivity	1 (1.07)
Hypertension	1 (1.07)
Leukopenia	1 (1.07)
Muscle contractions involuntary	1 (1.07)
Musculoskeletal pain	1 (1.07)
Nail discoloration	1 (1.07)
Palpitations	1 (1.07)
Purpura	1 (1.07)
Pyrexia	1 (1.07)
Respiratory distress	1 (1.07)
Rhabdomyolysis	1 (1.07)
Seizure	1 (1.07)
Syncope	1 (1.07)
Urticaria	1 (1.07)
Vasculitis	1 (1.07)
Visual impairment	1 (1.07)

Kaur RJ, et al. Infect Drug Resist. 2020;13:4427-4438

Table 1. Summary of the characteristics of all studies identified as providing evidence of the safety of the use of favipiravir in humans. Trials are organised into those phase 2 and 3 studies reporting safety data, trials with further safety evidence, studies for which results were inaccessible (grey) and ongoing trials (blue)

32 studies; 1200 mg per day ()

	Study	Author (Date) (Source)	Disease	*n*	PYFU	comparison	Study type	Country	Further findings on FPV
Phase 2+ controlled studies reporting safety data	**Chen *et al.*** (6)	Chen *et al.* (2020)	COVID-19	236	6.47	Umifenovir	Open label RCT	China	↑ uric acid
	Cai *et al.* (8)	Cai *et al.* (2020)	COVID-19	80	2.19	LPV/r	Open label	China	
	US213B/316/317	Unpublished (Correspondence)	Influenza	2547	146.54	Placebo	Phase 3 RCT	USA	↑ uric acid
	NCT01068912 (15)	Unpublished (ClinicalTrials.gov)	Influenza	518	7.10	Placebo	Dose ranging study	USA, Chile, NZ, Peru, SA	↑ uric acid
	JP205 (14)	Unpublished (PMDA Japan)	Influenza	160	2.19	Oseltamivir	Phase 2	Japan	↑ total AE ↑ GI AE
	JPKT312 (14)	Unpublished (PMDA Japan)	Influenza	758	10.38	Oseltamivir	Phase 3	Japan, Korea, Taiwan	↑ uric acid
	Wang *et al.* (9)	Wang *et al.* (2019)	Influenza	168	12.89	Oseltamivir	Mixed Regimen	China + Japan	
	QT study (10)	Kumagai *et al.* (2015)	Healthy	56	0.31	Placebo	Phase 1	Japan	
	JP101 (14)	Unpublished (PMDA Japan)	Healthy	48	0.13	Placebo	Phase 1	Japan	↑ triglycerides ↑CCK
	JP102 (14)	Unpublished (PMDA Japan)	Healthy	12	0.23	None	Phase 1	Japan	↑ lymphocytes ↑bilirubin ↑TGs
	JP103 (14)	Unpublished (PMDA Japan)	Healthy	24	0.46	Placebo	Phase 1	Japan	↑uric acid ↑TGs ↑CCK
	JP104 (14)	Unpublished (PMDA Japan)	Healthy	16	0.04	Placebo	Phase 1	Japan	↓CCK ↑TGs
	JP106 (14)	Unpublished (PMDA Japan)	Healthy	16	0.22	Placebo	Phase 1	Japan	↑ uric acid

Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic? Journal of Virus Eradication. 2020;6(2):45-51.

