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Article

High Colchicine Doses Are More Effective in COVID-19 Outpatients than Nirmatrelvir/Ritonavir, Remdesivir, and Molnupiravir

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Abstract: Colchicine has an excellent basis for being effective against COVID-19 due to its anti-inflammatory, immunomodulatory, cardioprotective effects, and prevention of microvascular thrombosis. In addition colchicine has also antiviral effect, extremely favorable safety profile and since it does not exert any overt immunosuppressive activity, does not interfere with the effective viral clearing nor is associated with the occurrence of secondary infections. However, all studies to date on the effects of colchicine with low doses for COVID-19 treatment are conflicting and rather disappointing. As colchicine has the remarkable ability to accumulate intensively in leukocytes, where the cytokine storm is generated, we started high, but save doses colchicine for COVID-19 patient treatment. Our assumption was that a safe increase in colchicine doses to reach micromolar concentrations in leukocytes will result in NLRP3 inflammasome/cytokine storm inhibition and will enhance its antiviral effect by inducing microtubule dissociation. Outpatients' high-dose colchicine treatment practically prevents hospitalizations. The total colchicine uptake analysis demonstrates reverse relationship with hospitalization. The period of colchicine uptake analysis demonstrates reverse relationship with hospitalization and post-COVID-19 symptomatics. Unlike the WHO-recommended antiviral preparations molnupiravir, remdesivir and paxlovid, colchicine, in addition to its antiviral effect, prevents the cytokine storm, and therefore has a strong effect not only in outpatients, but also in inpatients. Unlike antivirals, colchicine significantly reduces post-COVID-19 symptoms. The side effects of colchicine are similar to those of paxlovide. Colchicine price is incomparably lower and it is also easily available.

Keywords: COVID-19; colchicine; colchicine doses; colchicine side effects; antiviral drugs; cytokine storm

Introduction

Successful treatment of COVID-19 outpatients is the biggest challenge. Around 80% of patients with COVID-19 were classified as mild (non-or mild pneumonia) and recover without specific

treatment. However, about 15% of patients deteriorated (severe COVID-19) and 5% were critical [1]. These 20% of patients, who require hospitalization. The criterion for successful outpatient treatment is a reduction in hospitalizations. After millions of publications and tens of thousands of preclinical and/or clinical studies, more than 700 agents that have been reported with anti-SARS-CoV-2 effect [2], the World Health Organization (WHO) recommends only 3 antiviral drugs for outpatient use – molnupiravir (lagevrio), remdesivir (veklury) and ritonavir-boosted nirmatrelvir (paxlovid). All these drugs that inhibit viral replication, have serious side effects, their effectiveness varies widely and are very expensive [3–5].

In theory, colchicine has an excellent basis for being effective against COVID-19 due to its antiviral effects, anti-inflammatory effects, immunomodulatory effects, prevention of microvascular thrombosis and cardioprotective effects [4,6–9]. However, all studies to date on the effects of colchicine have been conducted with low doses of colchicine and the results are conflicting and rather disappointing, when evaluating its efficacy in inpatients [4,10–13].

In previous publications we demonstrated an excellent effect of high-dose colchicine in 785 inpatients, whose mortality decreased in a dose-dependent manner between 2- and 7-fold [14–17]. We are now demonstrating the effect of colchicine in the treatment of outpatients, while also monitoring their post-COVID-19 symptoms.

Materials and Methods

The therapy with high doses colchicine for COVID-19 patients was approved by the Medical Control Commission of UMBAL "Aleksandrovska" EAD, Sofia, Bulgaria (Protocol No. LKK-17-3-54-2020). All the patients were particularly questioned about liver and kidney chronic diseases and possible drug-drug interactions, informed about the side effects of high doses of colchicine and their consent was acquired.

