Anti-Coronavirus Therapies (ACT) trials

Colchicine and Aspirin in community patients with COVID-19

An open-label, factorial, randomized trial

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The problem

- Estimated 3.8 billion people infected and 18 million deaths by end 2021
- Health care systems overwhelmed
- Existing treatments incompletely effective, often expensive
- Vaccination not readily accessible in many countries
 - Widely-applicable treatments needed for patients
 with mild, moderate, severe disease



Targets: inflammation & hypercoagulability



ESC CONGRESS 2022 Barcelona & Online Godoy LC, et al. CMAJ 2020; 92 (40) E1156-E1161





Objectives of the ACT trial program

To determine in patients with symptomatic, laboratory confirmed COVID-19 whether:

- **1**. Anti-inflammatory therapy with colchicine
- 2. Antithrombotic therapy with aspirin (mild disease) or the combination of rivaroxaban and aspirin (moderate or severe disease)

can prevent disease progression or death across the spectrum of disease severity.



Outpatient trial design (mild disease)



Primary outcomes

Colchicine: hospitalization or death

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Aspirin: Major thrombosis, hospitalization or death



Eligibility

Inclusion

- Symptomatic, laboratory-confirmed COVID-19
- Age ≥30 years
- High risk*
- Within 7 days of diagnosis or worsening clinically Exclusion:
- Advanced kidney or liver disease
- Pregnancy (known or potential) or lactation.
- Allergy or planned use of study interventions

*One or more of age ≥70, male, BMI ≥30, chronic disease, active cancer, diabetes **ESC CONGRESS 2022** Barcelona & Online

Country recruitment (n=3,917)



Region	Country	Ν
Middle East	Egypt	1,971
	UAE	70
Eurasia	Russia	614
North America	Canada	354
South Asia	Nepal	317
	Philippines	129
	India	77
	Pakistan	8
South America	Colombia	181
	Brazil	122
	Ecuador	74

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Baseline characteristics

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Characteristic	Colchicine (n=3,917)		Aspirin (n= 3,917)		
Randomized, n	1,956	1,961	1,964	1,953	
Age, mean (SD)	45.0 (13.7)	45.0 (13.3)	45.2 (13.5)	44.9 (13.4)	
Males, n (%)	1,173 (60.5%)	1,177 (60.6%)	1,195 (61.4%)	1,155 (59.7%)	
Diabetes, n (%)	256 (13.2%)	264 (13.6%)	247 (12.7%)	273 (14.1%)	
Hypertension, n (%)	435 (22.4%)	422 (21.7%)	440 (22.6%)	417 (21.5%)	
Fully vaccinated	419 (21.6%)	402 (20.7%)	425 (21.9%)	396 (20.5%)	



Adherence and completeness of follow-up

Adherence = take ≥80% of interventions at 45 days Follow up = for primary outcome

Colchicine:

- Adherence: 89.1%
- Follow up: 99.7%

Aspirin:

- Adherence: 90.0%
- Follow up: 99.7%





Colchicine: hospitalization or death





Colchicine: key subgroups

					P value
Group	Colchicine	Control	Hazard Ratio	HR (95% CI)	(interaction)
Randomized Overall	1939	1942			
Overall	66/ 1939 (3.4%)	65/ 1942 (3.3%)		1.02 (0.72-1.43)	0.55
Sex Male Female	43/ 1173 (3.7%) 23/ 766 (3.0%)	39/ 1177 (3.3%) 26/ 765 (3.4%)		1.10 (0.71-1.70) 0.88 (0.50-1.55)	0.55
Age	,			,	0.77
<50 Years 50-69 Years >=70 Years	29/ 1225 (2.4%) 29/ 632 (4.6%) 8/ 82 (9.8%)	25/ 1234 (2.0%) 32/ 634 (5.0%) 8/ 74 (10.8%)		1.17 (0.69-2.00) 0.90 (0.55-1.50) 0.94 (0.35-2.53)	
No Yes	58/ 1542 (3.8%) 8/ 397 (2.0%)	61/ 1551 (3.9%) 4/ 390 (1.0%)		0.96 (0.67-1.37) 2.01 (0.60-6.69)	0.26
History of Diabetes					0.97
No Yes	52/ 1683 (3.1%) 14/ 256 (5.5%)	51/ 1678 (3.0%) 14/ 264 (5.3%)		1.02 (0.69-1.50) 1.03 (0.49-2.16)	
History of					0.85
No Yes	40/ 1504 (2.7%) 26/ 435 (6.0%)	41/ 1520 (2.7%) 24/ 422 (5.7%)		0.98 (0.64-1.52) 1.06 (0.61-1.84)	
CV Disease					0.95
Yes	58/ 1841 (3.2%) 8/ 98 (8.2%)	58/ 1853 (3.1%) 7/ 89 (7.9%)		1.01 (0.70-1.45) 1.08 (0.39-2.98)	
Covid-19 vaccine					0.20
Confirmed not vaccinated Partially vaccinated Fully vaccinated	46/ 1388 (3.3%) 4/ 118 (3.4%) 15/ 419 (3.6%)	55/ 1421 (3.9%) 3/ 103 (2.9%) 7/ 402 (1.7%)		0.85 (0.58-1.26) 1.20 (0.27-5.41) 2.06 (0.84-5.07)	
Time from Covid-19 symptom onset to randomization (days)*					0.40
Tertile 1: (0, 4) Tertile 2: (5, 6) Tertile 3: (7, 28)	22/ 787 (2.8%) 16/ 586 (2.7%) 28/ 564 (5.0%)	29/ 789 (3.7%) 13/ 571 (2.3%) 23/ 579 (4.0%)		0.76 (0.43-1.32) 1.19 (0.57-2.48) 1.25 (0.72-2.17)	
Groups based on randomization date					0.56
2020AUG24 - 2021FEB21 2021FEB22 - 2021MAY23 2021MAY24 - 2021AUG22 2021AUG23 - 2021NOV21 2021NOV22 - 2022FEB10	7/ 158 (4.4%) 18/ 431 (4.2%) 20/ 430 (4.7%) 15/ 493 (3.0%) 6/ 427 (1.4%)	13/ 159 (8.2%) 18/ 436 (4.1%) 15/ 425 (3.5%) 12/ 494 (2.4%) 7/ 428 (1.6%)		0.53 (0.21-1.33) 1.01 (0.52-1.94) 1.32 (0.68-2.59) 1.26 (0.59-2.70) 0.86 (0.29-2.56)	
			0 1 2 3		

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Aspirin Better Control Better



Colchicine: other outcomes

Outcome	Colchicine (n=1,956)	Control (n=1,961)	HR (95% CI)	p-value
Hospitalization or death	66	65	1.02	0.93
nospitalization of death	(3.4%)	(3.3%)	(0.72-1.43)	
Hachitalization or rach doath	65	65	1.00	0.99
Hospitalization of resp. death	(3.4%)	(3.3%)	(0.71-1.41)	
Hospitalization	62	61	1.02	0.92
HOSPITAIIZATION	(3.2%)	(3.1%)	(0.71-1.45)	
Death	12	11	1.09	0.84
Death	(0.6%)	(0.6%)	(0.48-2.47)	
Pospiratory doath	10	7	1.43	0.47
Respiratory death	(0.5%)	(0.4%)	(0.54-3.75)	