Study	Author (Date) (Source)	Disease	*n*	PYFU	comparison	Study type	Country	Further findings on FPV
JP107 (14)	Unpublished (PMDA Japan)	Healthy	16	0.22	Placebo	Phase 1	Japan	↓ albumin
JP108 (14)	Unpublished (PMDA Japan)	Healthy	10	0.68	None	Phase 1	Japan	↑ uric acid
JP109 (14)	Unpublished (PMDA Japan)	Healthy	10	0.47	Oseltamivir	Phase 1	Japan	
JP110 (14)	Unpublished (PMDA Japan)	Healthy	24	0.07	None	Phase 1	Japan	↑ bilirubin ↑APTT
JP111 (14)	Unpublished (PMDA Japan)	Healthy	12	0.23	Placebo	Phase 1	Japan	↑ uric acid
JP114 (14)	Unpublished (PMDA Japan)	Healthy	16	0.61	None	Phase 1	Japan	↓CCK
JP115 (14)	Unpublished (PMDA Japan)	Healthy	68	2.61	Placebo	Phase 1	Japan	
JP313 (14)	Unpublished (PMDA Japan)	Influenza	16	0.22	None	Phase 3 open label	Japan	↑ uric acid
US105 (14)	Unpublished (PMDA Japan)	Healthy	116	1.59	Placebo	Phase 1	USA	
US101/2 (14)	Unpublished (PMDA Japan)	Healthy	48	0.13	Placebo	Phase 1	USA	
US103 (10)	Unpublished (PMDA Japan)	Healthy	16	0.22	Placebo	Phase 1	USA	
US103b (10)	Unpublished (PMDA Japan)	Healthy	32	0.44	Placebo	Phase 1	USA	↑ uric acid
Kerber ***et al.*** (11)	Unpublished (PMDA Japan)	Ebola	163	13.40	None	Observational	Guinea	Distorted by baseline organ dysfunction
Bai ***et al.*** (12)	Bai *et al.* (2016)	Ebola	124	10.19	None	Case series	Sierra Leone	Distorted by baseline organ dysfunction
JIKI Trial (13)	Sissiko *et al.* (2016)	Ebola	99	2.44	None	Phase 2 - single arm	Guinea	Distorted by baseline organ dysfunction
Fever Study	Unpublished (Correspondence)	Fever	23		Standard care	Single arm	Japan	

Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic? Journal of Virus Eradication. 2020;6(2):45-51.

Table 2. Summary of the safety data extracted from the six phase 2 and 3 controlled studies with adverse event reporting. Extracted data for six reported safety endpoints is displayed for each included study

STUDY	Disease /Drugs	PYFU	Grade 1–4 AE		DcAE		SAE		GI AE		LFT elevations		Uric acid elevations	
			Favipiravir	Comparator	Favipiravir	Comparator	Favipiravir	Comparator	Favipiravir	Comparator	Favipiravir	Comparator	Favipiravir	Comparator
			Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)	Events /Total (%)
Chen *et al.* (6)	COVID -19 FPV *vs* Umifenovir	6.47	37/116 (31.9)	28/120 (23.3)					16/116 (13.8)	14/120 (11.7)	9/116 (7.8)	12/120 (10.0)	16/116 (13.8)	3/120 (2.5)
Cai *et al.* (8)	COVID -19 FPV *vs* LPV/r	2.19	4/35 (11.4)	25/45 (55.6)					2/35 (5.7)	16/45 (35.6)				
US213B/316/317 (20,21)	Influenza FPV *vs* Placebo	147	419/1653 (25.3)	227/894 (25.4)	18/1653 (1.1)	10/894 (1.1)	5/1653 (0.3)	4/894 (0.4)	122/1653 (7.4)	75/894 (8.4)	31/1653 (1.9)	11/894 (1.2)		
NCT01068912 (15)	Influenza FPV *vs* Placebo	7.10	114/321 (35.5)	80/197 (40.6)			2/321 (0.6)	1/197 (0.5)	39/321 (12.1)	34/197 (17.3)	3/321 (0.9)	6/197 (3.0)	10/321 (3.1)	5/197 (2.5)
JP205 (14)	Influenza FPV *vs* Oseltamivir	2.19	42/107 (39.9)	23/53 (43.4)	3/107 (2.8)	2/53 (3.8)	2/107 (1.9)	0/53 (0.0)	20/107 (18.7)	14/53 (26.4)				
JPKT312 (14)	Influenza FPV *vs* Oseltamivir	10.38	120/378 (31.7)	96/380 (25.3)	2/378 (0.5)	4/380 (1.1)	1/378 (0.3)	1/380 (0.3)	29/378 (7.7)	42/380 (11.1)			21/378 (5.6)	1/380 (0.3)
Total (Average)			736/2610 (28.2)	479/1689 (28.4)	23/2138 (1.1)	16/1327 (1.2)	10/2459 (0.4)	6/1524 (0.4)	228/2610 (8.7)	195/1689 (11.5)	43/2090 (2.1)	29/1211 (2.4)	47/815 (5.8)	9/697 (1.3)

AE: adverse events; DcAE: discontinuations due to adverse events; SAE: serious adverse events; GI: gastrointestinal; FPV: favipiravir; LFT: liver function tests; LPV/r: lopinavir /ritonavir; PYFU: person-years-of-follow-up.

