

QUESTION

Should Favipiravir vs. Arbidol be used for patient with COVID-19 pneumonia ?

POPULATION:	patient with COVID-19 pneumonia
INTERVENTION:	Favipiravir
COMPARISON:	Arbidol
MAIN OUTCOMES:	Clinical recovery; Cough relief; Pyrexia relief; Adverse event (Hyperuricemia);
SETTING:	in hospital
PERSPECTIVE:	population
BACKGROUND:	
CONFLICT OF INTERESTS:	none

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably <input type="radio"/> Probably <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't	no yes know	no specific treatment exists for COVID-19.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Trivial <input checked="" type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't	know	<ul style="list-style-type: none"> ● 主要アウトカムである有益効果（臨床回復）は、臨床回復率（overall）＝HR 1.29 (0.68-2.43) ● 絶対効果として、91 more/1000 (124 few～314 more/1000) ● 中等症患者に限定して、臨床回復率を2値化して単純比較すると、著者が発表しているように統計的にも有意（RR= 1.28 ; 1.04-1.57）。 ● 有害アウトカム（高尿酸血症）は、5 more/1000 (1 few～11 more/1000)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't <p style="text-align: right;">know</p>	<ul style="list-style-type: none"> ● 主要アウトカムである有益効果（臨床回復）は、臨床回復率（overall）＝HR 1.29 (0.68-2.43) ● 絶対効果として、91 more/1000（124 few～314 more/1000） ● 中等症患者に限定して、臨床回復率を2値化して単純比較すると、著者が発表しているように統計的にも有意（RR= 1.28； 1.04-1.57）。 ● 有害アウトカム（高尿酸血症）は、5 more/1000（1 few～11 more/1000） 	死亡例はなし

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																								
<ul style="list-style-type: none"> ○ Very ● Low ○ Moderate ○ High ○ No <p style="text-align: right;">low</p> <p style="text-align: right;">included studies</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2">Outcomes</th> <th rowspan="2">Relative effect (95% CI)</th> <th colspan="3">Anticipated absolute effects* (95% CI)</th> <th rowspan="2">Certainty of the evidence (GRADE)</th> <th rowspan="2">What happens</th> </tr> <tr> <th>Without Favipiravir</th> <th>With Favipiravir</th> <th>Difference</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Clinical recovery assessed with: >72hr recovery of body temp, respiratory rate, O2 saturation, cough relief follow up: mean 7 days N_e of participants: 236 (1 RCT)</td> <td rowspan="3">HR 1.29 (0.68 to 2.43) [Clinical recovery]</td> <td colspan="3">Moderate</td> <td rowspan="3">⊕⊕○○ LOW^{a,b,c,d}</td> <td rowspan="3"></td> </tr> <tr> <td>50.0%</td> <td>59.1% (37.6 to 81.4)</td> <td>9.1% more (12.4 fewer to 31.4 more)</td> </tr> <tr> <td colspan="3">High</td> </tr> <tr> <td></td> <td></td> <td>70.0%</td> <td>78.8% (55.9 to 94.6)</td> <td>8.8% more (14.1 fewer to 24.6 more)</td> <td></td> <td></td> </tr> <tr> <td rowspan="2">Cough relief follow up: mean 7 days N_e of participants: 122</td> <td rowspan="2">HR 2.73 (1.75 to 4.27) [Cough relief]</td> <td colspan="3">High</td> <td rowspan="2">⊕⊕⊕○ MODERATE^{a,b,c}</td> <td rowspan="2"></td> </tr> <tr> <td>70.0%</td> <td>96.3% (87.8 to 99.4)</td> <td>26.3% more (17.8 more to 35.4 more)</td> </tr> </tbody> </table>	Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens	Without Favipiravir	With Favipiravir	Difference	Clinical recovery assessed with: >72hr recovery of body temp, respiratory rate, O2 saturation, cough relief follow up: mean 7 days N _e of participants: 236 (1 RCT)	HR 1.29 (0.68 to 2.43) [Clinical recovery]	Moderate			⊕⊕○○ LOW ^{a,b,c,d}		50.0%	59.1% (37.6 to 81.4)	9.1% more (12.4 fewer to 31.4 more)	High					70.0%	78.8% (55.9 to 94.6)	8.8% more (14.1 fewer to 24.6 more)			Cough relief follow up: mean 7 days N _e of participants: 122	HR 2.73 (1.75 to 4.27) [Cough relief]	High			⊕⊕⊕○ MODERATE ^{a,b,c}		70.0%	96.3% (87.8 to 99.4)	26.3% more (17.8 more to 35.4 more)	
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	(1 RCT)				29.4 more)		
	Pyrexia relief follow up: mean 7 days of participants: 145 (1 RCT)	HR 2.42 (1.55 to 3.77) [Pyrexia relief]	High	70.0%	94.6% (84.5 to 98.9)	24.6% more (14.5 more to 28.9 more)	⊕⊕⊕○ MODERATE ^{a,b,c}
	Adverse event (Hyperuricemia) follow up: mean 7 days of participants: 236 (1 RCT)	RR 1.19 (0.95 to 1.45)	Study population	2.5%	3.0% (2.4 to 3.6)	0.5% more (0.1 fewer to 1.1 more)	⊕⊕○○ LOW ^{a,b,c,e}
<p>a. Bias due to deviations from intended interventions (Cochrane RoB 2.0): High b. Bias arising from the randomization process (Cochrane RoB 2.0): Some concern c. No reason for missing cases (withdrew consent) d. 95%CI includes both no effect and appreciable important benefit e. 95%CI includes both no effect and harm (may not be exceeding MID)</p>							

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input checked="" type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability	高尿酸血症は、5/1000（最悪 11/1000）であり、臨床回復と比較すると、その価値観は非常に低いだろう	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

<ul style="list-style-type: none"> ● Favours the comparison ○ Probably favours the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favours the intervention ○ Varies ○ Don't know 	benefits>>harm	対象患者は、中等症 COVID-19 肺炎患者である。診断は臨床的診断で、PCR 検査陽性は 40～50%
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Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know 		

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies 		

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input checked="" type="radio"/> Don't know 		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	18歳未満、肝障害 child-pugh(C)、HIV、妊婦、COVID 重症患者は除外	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes 		

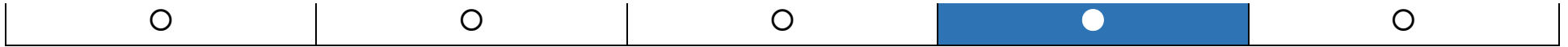
<ul style="list-style-type: none"> ● Yes ○ Varies ○ Don't know 	know		
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SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
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CONCLUSIONS

Recommendation

18 歳以上の中等症 COVID-19 患者に対して、アビガンの使用を提案する (GRADE 2C)

Justification

- 1.有益効果（臨床回復）は、絶対効果として、91 more/1000（124 few～314 more/1000）
- 2.害は高尿酸血症で、1/1000
- 3.CoE=Low

Subgroup considerations

重症例には効果なし。

Implementation considerations

COVID-19 診断に関して感染初期の PCR における偽陰性を考慮すると、入院を必要とする COVID-19 臨床診断患者には PCR 検査の結果にかかわらず、（標準治療でも改善される可能性を説明しつつ）アビガンを 1 週間投与することを考慮すべきだろう。

Monitoring and evaluation

Research priorities

More research is needed to understand the effects of favipiravir on COVID-19
海外においてメタアナリシスが計画されている