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LE SAVOIR PREND FORME

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PRELIMINARY POSITION

Preliminary position in light of the analysis of the COLCORONA study preprint

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Preliminary position in light of the analysis of the COLCORONA study preprint

HIGHLIGHTS

The COLCORONA study is a randomized, double-blind, placebo-controlled trial that was performed in 6 countries, and for which 75% of the participants were recruited in Québec. The study protocol was of good methodological quality, and the design was suitable to meet the investigators' primary objective, which was to determine whether colchicine, a drug that is familiar to clinicians and that has a simple route of administration, reduces hospitalizations and deaths in patients infected with SARS-CoV-2 and who have at least one risk factor for developing COVID-19 complications.

The study, which was conducted under difficult conditions, was stopped early, mainly because of logistical issues, and, as reported by the authors, due to a concern to provide the healthcare system with results in a timely manner given the state of the COVID-19 pandemic. Of the 6,000 participants initially planned, approximately 4,500 were recruited, which had the effect of reducing the statistical power below the initially planned 80%.

The study aimed to recruit non-hospitalized participants of at least 40 years of age with a diagnosis of COVID-19 confirmed by an RT-PCR test or by an epidemiological link within the past 24 hours, and who had at least one risk factor for developing COVID-19 complications.

The results of this clinical trial were pre-published on the medRxiv platform on January 27, 2021. Consequently, they have not yet been peer-reviewed.

No statistically significant effect on the primary efficacy endpoint combining hospitalization and death was observed when considering the entire study population, i.e., those patients with a positive RT-PCR test result or who were reported positive based on an epidemiological link.

For the subgroup with a positive RT-PCR test result, a 25% relative risk reduction in the colchicine-treated group compared to the placebo group was observed for the composite hospitalization/death endpoint.

Although statistically significant in the RT-PCR-positive subgroup, efficacy was associated with a margin of error or uncertainty that renders the result fragile, since transfer of a single event from one group to another would make it nonsignificant. This fragility is all the more important considering that a certain number of participants did not complete the study or were lost to follow-up from the study population.

The magnitude of this effect translates into an absolute risk reduction of 1.4% (4.6% for the colchicine group and 6.0% for the placebo group), which means that 71 patients would need to be treated with colchicine to prevent one event.

The reasons for subsequent COVID-19-related hospitalization and mean length of hospital stay are not reported in the unrefereed preprint. Thus, the magnitude of the impact on hospitalization is difficult to assess.

Adverse events, mainly gastrointestinal in nature, were more frequent in the colchicine-treated participants (24.2% vs. 15.5%; $p < 0.0001$).

There was a significantly higher number of pulmonary embolisms in the colchicine group (0.5% vs. 0.1% $p = 0.01$), a worrisome and unexpected finding. However, information on the type, severity and outcome of these events occurring during the study period is not provided by the preprint.

PRELIMINARY POSITION

INESSS's analysis is based on limited unrefereed preprint data

INESSS may revise its position in light of additional data, especially after publication of an article in a peer-reviewed journal.

In light of the currently available scientific data, the perspectives of the stakeholders consulted, and the current epidemiological context:

INESSS **considers it premature to support the use of colchicine** in non-hospitalized persons with a diagnosis of COVID-19 confirmed or not by an RT-PCR test, even if they meet the study's selection criteria (at least 40 years of age with at least one risk factor for complications).

This position takes the following into account:

- the inability to draw any conclusion regarding the impact of colchicine on mortality or on the need of recourse to mechanical ventilation;
- the inability to draw any conclusion regarding the impact of colchicine on hospitalization across the total study population;
- the statistical fragility of the demonstration of the impact of colchicine on the combined primary efficacy endpoint (hospitalization/death) in the subgroup of RT-PCR-positive participants;
- the clinical significance of the impact, considered uncertain by the expert panel enlisted by INESSS, since treating 1,000 patients who meet the study's eligibility criteria for 30 days with colchicine would avoid 14 hospitalizations, the reason for and length of which are not reported;
- concerns about the possible occurrence of pulmonary embolism following the use of colchicine in non-hospitalized persons infected with SARS-CoV-2.

The currently available data confirm the interest in continuing research efforts to document the impact of colchicine in preventing COVID-19 complications in non-hospitalized RT-PCR-positive persons, in order to better characterize the population most likely to benefit. In addition, the evolution of the safety signal data concerning the observed pulmonary embolisms remains relevant. To this end, Health Canada's assessment of the safety of colchicine in COVID-19 patients will provide important additional insight.

Clinicians who would nonetheless consider prescribing colchicine treatment at the patient's request should exercise caution and clearly explain the balancing between potential risks and benefits in the context of shared decision-making. In these circumstances, treatment can only be offered to patients of 40 years of age or older with no contraindications, with a diagnosis of COVID-19 confirmed by a positive RT-PCR test result, and with at least one risk factor for developing a complication related to the infection.