Serious ADEs were more common among those aged 64 and above than those aged below 64 (48% vs 26%, respectively)

Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic? Journal of Virus Eradication. 2020;6(2):45-51.

Drug interaction

- Inhibited irreversibly AO in a dose and time dependent manner
- Inhibited CYP2C8 in a dose dependent manner
- no inhibitory activity to XO
- Weakly inhibited :
  - CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 {active drug}
  - CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 {hydroxylated metabolite}

Drug interactions

- Favipiravir มีการเปลี่ยนสภาพที่ตับส่วนใหญ่ผ่านทางเอนไซม์ aldehyde oxidase (AO) และมีบางส่วนที่เปลี่ยนสภาพผ่านทางเอนไซม์ xanthine oxidase (XO) ไม่มีการเปลี่ยนสภาพโดยผ่าน CYP450 แต่มีความสามารถในการยับยั้ง CYP2C8 และ AO จึงต้องระวังการเกิดอันตรกิริยาระหว่างยา เช่น
- การใช้ร่วมกับยา Paracetamol ทำให้ระดับยา Paracetamol เพิ่มขึ้น แนะนำขนาดยา Paracetamol ไม่เกิน 3 กรัมต่อวัน
- Pyrazinamide: Concomitant use of pyrazinamide with favipiravir increases the levels of uric acid. เนื่องจากมีการดูดซึม uric acid กลับเพิ่มขึ้นที่ท่อหน่วยไต และผู้ป่วยโรคเก๊าท์ แนะนำการติดตามระดับ uric acid
- Repaglinide: Favipiravir inhibits the metabolism of repaglinide through the CYP2C8 pathway, thus increasing its potential to cause toxicity (hypoglycemia, headache, increase incidence of upper respiratory tract infections, etc). Cautious concomitant use is recommended.
- Theophylline: Theophylline increases the blood levels of favipiravir and adverse reactions to favipiravir may occur.
- Famciclovir, sulindac: Efficacy of these drugs may be reduced when coadministered with favipiravir.
- Acyclovir: Acyclovir may delay the conversion of favipiravir into the active moiety, thus reducing its antiviral efficacy.

Table 2 Inhibition of drugs and xenobiotics on human AO at 50 μM and the IC_{50} values

Drug	Indication or use	Percentage of control activity (mean ± SD)	IC_{50} (μM) (mean ± SE)
Raloxifene	Antiosteoporotic	<1.0	0.0029 ± 0.0003
Perphenazine	Antipsychotic	1.2 ± 0.2	0.033 ± 0.011
Thioridazine	Antipsychotic	7.1 ± 3.9	0.16 ± 0.07
Menadione	Prothrombogenic	4.1 ± 0.5	0.20 ± 0.04
Trifluoperazine	Antipsychotic	8.0 ± 1.9	0.24 ± 0.08
Amitriptyline	Antidepressant	9.4 ± 4.7	0.26 ± 0.07
Estradiol	Estrogen	7.4 ± 3.3	
Felodipine	Antihypertensive/anti-anginal	7.0 ± 5.4	
Clomipramine	Antidepressant	18 ± 6	
Loratadine	Antihistaminic	7.3 ± 1.4	
Promethazine	Antipsychotic	10 ± 3	
Chlorpromazine	Antipsychotic	3.1 ± 2.5	
Ethinyl estradiol	Oral contraceptive	6.2 ± 8.1	
Norclomipramine	Antidepressant	11 ± 2	
Amodiaquine	Antimalarial	11 ± 3	
Nortriptyline	Antidepressant	7.5 ± 0.7	

Potential Interaction

Favipiravir

Cimetidine

Quality of Evidence: Very Low

Summary:

Coadministration has not been studied. Cimetidine is primarily eliminated by the kidneys. Favipiravir is metabolised by aldehyde oxidase and cimetidine is known to inhibit this enzyme in vitro and to affect some aldehyde oxidase substrates in vivo. However, the clinical relevance of aldehyde oxidase inhibition for favipiravir remains to be established. Absorption of favipiravir is unlikely to be influenced by changes in gastric pH.