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Aspirin: key subgroups

					P value
Group	Aspirin	Control	Hazard Ratio	HR (95% CI)	(interaction)
Randomized Overall	1945	1936			
Overall	59/ 1945 (3.0%)	73/ 1936 (3.8%)		0.80 (0.57-1.13)	
Sex					0.32
Male Female	35/ 1195 (2.9%) 24/ 750 (3.2%)	48/ 1155 (4.2%) 25/ 781 (3.2%)	·	0.70 (0.45-1.08) 1.01 (0.57-1.77)	
Age					0.77
<50 Years 50-69 Years >=70 Years	24/ 1223 (2.0%) 29/ 642 (4.5%) 6/ 80 (7.5%)	30/ 1236 (2.4%) 33/ 624 (5.3%) 10/ 76 (13.2%)		0.81 (0.47-1.38) 0.85 (0.51-1.40) 0.56 (0.20-1.57)	
Current Smoking				. ,	0.14
No Yes	51/ 1542 (3.3%) 8/ 403 (2.0%)	69/ 1551 (4.4%) 4/ 384 (1.0%)		0.74 (0.52-1.06) 1.96 (0.59-6.54)	
History of Dishster					0.62
No	46/ 1609 (2 7%)	E9/ 1662 (2 E%)		0 77 (0 52 1 14)	0.62
Yes	13/ 247 (5.3%)	15/ 273 (5.5%)		0.96 (0.45-2.02)	
History of Hypertension					0.08
No	41/ 1505 (2.7%)	41/ 1519 (2.7%)		1.01 (0.66-1.56)	
Yes	18/ 440 (4.1%)	32/ 417 (7.7%)		0.52 (0.29-0.94)	
CV Disease					0.22
No Yes	54/ 1845 (2.9%) 5/ 100 (5.0%)	63/ 1849 (3.4%) 10/ 87 (11.5%)		0.86 (0.60-1.24) 0.43 (0.15-1.25)	
Covid-19 vaccine				,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	0.99
status					
Confirmed not vaccinated Partially vaccinated Fully vaccinated	45/ 1390 (3.2%) 3/ 114 (2.6%) 10/ 425 (2.4%)	57/ 1419 (4.0%) 4/ 107 (3.7%) 12/ 396 (3.0%)		0.80 (0.54-1.19) 0.69 (0.15-3.12) 0.81 (0.35-1.87)	
T dify Facentated	10/ 425 (2.470)	12/ 556 (5.676)		0.01 (0.00 1.07)	
Time from Covid-19 symptom onset to randomization (days)					0.41
Tertile 1: (0, 4) Tertile 2: (5, 6) Tertile 3: (7, 28)	21/ 771 (2.7%) 11/ 590 (1.9%) 27/ 581 (4.6%)	30/ 805 (3.7%) 18/ 567 (3.2%) 25/ 562 (4.4%)		0.73 (0.42-1.27) 0.58 (0.28-1.24) 1.05 (0.61-1.81)	
	2	20.002 ()			
Groups based on randomization date					0.11
2020AUG24 - 2021FEB21 2021FEB22 - 2021MAY23 2021MAY24 - 2021AUG22 2021AUG23 - 2021NOV21 2021NOV22 - 2022FEB10	11/ 161 (6.8%) 10/ 430 (2.3%) 20/ 427 (4.7%) 12/ 493 (2.4%) 6/ 434 (1.4%)	9/ 156 (5.8%) 27/ 437 (6.2%) 15/ 428 (3.5%) 15/ 494 (3.0%) 7/ 421 (1.7%)		1.18 (0.49-2.87) 0.37 (0.18-0.76) 1.35 (0.69-2.64) 0.80 (0.37-1.70) 0.83 (0.28-2.48)	
			0 1 2 3		

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Aspirin Better Control Better



Aspirin: other outcomes

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Outcome	Aspirin N=1,964	Control N=1,953	HR (95% CI)	P-value	
Major thrombosis,	59	73	0.80	0.21	
hospitalization, or death*	(3.1%)	(3.7%)	(0.57-1.13)	0.21	
Any thromhosis	2	5	0.40	0.27	
Any thrombosis	(0.1%)	(0.3%)	(0.08-2.06)	0.27	
Dooth	12	11	1.09	0.84	
Death	(0.6%)	(0.6%)	(0.48-2.46)	0.04	
Pospiratory doath	10	7	1.42	0 / 8	
Respiratory death	(0.5%)	(0.4%)	(0.54-3.73)	0.40	
Hospitalization	56	67	0.83	0.21	
ΠυδριταιιΖατίστι	(2.9%)	(3.4%)	(0.58-1.19)	0.51	



Hospitalization or death event rates over time





Conclusions

- Colchicine and aspirin appear to provide no benefits in outpatients with COVID-19 (supported by the results of an updated meta-analysis to be presented by next speaker)
- Severity of COVID-19 appears to be diminishing (but patients will continue to have severe disease and die)
- The world *still* needs additional inexpensive, widelyapplicable treatments for COVID-19





PROOF (not for distribution)

Colchicine and aspirin in community patients with COVID-19 🐴 🆲 (ACT): an open-label, factorial, randomised, controlled trial



John WEikelboom, Sanjit S Jolly, Emilie P Belley-Cote, Richard P Whitlock, Sumathy Rangarajan, Lizhen Xu, Laura Heenan, Shrikant I Bangdiwala, Wadea M Tarhuni, Mohamed Hassany, Anna Kontsevaya, William Harper, Sanjib Kumar Sharma, Patricio Lopez-Jaramillo, Antonio L Dans, Lia M Palileo-Villanueva, Alvaro Avezum, Prem Pais, Denis Xavier, Camilo Felix, Afzalhussein Yusufali, Renato D Lopes, Otavio Berwanger, Zeeshan Ali, Sean Wasserman, Sonia S Anand, Jackie Bosch, Shurjeel Choudhri, Michael E Farkouh, Mark Loeb, Salim Yusuf

Summary

Background The large number of patients worldwide infected with the Sars-CoV-2 virus has overwhelmed health-care systems globally. The Anti-Coronavirus Therapies (ACT) outpatient trial aimed to evaluate anti-inflammatory therapy with colchicine and antithrombotic therapy with aspirin for prevention of disease progression in community patients with COVID-19.

Lancet Respir Med 2022

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