CONTEXT OF THE REQUEST

Following the pre-publication of the COLCORONA study results, the Ministère de la Santé et des Services (Québec) asked INESSS to analyze the data and assess the possible role of colchicine in the treatment of COVID-19 patients whose condition does not require hospitalization. Colchicine is an anti-inflammatory drug used to prevent and treat gout attacks, to treat familial Mediterranean fever, and for various heart conditions. Among other factors, colchicine inhibits the NLRP3 inflammasome, thereby affecting the inflammatory response associated with this complex. Based on such biological plausibility, the immunomodulatory properties of colchicine, its relatively favourable safety profile and the complications of SARS-CoV-2 infection being generally attributed to an exaggerated inflammatory response, study of this drug for COVID-19 disease was of interest to researchers. An international clinical trial conducted by Québec researchers targeted the population of patients with a positive SARS-CoV-2 test result but who were not hospitalized, to test the hypothesis that early prevention of the inflammatory cascade after diagnosis could reduce complications, notably hospital admission, recourse to mechanical ventilation and, ultimately, death. The COLCORONA clinical trial began in March 2020, and its results were released as an unrefereed preprint on the medRxiv platform on January 27, 2021 [Tardif, 2021].

METHODOLOGY

INESSS examined the unrefereed preprint and had privileged access to the protocol and the statistical analysis plan, which were shared by the principal investigator.

Other data sources were also consulted to complete the analysis: public health agencies (Québec, Canada and France), health technology assessment agencies and websites of ministries and departments of health in other countries whose healthcare system is comparable to Canada's (e.g., the United Kingdom, Australia, Belgium and France), the World Health Organization (WHO), the U.S. Centers for Disease Control (CDC), and recognized learned societies in the field of infectious diseases (e.g., the Infectious Diseases Societies of America). The Google search engine was also used. The current colchicine product monograph and drug interaction databases were consulted as well. In addition, the stakeholders were invited to share any documents relevant to this critical analysis.

The scientific data were extracted from the preprint by a professional scientist and validated by a second (Appendix A: Tables A-1 and A-2). The analysis and the assessment of the level of scientific evidence for the clinical endpoints examined were performed by a professional based on the examination of the available scientific data according to four criteria: methodological and scientific limitations of the study, consistency/reliability, clinical impact, and generalizability. An overall level of scientific evidence was assigned, allowing for judgement of the level of confidence in the pre-published results according to a four-level scale: high[1], moderate[2], low[3] and insufficient[4]. Table A-3 in Appendix A shows the integration of the results of the four criteria for appraising scientific evidence in order to display the associated level of confidence. This critique of the pre-published study – its different endpoints, the assessment criteria and the confidence levels – were validated by the project team and discussed with a panel of experts.

A biostatistician was enlisted to perform additional analyses, which included calculation of a statistical fragility index[5]. Essentially, this index indicates the minimum number of participants (whose status might convert from a non-event to an event) needed in order to move from a statistically significant result to a nonsignificant one. A two-sided Fisher's exact test was recalculated until the *P*-value reached or exceeded 0.05 [Walsh *et al.*, 2014]. In addition, the number needed to treat (NNT) and its 95% confidence interval were calculated. The relative risk (RR) of the occurrence of an event was

[1] All the criteria are assessed positively (methodological limitations, consistency/reliability, clinical impact, and generalizability). The evaluators are highly confident that the estimated impact is comparable to the objectives of the intervention. It is unlikely that the conclusion drawn from the scientific data will be significantly affected by the results of future studies.
[2] Most of the criteria are assessed positively, despite the methodological limitations. The evaluators are moderately confident that the estimated impact is comparable to the objectives of the intervention. It is quite likely that the conclusion drawn from these data will be affected by the results of future studies.
[3] Most or all of the criteria are assessed negatively. The evaluators have a low level of confidence that the estimated impact was comparable to the objectives of the intervention. It is very likely that the conclusion drawn from these data will be strongly affected by the results of future studies.
[4] The available data are insufficient. The evaluators have no confidence in the link between the estimated impact and the objectives of the intervention.
[5] Source: https://clincalc.com/Stats/FragilityIndex.aspx

calculated and the NNT was then calculated according to the following formula [Furukawa *et al.,* 2002]:

NNT = 1 / (PEER x (1-RR)), where PEER = patient expected event rate

In line with standard production processes, put in place by INESSS at the beginning of the public health crisis to assess the relevance of treatments, an expert panel (Appendix B) was called upon, which brings together various specialties and areas of expertise (both clinical and research-based) and has been assisting INESSS since the spring of 2020. INESSS representatives and the panel of 17 experts also had the opportunity to speak with the principal investigator and his team to clarify certain information and ask questions about the pre-published manuscript.

During the week of January 25, 2021, the experts were invited twice for discussions, the first on the unpublished results, the second on the preprint's safety and efficacy data. The principal investigator also confidentially shared the study protocol and analysis plan. The experts were then asked to share their opinion on the methodology, the magnitude of the reported clinical results and their generalizability/transferability, and to take a position on the relevance of offering or not offering colchicine to the study's target population. The experts were also invited to comment on whether they were open to its use on a case-by-case basis.

The final version of this document reflects the consultative process, but its content and form are not the responsibility of the persons consulted. Conflicts of interest and roles were declared and managed in accordance with INESSS policy. Some of the experts are involved in ongoing clinical trials with patients hospitalized for COVID-19, including CONCOR-1, RECOVERY, REMAP-CAP, SOLIDARITY, ACTIV-2, NCT04327388 and COVACTA (no confidential information was provided to INESSS or the other participants regarding the preliminary results of any ongoing or completed but unpublished study).