Description:

(See Summary)

Du, Y.-X. and Chen, X.-P. (2020), Clin. Pharmacol. Ther., 108: 242-247.

Back to the case…

Case: A 70 year-old Thai woman

- ผู้ป่วยหญิงไทยคู่ อายุ 70 ปี (สามารถใช้ชีวิตประจำวันได้ตามปกติ)
- TBW 94.5 kg , Ht 146 cm BMI 44.3 kg/m^2
- โรงพยาบาล 1 (9-15/1/64)
- CC: รู้สึกมีไข้เป็นๆ หายๆ ไอ มีเสมหะ มีน้ำมูก
- HPI:
  - 9 days PTA สัมผัสญาติที่เป็น confirmed case COVID-19
  - 1 day PTA กินได้ลดลง
- Underlying disease
  - T2DM (Last HbA1C 6.8%)
  - DLP
  - HT
  - ESRD (urine output 200-300 ml/day)

Case: A 70 year-old Thai female

- 9/1/64
- Lab
- DTX 27%, BUN 58, Scr 6.4 (baseline 3.6), Na 135, Cl 110, K 4.86, Ca 6.3, PO4 4.6, Alb 4.3, TB 0.2, DB 0.1, SGOT 30, SGPT 15, ALP 82
- Hb 10.2, Hct 30, WBC 7600 N 50%, L 6.4%, plt 221,000, INR 1.14
- Nasopharyngeal swab for SARS-Co-V_2 PCR positive
- 10/1/64
- CXR: reticular infiltration, cardiomegaly
- Echo EF 70%

Leading question from case study

- Does she need to receive and antiviral ? Which one ?

Adult

Symptomatic COVID-19
without pneumonia and
no risk factors for severe disease

FPV 5 d

- การให้ FPV ภายใน 4 วัน เป็นปัจจัยที่ลด high flow oxygenation, invasive ventilator, ICU admission, death
- ลดปริมาณไวรัสได้ดี
- ควรเริ่มยาก่อนที่ผู้ป่วยมีอาการหนัก **พิจารณาให้ FPV ในผู้ที่ มีอาการมาก หรือมีไข้ทุกคน**

Symptomatic COVID-19
with risk factors for severe disease
or having co-morbidity or mild pneumonia

FPV
5-10 d

Pneumonia with hypoxia (resting O2 saturation <96 % or exercise-induced hypoxemia positive (decreasing of SpO2 ≥3%) or progression of pulmonary infiltrates

FPV
5-10 d

LPV/r
5-10 d

Corticosteroid

- SpO2 <94% on room air
- non-invasive หรือ invasive ventilation
- ECMO

RDV

ข้อพิจารณาอื่น

- มีข้อห้ามในการบริหารยาทางปาก หรือมีปัญหาการดูดซึม
- ไม่ตอบสนองต่อยาอื่นภายใน 72 ชั่วโมง
- เลือกใช้ FPV หรือ RDV อย่างใดอย่างหนึ่ง

Risk factor

1. Age >60 yo, or < 1 yo
2. COPD, chronic lung disease
3. CKD
4. Cardiovascular disease, congenital heart disease
5. Cerebrovascular disease
6. Uncontrolled DM
7. Obesity BW > 90 kg
8. Cirrhosis
9. Immunocompromised patient
10. Lymphocyte <1,000 cells/mm^3

Drug dosing in obese adults

- BMI can be used as a guide and clinicians should start to reconsider drug dosing in patients with a BMI over 30
- Vd is important for determining the loading dose (LD)
  - Hydrophilic drugs typically remain in extracellular fluid and their Vd correlates with lean mass, should not be significantly influenced by excess adipose tissue
  - Lipophilic drugs volume of distribution is more likely to correlate with total body weight.
  - Drugs with a large volume of distribution often require loading doses followed by a constant dose rate to maintain steady-state plasma concentrations. Steady- state concentrations are dependent on drug clearance.
- CL is important to determine the maintenance dose
  - Clearance is correlated to lean rather than adipose weight as adipose tissue has little metabolic activity.