We prepared a questioner for the outpatients treated with high colchicine doses for the period of October 2020 – May 2021. This period includes the two major COVID-19 waves in Bulgaria and all then existing SARS-CoV-2 variants, including delta (https://ncpha.government.bg/uploads/pages/103/AnalyticalReport_COVID_19.pdf). The collected data was analyzed statistically.

Statistical Analysis

Statistical analysis included the following:

- (a) Summary statistic tables of baseline characteristics: age, BMI and number of comorbidities, smoking status alongside disease specific information such as previous COVID-19 infections, subsequent COVID-19 infections despite therapy, days of prophylaxis, total number of tablets taken, total milligrams (mg) taken.
- (b) Chi-square analysis of proportions: proportion experiencing reinfection, proportion of patients requiring hospitalization
- (c) Student t-test for mean comparisons
- (d) Relative risk calculations
- (e) Sample size estimation

All statistics calculations were conducted in MedCalc Statistical Software Version 22.0014 (© 2023 MedCalc Software Ltd.)

Results

Sample size Estimation

Age-adjusted mortality in Bulgaria is around 15.5%, with the estimated mortality during peak COVID-19 contagion reaching 20.2%. Thus, we aimed to capture a sufficient sample size that would capture this 4.7% difference, meaning colchicine reduced mortality to pre-COVID levels within a 5% (Δ) margin of error and 95% confidence (type I error probability $\alpha = 0.05$, type II error $\beta = 0.20$) which resulted in a minimum sample size of 540 patients

Baseline Characteristics

A total of 547 responses were collected. Baseline characteristics of questioned patients are summarized in Tables 1 and 2 with the respective number of patients with available data, as well as missing data. Majority of patients filled in the sections on demographics and duration of Colchicine use. As well as post-COVID-19 symptoms. Majority of patients were elderly, with slightly elevated BMI, however low number of comorbidities. Mean duration of prophylactic intake of colchicine was 46 days. Vaccination coverage was reported at 29.07% which seems consistent with other official data from Bulgaria, as well as the percentage share of smokers (40.32%). Age distribution histogram of responders (Figure 1) indicates a heterogeneous mix of interviewees, which is a potential bias-minimization indicator.

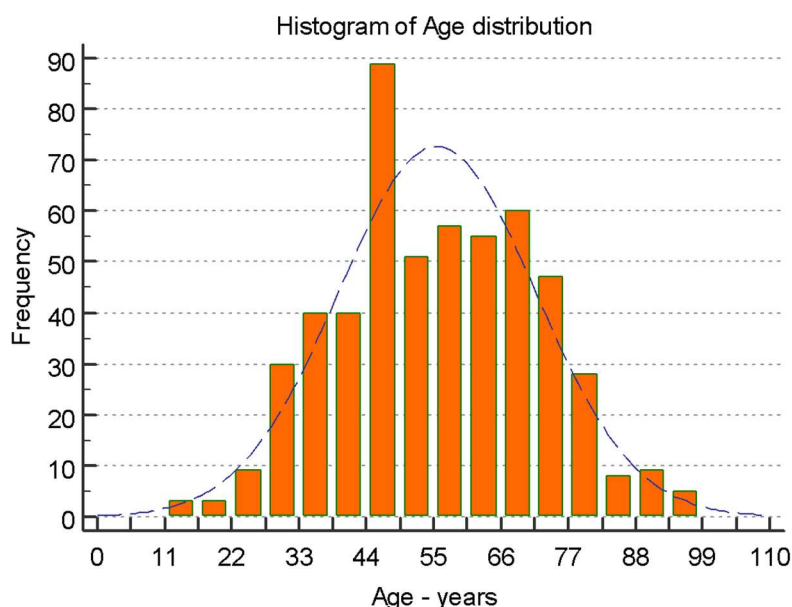


Figure 1. Age distribution histogram of responders.

Table 1. Baseline characteristics of included patients.