This document was validated by the scientific coordinator and the division responsible for its production. The statistical analyses and interpretation were validated by an INESSS biostatistician. The document was critically proofread by the Bureau - Méthodologie et éthique under the responsibility of INESSS's scientific vice-presidency. This document did not undergo an external review.

EVALUATION OF THE COLCORONA STUDY

Brief description

The COLCORONA study was a six-country, phase III, double-blind, randomized controlled trial for which 75% of the participants were recruited in Québec [Tardif, 2021]. For logistical reasons and due to the authors' concern to provide the health care system with results in a timely manner during the public health crisis, the study was terminated early after the recruitment of 75% of the initially planned number of participants. The characteristics and results of this clinical trial are presented in Tables A-1 and A-2 of Appendix A, respectively.

Briefly, participants had to be at least 40 years of age, have tested positive on RT-PCR in the 24 hours prior to recruitment or have been declared positive on the basis of an epidemiological link or a clinical algorithm originating from official public health directives, not be hospitalized nor in a state suggesting a need for hospitalization, and have at least one of the following risk factors: age ≥ 70 years, body mass index (BMI) ≥ 30 kg/m^2, diabetes, uncontrolled hypertension (≥ 150 mm Hg), known respiratory disease, known heart failure, known coronary artery disease, fever ≥ 38.4 degrees Celsius in the 48 hours prior to recruitment, dyspnea at presentation, bicytopenia, pancytopenia, or the combination of low lymphocyte and high neutrophil counts. Individuals were excluded if they had contraindications or certain conditions[6].

Participants were randomized in a 1:1 ratio to receive either placebo or colchicine 0.5 mg twice daily for 3 days, then 0.5 mg once daily for the next 27 days.

The primary endpoint was a composite of the incidence of COVID-19 hospitalization and death at day 30. The secondary endpoints were the incidence of COVID-19 deaths, the incidence of COVID-19 hospitalizations, and the proportion of participants who required mechanical ventilation.

Prespecified subgroup analyses using logistic regression models had also been planned. The preprint manuscript states that no adjustments for multiple testing between the different methods used to assess the primary endpoint and the secondary endpoints had been predefined. The same applies to the multiple comparisons. Thus, the inferences drawn may not be reproducible according to the authors [Tardif, 2021].

[6] Inflammatory bowel disease, chronic diarrhea or a malabsorption disorder, pre-existing progressive neuromuscular disease, estimated glomerular filtration less than 30 ml/min/1.73 m^2, or severe liver disease. They were also excluded if they were being treated with colchicine for another clinical condition, currently undergoing chemotherapy for cancer, had a history of significant sensitivity to colchicine or, in the case of women of childbearing age, not practicing adequate contraception.

Main results of the intent-to-treat analysis

Primary endpoint – Entire study population (N = 4,488)

After 30 days of treatment, 4.7% of the participants in the colchicine group had been hospitalized or had died because of COVID-19, compared to 5.8% of those in the placebo group. This 1.16% reduction in the absolute risk, or 21% reduction in the relative risk, is not statistically significant (odds ratio (OR): 0.79; 95% confidence interval (CI) [95% CI: 0.61 to 1.03]; $p = 0.08$) [Tardif, 2021].

Secondary endpoints – Entire study population (N = 4,488)

The risk of hospitalization was 4.5% in the colchicine group compared to 5.7% in the placebo group. This 1.2% reduction in the absolute risk, or 21% reduction in the relative risk, is not statistically significant (OR: 0.79 [95% CI: 0.60 to 1.03] [Tardif, 2021].

Death occurred in 5 participants in the colchicine group (0.2%) compared to in 9 in the placebo group (0.4%) (OR: 0.56 [95% CI: 0.19 to 1.67]), a non-statistically significant difference [Tardif, 2021].

Fewer participants in the colchicine group required mechanical ventilation than in the placebo group, but the difference is not statistically significant (0.5% vs. 0.9%; OR: 0.53 (95% CI: 0.25 to 1.09)) [Tardif, 2021].

Primary endpoint – Subgroup of RT-PCR-positive participants (N = 4,159)

The results of a subgroup analysis including only those participants whose diagnosis was confirmed by RT-PCR show a statistically significant reduction in hospitalization or death in the colchicine group compared to the placebo group (4.6% vs. 6.0%; OR: 0.75 [95% CI: 0.57 to 0.99]; $p = 0.04$). A 25% relative risk reduction or a 1.4% absolute risk reduction in the number of hospitalizations was observed [Tardif, 2021]. Calculated from the raw data presented in the pre-publication, the NNT with colchicine for 30 days to achieve one less event than in the placebo group is 71 (NNT: 71 [95% CI: 41 to 1,821]).

Secondary endpoints – Subgroup of RT-PCR-positive participants (N = 4,159)

A decrease in the number of hospitalizations in the colchicine group relative to the placebo group was observed in this subgroup (4.5% vs. 5.9%; OR: 0.75 [95% CI: 0.57 to 0.99]). This 1.4% reduction in the absolute risk, or 25% reduction in the relative risk, is statistically significant [Tardif, 2021]. The same NNT as that for the primary endpoint was obtained, but with a slightly narrower confidence interval (NNT: 71 [95% CI: 41 to 1,325]).