Barras M, Legg A. Drug dosing in obese adults. *Aust Prescr*. 2017;40(5):189-193. doi:10.18773/austprescr.2017.053

Lean : adipose weight ratio

4:1

Total body weight

Adipose weight (20%)

Lean weight (80%)

Normal weight

3:2

Adipose weight 40%)

Lean weight (60%)

Obese

Total body weight

(excess adipose weight 20-40%)

Body size descriptors used to calculate drug doses

	Total body weight	Lean body weight	Adjusted body weight	Body surface area	Ideal body weight
Issue to be consider	• we cannot assume that a 150 kg patient eliminates a drug twice as fast as a 75 kg • Arbitrary dose reductions or 'caps' are used to avoid these toxicities, but if too low can result in sub-therapeutic exposure and treatment failure.	• reflects the weight of all 'non-fat' body components • contributes to approximately 99% of a drug's clearance it is useful for guiding dosing in obesity • Cheymol's fomula	• mainly used for aminoglycosides • It was developed to account for adipose tissue, which does not affect drug clearance.	• function of weight • and height and has been shown to correlate with cardiac output, blood volume and renal function • it is controversial in patients at extremes of size because it does not account for varying body compositions \ • 'capped' (commonly at • 2 m2) potentially resulting in sub-therapeutic	• developed for insurance purposes not for drug dosing • does not consider body composition • generally, results in under-dosing

Lean body weight (kg)[15]

males $$\frac{9270 \times \text{TBW (kg)}}{6680 + 216 \times \text{BMI (kg/m}^2\text{)}}$$

females $$\frac{9270 \times \text{TBW (kg)}}{8780 + 244 \times \text{BMI (kg/m}^2\text{)}}$$

Barras M, Legg A. Drug dosing in obese adults. *Aust Prescr*. 2017;40(5):189-193. doi:10.18773/austprescr.2017.053

Leading question from case study

In case of disease progression after the treatment of favipiravir, what we should do next ?

Case: A 70 year-old Thai female

- 10/1/64 on O2 canula 3 LPM (SpO2 100%)
- Favipiravir (200) 8 tabs po q 12 h x 2 doses then 3 tabs po q 12 h (plan for 10 days)
- Dexamethasone 6 mg iv OD (10-14/1/64) then dexamethasone 10 mg iv q 8 h (14/1/64)
- On CVVH 12-13/1/64
- Ceftriaxone 2 g iv OD + azithromycin 250 mg 2 tabs po ac OD (11-13/1/64)
- 13/1/64 on mask with bag (SpO2 92-95%)>>HFNC FiO2 1.0 Flow 60 LPM
- 14/1/64 on ETT No 7.0 depth 22 cm PEEP due to ARDS Ventilator volume A/C RR 32 TV 350 flow 50 PEEP 18 FiO2 0.9 fentanyl (10:1) iv 10 ml/h , Midazolam (1:2) iv 4 ml/h, Cisatracurium (1:2) iv 8 ml/h
- Step up to meropenem 1 g iv q 8 h x 3 dose then 1 g iv q 24 h (14-15/1/64)