Parameter (n)	Min	1st Qu. 25%	Media n 50%	Mean	3rd Qu. 75%	Max.	95% CI	Stand. Dev	Variance
Age (years) (534)	20	57	65	64.57	72	95	62.83 66.31	12.49	259.9109
BMI (kg/m ²) (390)	14.53	22.49	25.25	25.56	27.76	65.74	25.06 to 26.05	4.956	24.5662
Days of C. intake (493)	1	7	10	13.36	20	45	12.65 to 14.06	7.98	63.7474
Number of tablets (492)	3	25	40	46.51	62	172	43.91 to 49.13	29.47	868.5608
Total mg of intake (492)	1.5	12.5	20	23.29	31	86	21.95 to 24.56	14.73	217.1402
Number of	0	0	1	1.02	1	5	0.93 to 1.17	0.92	0.8524

Comorbidi ties (375)									
Number of Post- COVID-19 symptoms	0	0	3	3.274	5	12	3.016 – 3.532	2.9235	8.5469
Colchicine group(496)									
Number of post- COVID-19 symptoms NO	0	1	6	5.326	9	12	4.751-6.321	3.193	15.1142
Colchicine group (112)									
Number of Cigarettes per day (224)	0	10	15	13.83	20	40	12.65 to 15.01	8.93	79.8425

The analysis shows decrease by 2.052 of the post-COVID-19 symptoms/patient ($p < 0.001$).

Table 2. Percent share distribution of responses to yes and no questions.

Colchicine Intake	N=547
Yes	496 (91.91%)
No	51 (7.59%)
unknown	0 (0.0%)
Vaccination Status	N = 547
Yes	159 (29.07%)
No	382 (69.84%)
Unknown	6 (1.09%)
Have you had COVID-19 More than once?	N = 547
Yes	135 (24.68%)
No	377 (68.92%)
Unknown	35 (6.04%)
Smoking Status	N = 547
Yes	219 (40.32%)
No	321 (58.48%)
Not specified	7 (1.2%)
Hospitalizations due to COVID-19 prior to Colchicine	N = 531
Yes	145 (26.51%)
No	402 (73.49%)
Hospitalizations due to COVID-19 after Colchicine	N = 496
Yes	32 (6.05%)
No	464 (93.95%)
Not specified	0 (00.00%)
Diarrhoea related to colchicine use	N = 496

Yes	426 (86.06%)
No	70 (13.94%)
Bromhexine Inhalations during treatment	N = 442
Yes	349 (78.96%)
No	93 (21.04%)
Unknown	N = 114
Bromhexine table form intake	N = 468
Yes	149 (31.84%)
No	319 (68.16%)
Unknown	n = 79

Highlighted is the number of hospitalized patients prior and after colchicine treatment.

Relative risk calculations show that there is a significant reduction in hospitalizations. The relative risk reduction in the treatment group was 76.38% lower from the control with an Absolute risk reduction of 20.86% in the entire population.

Relative risk -	0.2434
95% CI	0.1693 to 0.3499
z statistic	7.630
Significance level	P < 0.0001

Odds ratio calculations show similar significant reductions in the hospitalization rate of 80.88%, conclusively showing that the subsequent hospitalization rate is reduced in the active treatment group.

Odds ratio	0.1912
95% CI	0.1275 to 0.2868
z statistic	7.998
Significance level	P < 0.0001

Analysis shows a significant (about 4-fold) decrease of hospitalization due to the administration of high colchicine doses in outpatients. The decrease could be even bigger because part of the patients admitted to have been hospitalized not because they needed to, but as a preventive measure in the beginning of the pandemics.

Effect on Colchicine on Re-Infection Likelihood

As mentioned in the introduction section and in previous publications, the main effect of Colchicine is inhibition of the NLRP3 inflammasome after infection, which is why re-infection rates should not be affected by colchicine use. The purpose of this analysis was to confirm that no bias indicators were present and that groups were heterogeneous and randomly selected. Table 3 shows that there is no mean difference in the proportion of re-infected individuals. Because of the lack of colchicine on the re-infection rate we do not advise prophylactic colchicine administration.