In this subgroup (RT-PCR-positive), 5 participants died in the colchicine group (0.2%), compared to 9 in the placebo group (0.4%) (OR: 0.56 [95% CI: 0.19 to 1.66]), a non-statistically significant difference [Tardif, 2021].

In the subgroup consisting of RT-PCR-positive participants, the observed difference of 10 fewer patients requiring mechanical ventilation in the colchicine group was not statistically significant (0.5% vs. 1.0%; OR: 0.50 [95% CI: 0.23 to 1.07]) [Tardif, 2021].

Safety

Serious adverse events were less frequent in the colchicine group than in the placebo group (4.9% vs. 6.3%; $p = 0.05$). However, 11 participants in the colchicine group experienced a pulmonary embolism compared to 2 in the placebo group (0.5% vs. 0.1%; $p = 0.01$), a statistically significant difference [Tardif, 2021].

A higher proportion of participants in the colchicine group experienced adverse events than in the placebo group (24.2% vs. 15.5%; $p < 0.0001$). The most frequent (and expected) adverse events were gastrointestinal in nature (23.9% vs. 14.8%; $p < 0.0001$), with diarrhea being the most frequently reported (13.7% vs. 7.3%; $p < 0.0001$) [Tardif, 2021].

Assessment of the scientific evidence

The scientific evidence for the endpoints for which a statistically significant result was observed was assessed according to four criteria: the study's methodological and scientific strengths and limitations, consistency/reliability, clinical impact, and generalizability/transferability. The details of this assessment are presented in Table A-3 in Appendix A. An overall level of scientific evidence was assigned according to the above-mentioned four-level scale.

The study protocol was of sound methodological quality, and the design was suitable for meeting the investigators' objective, which was to determine whether colchicine reduces hospitalization or death in RT-PCR-positive patients with at least one risk factor for developing COVID-19 complications.

Despite the strength of the study plan, certain limitations and uncertainties are noted. The clinical trial was terminated early after 75% of the planned number of participants had been recruited, which reduces the actual power of the study to a threshold below the 80% initially planned for detecting a 25% relative risk reduction in events with a critical threshold of 0.05%. This decision was made by the group of investigators mainly because of logistical issues in the context of the pandemic, and not by the data and safety monitoring board of the trial.

Secondly, the results reported in the preprint show, for the total study population, a non-statistically significant reduction in the study's endpoints. However, a statistically significant reduction in the primary endpoint was observed in the subgroup consisting of RT-PCR-positive participants. This result, which can be explained mainly by a difference in the occurrence of hospitalization, is uncertain, given:

- its statistical fragility, since the transfer of one event from the placebo group to the colchicine group makes it insignificant (fragility index = 1) and

- the number of participants who withdrew consent or who were lost to follow-up from both groups, which is relatively high (2.0%), given the low prevalence of events (5.2%).

Furthermore, the clinical impact of the statistically significant result for hospitalization is uncertain, given, on the one hand, the difficulty assessing its impact on the healthcare system, since the reasons for hospitalization and the mean length of stay are not provided by the preprint, and, on the other hand, the decrease being based on a difference of 30 events occurring in a subgroup of participants. In more simple terms, this result means that treating 1,000 patients who meet the study criteria for 30 days with colchicine would prevent 14 hospitalizations.

Analyses were performed by the study authors in an attempt to better characterize the subgroups of patients who might benefit more from this treatment (within prespecified subgroups). However, the authors do not propose any adjustments for the multiplicity of these subgroup comparisons based on the participants' characteristics. Consequently, the results of these analyses presented in the preprint are considered exploratory in nature.

Furthermore, despite a favourable safety profile based on the experience of using colchicine in rheumatology, immunology and cardiology, the unexpected occurrence of a statistically significant higher incidence of pulmonary embolism in the colchicine group is worrisome (0.5% vs. 0.1%; $p = 0.01$), although it cannot be ruled out that such observations may be due to chance.

Lastly, other elements related to the generalizability and transferability of the results were noted:

- Individuals aged 70 years or older accounted for fewer than 10% (403/4,488) of the study participants, yet they are the population most likely to be hospitalized or to succumb to COVID-19 disease;
- Information on the type, severity and outcome of the pulmonary embolisms occurring during the study period is not provided by the preprint.

Thus, given the methodological strengths and limitations, the clinical impact and the generalizability and transferability of the results, INESSS considers the level of scientific evidence for the hospitalization/death endpoint to be low. It cannot be concluded with certainty that the results in favour of colchicine observed in this clinical trial are or are not clinically significant.

CLINICIAN PERSPECTIVE

Regarding the design of the COLCORONA clinical trial, the experts consulted (see list in Appendix B) were of the unanimous opinion that the study was of sound methodological quality. As well, they emphasized the high degree of difficulty in recruiting such a number of non-hospitalized participants in a pandemic setting.