Case: A 70 year-old Thai female

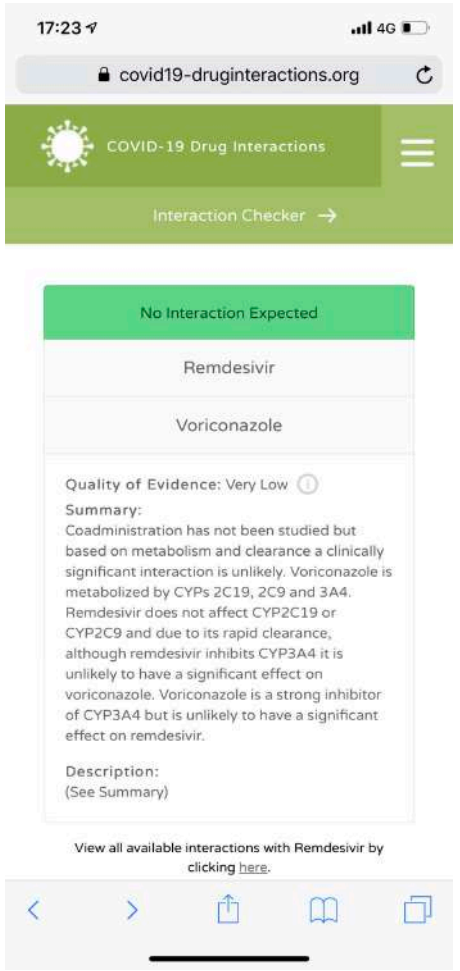
- 14/1/64 (โรงพยาบาล 1) Remdesivir 200 mg iv OD x1 dose
- ส่งต่อโรงพยาบาล 2
- Remdesivir 100 mg +NSS 100 ml iv drip in 1 h
- Meropenem 500 mg + NSS 50 ml iv drip in 3 g q 24 h
- Dexamethasone
- V/S BT 35.5, BP 140/67, E1V1VT QTc 409
- LAB :
- Hb 9.3, Hct 28.3, MCV 91, WBC 9420, N 92.2, L 5.4, Plt 232,000, INR 1.13
- BUN 74, Scr 3.8, TB 0.2, DB 0.1, SGOT 23, SGPT 14, Alb 3.3, Ca 7.5, PO4 5.7, Na 139, K 4.4, Cl104, HCO3 20
- 18/1/64 BUN 119, Scr 5.6 SLED 6 h

การใช้ยา Remdesivir ในโรงพยาบาลจุฬาลงกรณ์

ลำดับ	อายุ (ปี)	U/D	Duration (วัน)	Renal		Hepatic function						Blood	
				SCr		AST		ALT		ALP		Hb	
				ก่อน	หลัง	ก่อน	หลัง	ก่อน	หลัง	ก่อน	หลัง	ก่อน	หลัง
1	70	T2DM, DLP, HTN, CKD stage V (on SLED)	10	4.07	3.67	24	17	17	9	63	77	9.3	8.2
2	75	HTN, Thalassemia,	10	1.67	0.70	62	24	34	23	48	39	9.3	8.6
3	56	HTN	5	1.00	0.86	67	43	68	107	57	62	12.1	13.4
4	54	No U/D	8 (start 3/2/64-now)	0.72	0.67	37	42	25	48	58	78	13.3	12.4
5	67	HTN, poor control DM, DLP, Gout, CKD stage 3, Psoriasis	2 (start 10/2/64- now)	1.78	1.44	35	38	26	23	91	82	12.2	12.2

Pharmacist's role during COVID-19 pandemic

- Medication reconciliation
- Current drug reviewing for COVID-19 tx
- Consultant for dosing
- Consultant for drug interaction
- Consultant for monitoring ADRs
- Etc.



ข้อมูลยาสำหรับการรักษาโรคติดเชื้อไวรัสโคโรนา 2019 (COVID-19)

Drug	Favipiravir (Avigan®)	Remdesivir (COVIFOR)
Dosage form	200 mg film-coated tablet	100 mg/Vial Lyophilized,
Dose	Favipiravir 200 mg 8 เม็ด ทุก 12 ชั่วโมง x วันแรก หลังจากนั้น 3 เม็ด ทุก 12 ชั่วโมง **Higher dose:** 200 mg 9 เม็ด ทุก 12 ชั่วโมง x วันแรก หลังจากนั้น 4 เม็ด ทุก 12 ชั่วโมง	-อายุ 12 ปีขึ้นไปและมีน้ำหนักตัวอย่างน้อย 40 kg Loading dose: 200 mg ครั้งเดียวในวันที่ 1 Maintenance dose: 100 mg วันละ 1 ครั้ง ระยะเวลาในการรักษา: 5-10 วัน

Colorized scanning electron micrograph of a cell heavily infected with SARS-CoV-2 virus particles (yellow), isolated from a patient sample.

Thank you for your attention