Table 3. Mean re-infection rates as reported by participants and respective mean difference.

	Sample size	Mean	Std. Dev.	Variance	95% CI	Difference from No colchicine	P-value from no colchicine
No colchicine	51	34.09%	47.95	22.99	19.51 – 48.67	-	
Up to 10 days of colchicine Intake	276	25.00%	43.38	18.82	19.86 – 30.14	14.09%	P = 0.2043
Up to 20 days of colchicine Intake	153	26.80%	44.44	19.75	19.7 – 33.89	7.29%	P = 0.3471
Up to 30 days of colchicine Intake	55	23.64%	42.88	18.38	12.05 – 35.23	10.45%	P = 0.2556

Over 30 days of colchicine Intake	10	10%	31.62	10	1.01 – 32.62	24.09	P = 0.2043
Total with colchicine	496	25.05%	43.38	18.81	21.19 – 28.91	9.045	P = 0.1901

The table shows no effect of colchicine of the re-infection rates.

Effect of Vaccine status on Re-Infection Likelihood

524 responders provided information regarding re-infection rate (Table 4), corresponding to n=23 missing data (4.2%). According to their reported outcomes, we confirm that colchicine does not reduce the likelihood of reinfection. However, Chi-Square analysis revealed that a significantly higher percentage share of vaccinated individuals have been re-infected (33.3% vs 22.6%) p= 0.0126.

Table 4. Chi-square 2x2 table of vaccinated vs unvaccinated individuals treated with colchicine and re-infection likelihood.

Have you been vaccinated?	Have you had COVID-19 more than once since treatment start		Total
	No	Yes	
No	288 (77.4%)	84 (22.6%)	372 (71.00%)
Yes	101 (66.7%)	51 (33.3%)	152 (29.4%)
Total	389 (74.2%)	135 (25.8%)	524
Chi-Squared	6.231	Significance	P = 0.0126

Effect of Colchicine on Hospitalizations

The hospitalization rate among responders was 25.5% for the No colchicine group, and 6.05% for the entire colchicine group. The lowest hospitalization rate was observed in the group with 30 consecutive days of colchicine use. There was no significant observed difference in mean hospitalization rates within the colchicine prophylaxis group. However, hospitalization rates of each group showed a significant difference from the control group with the respective P-values shown right (Table 5). No patients died.

Table 5. Mean hospitalization rates reported by responders after colchicine treatment initiation.

Hospitalizations due to COVID-19 after consultation	Sample size	Mean	Std. Dev.	Variance	95% CI	Difference from No colchicine	
						No	P-value
No colchicine	51	25.5%	45.07	19.37	13.1 – 37.9	-	
Any intake of colchicine	496	6.05%	23.86	5.69	3.94 – 8.15	19.45%	P < 0.0001
Up to 10 days of colchicine	275	5.82%	23.45	5.5	3.03 – 8.6	19.68%	P < 0.0001
Up to 20 days of colchicine	159	6.92%	25.46	6.48	2.93 – 10.9	18.58%	P = 0.0007
Up to 30 days of colchicine	52	3.85%	19.42	37.71	1.56 – 9.25	21.65%	P = 0.0046

All colchicine users were analyzed in regard to their vaccination status and its effect on hospitalizations (Table 6). No significant difference was observed in vaccine effectiveness on hospitalization. From all 496 ambulatory patients, 31 total hospitalizations were observed with 5.9% of those being unvaccinated and 6.6% vaccinated. Among hospitalized patients the higher percentage

share was of unvaccinated (70% vs 30%). Both Tables 5 and 6 indicated that for one colchicine lowers hospitalization rates significantly with the benefit being more pronounced in vaccinated individuals.