With regards to efficacy, the experts consulted were also unanimous as to the difficulty assessing the impact of colchicine on preventing hospitalization from the preprint data. The lack of statistically significant results for the main endpoint of interest (composite hospitalization/death), together with the uncertainty of the results for the events in the subgroup of participants who tested positive for SARS-CoV-2 on RT-PCR, left a majority of the experts unconvinced of the clinical relevance of colchicine in the management of non-hospitalized persons with COVID-19 disease. These experts considered the magnitude of the effect to be uncertain. Thus, caution was advised, without ruling out the possibility that new information could change their position after publication of the article in a peer-reviewed journal, given that this exercise generally leads to more nuanced final analyses and conclusions. The experts found it regrettable that the study was terminated early, but nonetheless consider the investigation as a first step, whose results should be supplemented with those from other clinical trials, that may allow one to rule on the efficacy of colchicine in preventing COVID-19 complications in non-hospitalized patients with a confirmed diagnosis. The experts did not seem to have a problem with transposing the results from a 0.5 mg colchicine dose to the 0.6 mg dosage currently available on the market.

Regarding safety, the experts were of the opinion that colchicine is safe and relatively well tolerated when used at the usual doses, based on clinical experience with this drug. However, colchicine should be used with caution in the elderly because of the high prevalence of polypharmacy (posing a risk of drug interactions, particularly with cytochrome P450 3A4) and decreased renal function in this population. In addition, the diarrhea it can cause may lead to dehydration and electrolyte disorders, exacerbating underlying conditions. Furthermore, the unexpected occurrence of a significantly higher risk of pulmonary embolism in the colchicine group in the COLCORONA study was considered worrisome, especially since there was no such signal from recent clinical studies involving several thousands of patients with acute coronary artery disease who took colchicine for several months [Nidorf *et al.*, 2020; Tardif *et al.*, 2019]. Given these concerns, some of the experts were uneasy with the idea of prescribing colchicine at this time, particularly in the non-hospitalized population. While none of them would prescribe colchicine on their own initiative, a minority said that if a patient requested the drug, there would have to be a discussion during which the uncertainty regarding the anticipated benefits and possible adverse effects, including pulmonary embolism, would be appropriately explained to the patient in order to obtain informed consent for a 30-day course of treatment.

After examining the currently available scientific data, the panel of experts unanimously ruled against routine use of colchicine in patients diagnosed with COVID-19 disease

who meet the COLCORONA study criteria. When asked whether they were open to case-by-case use, opinions were divided.

PUBLISHED CLINICAL RECOMMENDATIONS

Since the pre-publication of the COLCORONA trial, it appears that only the Greek Medicines Agency has recommended prescribing colchicine for the treatment of COVID-19[7]. British Columbia has not recommended routine use of colchicine in non-hospitalized patients with mild COVID-19 disease, but states that colchicine could be considered on a case-by-case basis – following a shared decision with the physician and informed consent regarding the uncertainty about potential benefits and risks – for patients who meet the COLCORONA study eligibility criteria [BCCDC, 2021]. No other organization in a healthcare system comparable to Canada's (e.g., Health Canada, IDSA, NIH, NICE, NHS, WHO or HAS) has yet expressed its opinion on the clinical relevance of using colchicine in non-hospitalized COVID-19 patients.

[7] COVID-19 | L'étude montréalaise sur la colchicine mène à l'approbation en Grèce | La Presse (consulted on January 27, 2021)

CONCLUSION

Based on the analysis of the data available at this time in the COLCORONA study unrefereed preprint and consultations with the expert panel, uncertainties remain regarding the clinical significance of the results and the safety of this treatment in non-hospitalized, RT-PCR-positive patients 40 years of age or older with at least one risk factor for developing COVID-19 complications. INESSS is of the opinion that the methodological limitations and the absence of documentation of the reasons for and the length of the hospitalizations render it difficult to assess the risk/benefit ratio, and considers it premature to support the use of colchicine in non-hospitalized patients with a confirmed diagnosis of COVID-19, even if they meet the study's selection criteria. While the results observed are certainly of great interest, research efforts to document the impact of colchicine on preventing COVID-19 complications must continue, in particular to characterize, in sufficient detail and with a high level of confidence, the populations most likely to benefit.

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ANNEXE A
Caractéristiques, résultats et appréciation de la preuve scientifique

Tableau A-1 Caractéristiques de l'étude

Auteurs, année, référence		**Tardif et coll. (2021)**
Journal, plateforme		Plateforme medRxiv
Pays		Canada + 5 autres pays
Période de recrutement/ révision dossiers médicaux		Mars 2020 à Décembre 2020
Devis, design Nbre d'établissement # de l'étude (NCT, CHCTR, EuDRA CT)		ECRA à double insu NCT04322682 (COLCORONA)
N	Total	n = 4 488
	Groupe intervention	n = 2 235
	Groupe comparateur	n = 2253
Caractéristiques population incluse	Stade de la COVID-19	- ≥ 40 ans - Diagnostic de COVID-19 depuis ≤ 24 h avant le recrutement - Non hospitalisé ou sans considération immédiate d'hospitalisation - Présenter au moins un des facteurs de risque suivant: • ≥ 70 ans • Obésité (IMC ≥ 30 kg/m^2) • Diabetes • Hypertension non controlée (pression artérielle systolique ≥ 150 mmHg) • Maladie respiratoire connue • Insuffisance cardiaque connue • Maladie coronarienne connue • Présence d'au moins 38,4°C de fièvre durant les derniers 48 h • Dyspnée au moment de la présentation • Bicytopénie • Pancytopénie • Combinaison d'un compte de neutrophile élevée et de lymphocyte bas.
	Âge	Age moyen (± ET) : Groupe colchicine: 54,4 ± 9,7 ans Groupe placébo: 54,9 ± 9,9 ans Total : 54,7 ans
	Homme	Groupe colchicine : 44,6 % Groupe placébo : 47,5 % Total : 46,1 %
	Comorbidités	<u>Hypertension (%)</u> Groupe colchicine : 34,9 % Groupe placébo : 37,6 % <u>Diabète (%)</u>