Table 6. Chi-square analysis of hospitalization rates among vaccinated and unvaccinated individuals post colchicine intake.

		Have you been hospitalized due to COVID-19?		
Have you been vaccinated?	No	Yes		Total
No	336	22		358 (72.2%)
	94.1% RT	5.9% RT		
	72.4% CT	70.0% CT		
	68.0% GT	4.3% GT		
Yes	128	9		139 (27.8%)
	93.4% RT	6.6% RT		
	27.6% CT	30.0% CT		
	25.95% GT	1.75% GT		
Total	465 (93.95%)	31 (6.05%)		496
Chi-Squared = 0.005		DF = 1	Significance P = 0.9453	Contingency = 0.003

RT: % of Row Total; CT: % of Column Total; GT: % of Grand Total.

Relative Risk Calculations

To estimate the impact and risk reduction of colchicine 3 separate risk ratio analyses were conducted (Tables 7–9). The last group consisted of both patients taking colchicine no more than 30 days and more than 30 days which increased the sample size from 52 to 62. According to calculations, relative risks were respectively 0.2283, 0.2714, and 0.1898 for the groups no more than 10 days, no more than 20 days and 30 days or more of colchicine intake. The highest relative risk reduction (1 – RR) was observed in the 3rd group – 91.02%.

Table 7. Relative risk calculations for 2 subgroups - no colchicine vs up to 10 days of intake.

		Have you been hospitalized due to COVID-19?		
Colchicine dose	No	Yes		Total
No colchicine	38	13		51
Up to 10 days of colchicine	259	16		275
Total	297	29		326
Relative Risk = 0.2283		95 % CI = 0.1170 to 0.4452		Significance p < 0.0001

Table 8. Relative risk calculations for 2 subgroups - no colchicine vs up to 20 days of intake.

		Have you been hospitalized due to COVID-19?		
Colchicine dose	No	Yes		Total
No colchicine	38	13		51
Up to 20 days of colchicine	148	11		159
Total	186	24		210

Relative Risk	0.2714	95% CI – 0.1297 to 0.5680	Significance p = 0.0007
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Table 9. Relative risk calculations for 2 subgroups - no colchicine vs up to 30 days or more of Colchicine.

Colchicine dose	Have you been hospitalized due to COVID-19?		
	No	Yes	Total
No colchicine	38	13	51
Up to 30 days of colchicine	59	3	49
Total	97	16	155
Relative Risk	0.1898	95% CI – 0.05720 to 0.6299	Significance p = P = 0.0066

Despite the variability of sample sizes, all confidence intervals show a Relative Risk Ratio lower than 1, showing that outpatient treatment with colchicine reduces hospitalization risk.

Colchicine safety

Of 496 patients 426 confirmed the presence of diarrhea related to colchicine use (86.06%), with n=50 (10%) missing data (Figure 2). Light diarrhea consisting of 3 bowel movements per day for the duration of treatment was reported in 242 individuals (48.79%), moderate up to 5 bowels movements per day was reported in 123 individuals (24.8%) and severe diarrhea consisting of more than 5 movements in only 11 (2.22%).