Auteurs, année, référence	**Tardif et coll. (2021)**
	Groupe colchicine : 19,9 % Groupe placébo : 20,0 % <u>Maladie respiratoire (%)</u> Groupe colchicine : 26,1 % Groupe placébo : 26,9 % <u>Histoire d'infarctus du myocarde (%)</u> Groupe colchicine : 2,9 % Groupe placébo : 3,2 % <u>Histoire d'insuffisance cardiaque (%)</u> Groupe colchicine : 1,1 % Groupe placébo : 0,8 %
Critères d'exclusion de l'essai	- Maladie intestinale inflammatoire - Diarrhée chronique ou malabsorption; - Maladie neuromusculaire progressive préexistante - Filtration glomérulaire estimée à <30 ml / min / 1,73 m^2 - Maladie hépatique sévère; - Traitement à la colchicine en cours; - Chimiothérapie pour le cancer en cours - Antécédents de sensibilité significative à la colchicine. - Femmes en âge de procréer ou ne pratiquant pas une contraception adéquate - Patient en état de choc ou avec une instabilité hémodynamique (information tirée du site ClinicalTrial.gov)_
Intervention	Colchicine (0,5 mg BID les 3 premier jours et DIE les 27 jours suivants)
Comparateur	Placébo
Paramètres d'intérêts	**<u>Paramètre primaire</u>** Une combinaison hospitalisations/décès dus à une infection au COVID-19 dans les 30 jours suivant la randomisation. **<u>Parmètres secondaires</u>** Hospitalisations, mortalité et le besoin d'assistance respiratoire dans les 30 jours suivant la randomisation. La présence de pneumonie et d'effets indésirables a également été recensée.
Limites et biais	Arrêt prématuré de l'étude pour raisons logistiques Suivi court de 30 jours Paramètre d'intérêt principal combiné Difficile d'attribuer un effet de la colchicine sur la mortalité Manque d'information sur les critères d'hospitalisation Fragilité sur le plan statistique Déséquilibre dans les groupes pour les pertes au suivi

Tableau A-2 Résultats de l'étude

Auteur Année (Pays)	Paramètres d'intérêts	Résultats rapportés					Conclusions des auteurs
		Résultats intervention	Résultats comparateur	p	RR, RC, RA, RRI, RT (IC 95%)	Direction de l'effet (Φ ↑ ↓)	
Tardif et coll. 2021 (Canada)	Mortalité ou hospitalisation à 30 jours - n/tot (%) Population ITT	104/2235 (4,7 %)	131/2253 (5,8 %)	0,08	RC : 0.79 (0.61 ; 1.03)	**Φ**	In conclusion, among non-hospitalized patients with confirmed COVID-19, colchicine led to a lower rate of the composite of death or hospitalization than placebo.
	Population RT-PCR+	96/2075 (4,6 %)	126/2084 (6,0 %)	0,04	RC: 0,75 (0,57 ; 0,99)	↑ (en faveur)	
	Mortalité à 30 jours - n/tot (%) Population ITT	5/2235 (0,2%)	9/2253 (0,4 %)	N.D.	RC :0,56 (0,19 ; 1,67)	**Φ**	
	Population RT-PCR+	5/2075 (0,2 %)	9/2084 (0,4 %)	N.D.	RC : 0,56 (0,19 ; 1,66)	**Φ**	
	Hospitalisation à 30 jours - n/tot (%) Population ITT	101/2235 (4,5 %)	128/2253 (5,7 %)	N.D.	RC : 0,79 (0,60 ; 1,03)	**Φ**	
	Population RT-PCR+	93/2075 (4,5 %)	123/2084 (5,9 %)	N.D.	RC : 0,75 (0,57 ; 0,99)	↑ (en faveur)	
	Utilisation d'une assistance respiratoire mécanique - n/tot (%) Population ITT	11/2235 (0,5 %)	21/2253 (0,9 %)	N.D.	RC : 0,53 (0,25 ; 1,09)	Φ	
	Population RT-PCR+	10/2075 (0,5 %)	20/2084 (1,0 %)	N.D.	RC : 0.50 (0,23 ; 1,07)	Φ	
	Effets indésirable (EI) – n/tot (%)						