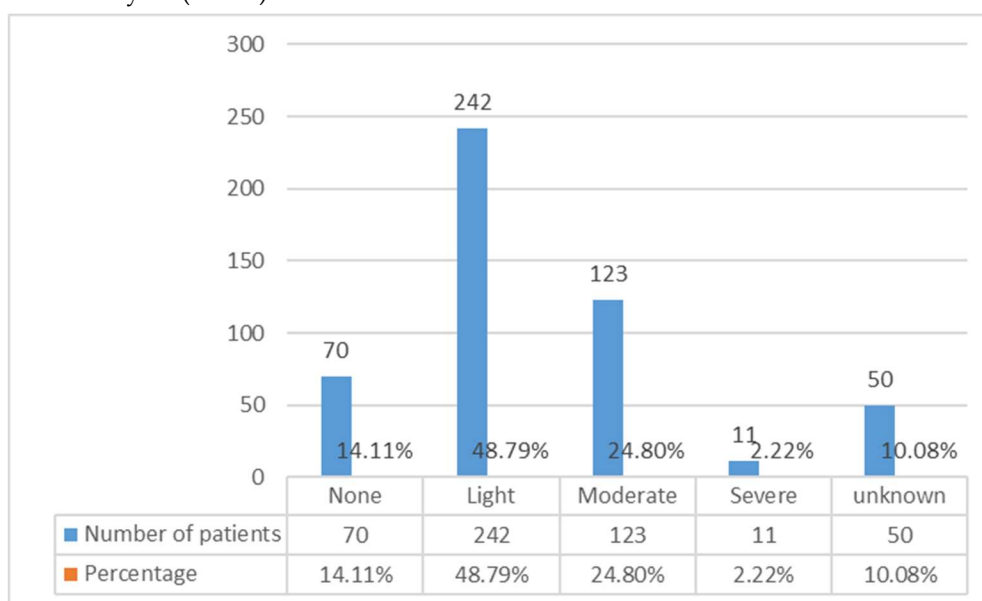


Figure 2. Distribution of Diarrhea and its severity among colchicine ambulatory patients.

Discussion

Our results demonstrate an 87% reduction in hospitalizations, which is consistent with the most optimistic data from the manufacturers of paxlovid and remdesivir. Table 10 clearly shows the advantages of high-dose colchicine compared to the antiviral drugs recommended by the WHO: simultaneous inhibition of viral replication and protection from hyperactivation of the NLRP3 inflammasome, strong effect not only in outpatients, but also in inpatients, side effects similar to paxlovid, and incomparably low cost and availability.

Table 10. Comparison between colchicine and WHO – recommended antiviral drugs: Molnupiravir, Remdesevir, Ritonavir/ Nirmatrelvir.

	Inhibition of NLRP3 inflammation	Reduced Hospitalization	Reduced Inpatient mortality	Side effects	*Cost of One course of treatment USD	References
Molnupiravir (Lagevrio)	No	30%	No	Mutagenically rejected by EMA	712	https://www.ema.europa.eu/en/medicines/human/withdrawn/applications/lagevrio .
Remdesevir (Veklury)	No	59%-87%	Conflicting results	Anaphylaxis acute liver failure	2613	19-25
Ritonavir boosted Nirmatrelvir (Paxlovid)	No	26%-88,9%	No	Contraindicated with drugs that are highly dependent on CYP3A	1158	26-29
Colchicine	Yes	76.38%	up to 7 fold	Contraindicated with drugs (Clarithromycin) that are highly dependent on CYP3A diarrhoea	14	4,11,14,16,17,70,71,81-85

*Prices in Bulgaria.

We have always recommended that bromhexine be inhaled for COVID-19 disease [11,14]. Our results demonstrate the lowest rate of hospitalization precisely with the combination of high doses of colchicine plus inhaled BRH, compared to colchicine plus BRH tablets or colchicine alone.

In addition, outpatients treated under our regimen have 2 post-COVID-19 symptoms less.

In our sample, significantly more vaccinated individuals had a secondary encounter and subsequent infection with COVID-19. Recently, Smart et al. reported that vaccinated individuals are more likely to engage in “high-risk” activities, such as avoiding social distancing, engaging in more-frequent public activities [18]. Although our questionnaire did not include a specific section on frequency of outdoor or public activities, we suspect the results from the Chi-square analysis confirm this observation, since a significantly higher proportion had a secondary COVID-19 infection. This result highlights that better strategies of patient education are needed, particularly in the country. Although healthcare specialists are aware of the benefits of vaccines in regards to hospitalization rates, this information does not seem to translate to patients. Despite the abundance of information by institutions such as the CDC and WHO [<https://www.cdc.gov/covid/vaccines/benefits.html>], patients continue to engage in risky behaviour in the face of multiple COVID mutations.