Auteur Année (Pays)	Paramètres d'intérêts	Résultats rapportés					Conclusions des auteurs
		Résultats intervention	Résultats comparateur	p	RR, RC, RA, RRI, RT (IC 95%)	Direction de l'effet (Φ ↑ ↓)	
	Safety population						
	- EI total	532/2195 (24,2 %)	344/2217 (15,5 %)	< 0,0001	N.D.	↓ (défaveur)	
	- EI graves	108/2195 (4,9 %)	139/2217 (6,3 %)	0,05	N.D.	↑ (en faveur)	
	- EI gastro-intestinal	524/2195 (23,9 %)	328/2217 (14,8 %)	< 0,0001	N.D.	↓ (défaveur)	
	- EI gastro-intestinal graves	6/2195 (0,3 %)	3/2217 (0,1 %)	0,31	N.D.	Φ	
	- Embolie pulmonaire	11/2195 (0,5 %)	2/2217 (0,1 %)	0,01	N.D.	↓ (défaveur)	
	- Pneumonie grave	63/2195 (2,9 %)	92/2217 (4,1 %)	0,02	N.D.	↑ (en faveur)	
	- Diarrhée	300/2195 (13,7 %)	161/2217 (7,3 %)	< 0,0001	N.D.	↓ (défaveur)	
	- Éruption cutanée	4/2195 (0,2 %)	13/2217 (0,6 %)	0,03	N.D.	↓ (défaveur)	

Tableau A-3 Appréciation de la preuve scientifique

Médicaments étudiés	Population COVID-19	Qualité méthodologique	Cohérence	Impact clinique	Généralisabilité	Niveau de preuve
Hospitalisations/mortalité et hospitalisation des patients COVID-19, confirmé par RT-PCR, non hospitalisés						
L'état actuel des connaissances scientifiques, basé sur la prépublication des résultats d'un ECRA de phase III à double insu cessé prématurément après le recrutement de 75% des participants (4 488), suggère que la colchicine, comparativement à un placébo, pourrait potentiellement réduire modestement la survenu des hospitalisations ou décès, ou la survenue d'hospitalisations pendant les 30 jours de la prise du traitement chez des personnes dont le diagnostic de COVID-19 a été confirmé, qui ont 40 ans et plus, présentent au moins un facteur de complication et dont l'état de santé ne requiert pas une hospitalisation.						
Colchicine	COVID-19 Non hospitalisée	Quantité d'études :1 N bras colchicine = 2 235 N bras placébo = 2 253 Devis : Analyse d'un ECRA à double insu cessé prématurément après le recrutement de 75% des participants Biais/limites: Modéré Précision : Puissance statistique en deçà du 80% initialement prévu % Indice de fragilité = 1	Modérée	n/a (Une seule étude)	Faible Hospitalisation ou décès : Diminution du risque absolu = 1,4 % Hospitalisation : Diminution du risque absolu = 1,4 %	Modérée Population, contexte clinique	Faible

Médicaments étudiés	Population COVID-19	Qualité méthodologique	Cohérence	Impact clinique	Généralisabilité	Niveau de preuve
Innocuité des patients COVID-19 non hospitalisés						
L'état actuel des connaissances scientifiques, basé sur la prépublication des résultats d'un ECRA de phase III à double insu, cessé prématurément après le recrutement de 75% des participants (4 488), suggère que la colchicine, comparativement à un placébo, augmente le risque d'effets indésirables d'ordre gastro-intestinal et pourrait augmenter le risque d'embolie pulmonaire chez des personnes atteintes de la COVID-19 dont l'état de santé ne requiert pas une hospitalisation.						
Colchicine	COVID-19 Non hospitalisée	Quantité d'études :1 N bras colchicine = 2 235 N bras placébo = 2 253 Devis : Analyse d'un ECRA à double insu cessé prématurément après le recrutement de 75% des participants Biais/limites: Modéré Précision : Puissance statistique = en deçà du 80% initialement prévu %	Modérée	n/a (Une seule étude)	Modéré EI d'ordre GI : 23,9 % contre 14,8 % Embolie pulmonaire : 11 évènements contre 2 évènements soit 0,5 % contre 0,1 %	Modérée Population, contexte clinique	Faible

ANNEXE B

Liste des experts ayant collaboré avec l'INESSS lors des deux consultations

Dr Patrick Bellemare MD, FRCPC, intensiviste et pneumologue, Hôpital du Sacré-Cœur, CIUSSS du Nord-de-l'Île-de-Montréal, Montréal

M. Luc Bergeron, B. Pharm., M.Sc., FCSHP, pharmacien, CHU de Québec – Université Laval (CHUL et Centre mère-enfant Soleil), Québec

Dr Alexandre Boudreault MD, FRCPC, microbiologiste-infectiologue, CHU de Québec – Université Laval (Hôtel-Dieu de Québec) et Institut universitaire de cardiologie et pneumologie de Québec – Université Laval, Québec

Dr Marc Brosseau MD, FRCPC, intensiviste et pneumologue, Hôpital Maisonneuve-Rosemont, Montréal, CIUSSS de l'est-de-l'Île-de-Montréal, Montréal

Dr Hugo Chapdelaine MD, FRCPC, immunologue, CHUM, Institut de recherches cliniques de Montréal, Montréal

Dr David Claveau MD, intensiviste et urgentologue, Centre hospitalier affilié universitaire régional, CIUSSS de la Mauricie-et-du-Centre-du-Québec, Trois-Rivières

Mme Alexandra Covrig, PharmD, M.Sc., pharmacienne, Hôtel-Dieu de Lévis, CISSS de Chaudière-Appalaches, Lévis

Dr Jeannot Dumaresq MD, FRCPC, microbiologiste-infectiologue, Hôtel-Dieu de Lévis, CISSS de Chaudière-Appalaches, Lévis

Dr Charles-Langis Francoeur MD, M.Sc., FRCPC, intensiviste et interniste, CHU de Québec – Université Laval (Hôpital de l'Enfant-Jésus), Québec

Dr Elie Haddad MD, PhD., immunologue, CHU-Sainte-Justine, Université de Montréal, Montréal

Dr Philippe Jutras MD, FRCPC, microbiologiste-infectiologue, Hôpital de Rimouski, CISSS Bas-St-Laurent, Rimouski

Dr Vilayvong Lougnarath MD, FRCPC, microbiologiste-infectiologue, CHU de Québec – Université Laval (Hôpital Enfant-Jésus), Québec

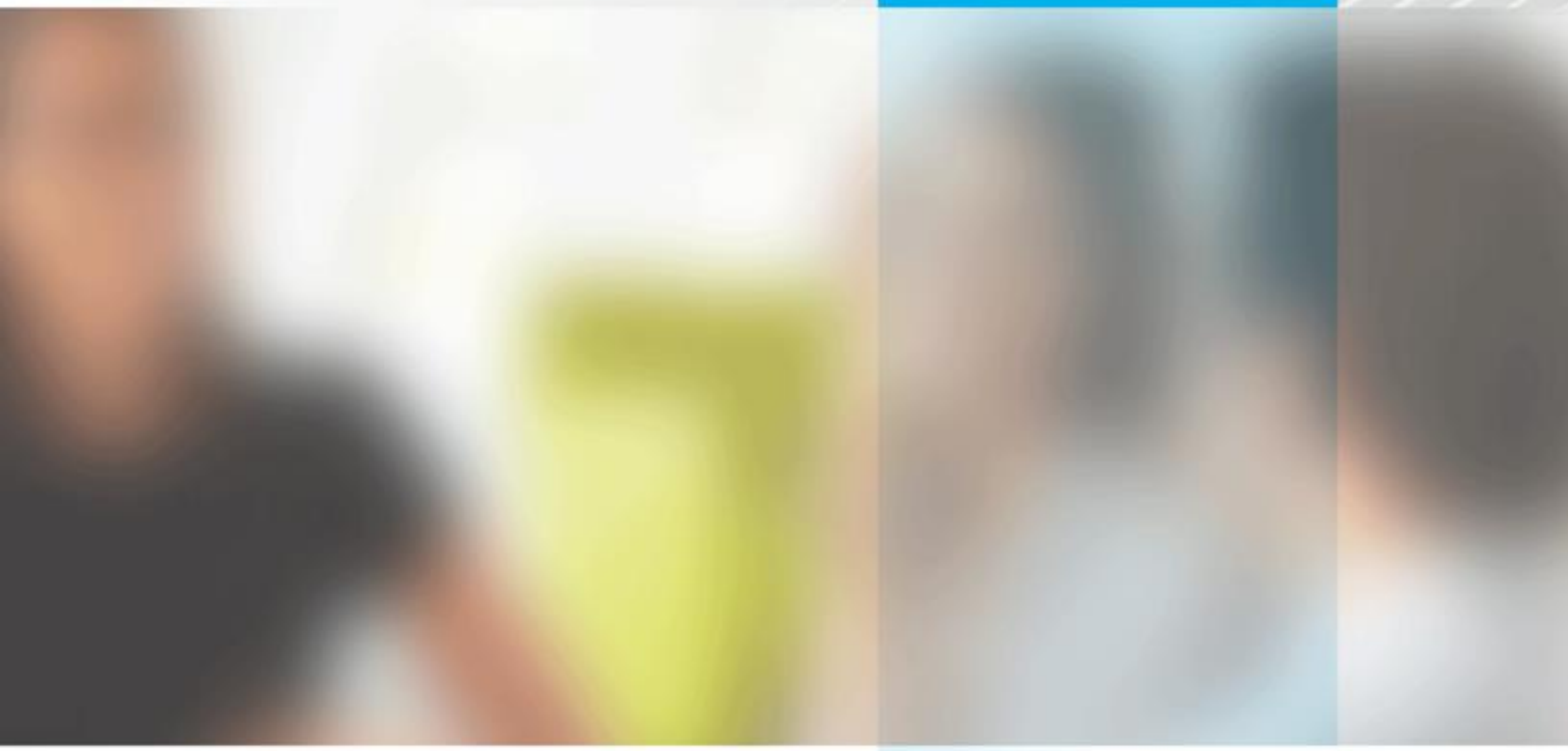
Dre Me-Linh Luong MD, FRCPC, microbiologiste-infectiologue, CHUM, Montréal

M. Christopher Marquis, B. Pharm., M.Sc., pharmacien, CHU-Sainte-Justine, Montréal

Dr Alexis Turgeon MD, M.Sc., FRCPC, intensiviste et anesthésiologiste, CHU de Québec – Université Laval (Hôpital de l'Enfant-Jésus), Québec

Dr Louis Valiquette MD, FRCPC, microbiologiste-infectiologue, CIUSSS de l’Estrie – CHUS, Sherbrooke

Dr Han Ting Wang MD, M.Sc., FRCPC, intensiviste et interniste, Hôpital Maisonneuve-Rosemont, CIUSSS de l'est-de-l'Île-de-Montréal, Montréal



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