WHO Recommendations for COVID-19 Outpatient Treatment

All three antiviral drugs recommended by the WHO were reported to be quite optimistic. Subsequent research, however, cooled the initial enthusiasm of the manufacturing companies.

The European Medicines Agency (EMA) rejected the low-potency (30% reduction in hospitalizations) and mutagenically questionable molnupinavir (lagevrio) from Merck&Co Inc. (https://www.ema.europa.eu/en/medicines/human/withdrawn_applications/lagevrio).

The effectiveness of remdesivir in reducing hospitalizations ranged from 87% to 59% [19,20]. Remdesivir has a number of serious side effects, including anaphylaxis, acute liver failure and death [3] and “this medicine is to be given only by or under the immediate supervision of your doctor” (<https://www.mayoclinic.org/drugs-supplements/remdesivir-intravenous-route/side-effects/drg20503608>).

Data on the effect of remdesivir in inpatients are highly contradictory, from no positive impact on the COVID-19 mortality to some minor effect [21–25].

It is not logical to expect a reduction in mortality in inpatients from antiviral agents, such as remdesivir, when COVID-19 has entered its immunological phase (usually after the 7th day) were the viral load is lower or not detectable.

The WHO's favorite remains to be ritonavir-boosted nirmatrelvir (paxlovid), which is “strongly recommended in favor” [11].

However, paxlovid has recently suffered a real meltdown [4]. The EPIC-SR RCT demonstrated no benefit from Paxlovid in a vaccinated population, and in unvaccinated patients without risk factors. Now the guidelines recommend paxlovid only for persons who are at high risk for disease progression [26].

It was originally announced an 88.9% reduction in risk of hospitalization in paxlovid-treated outpatients (26) but these percentages varied widely from 88.9% to 26% [27]. In addition, paxlovid was not effective in hospitalized patients [28], did not reduce the risk of developing long COVID [29] and caused rebounds, or just didn't prevent them [5].

The failure of antivirals to prevent the COVID-19 complications is due to the fact that there is no direct link between viral replication and the hyperresponsiveness of the NLRP3 inflammasome [11,30,31].

It is now clear that the hyperactivation of the NLRP3 inflammasome, leading to CS and tissue injury is related with lower or non-detectable viral load [11,32–34], suggesting that SARS-CoV-2 *per se* may not be required for continuous inflammasome activation. Disease progression in fatal cases of COVID-19 is related with increasing inflammasome activation and decreasing viral load [35].

However, some patients with higher viral loads died faster, with reduced inflammatory process, and increased disseminated intravascular coagulation [35]. Inflammation and coagulation/thrombosis are closely intertwined and are key features of severe COVID-19. The aberrant activation of the NLRP3 inflammasome may also promote hyperactivation of immunothrombosis programmes [36,37].

It is worth noting that SARS-CoV-2 S protein triggered the priming and activation of the NLRP3 inflammasome resulting in hypercoagulability - mature IL-1 β formation, which enhanced production of coagulation factors such as von Willebrand factor (vWF), factor VIII or tissue factor and enhanced levels of inflammatory markers including C-reactive protein, ferritin and cytokines, associated with hyper-coagulation state [9,38,39].

Why Colchicine Is So Effective for Outpatient and Inpatient Treatment?

Similarly, to the antiviral drugs recommended by the WHO, colchicine has also antiviral effect, but in addition it can inhibit the NLRP3 inflammasome, preventing the hyper-coagulation state and the CS. Moreover, colchicine has an extremely favorable safety profile and since it does not exert any overt immunosuppressive activity, it does not interfere with the effective viral clearing nor is associated with the occurrence of secondary infections [40].

Antiviral Effects of Colchicine

Microtubules are long polymers of tubulin, that are polarized both in their intrinsic structure. They form part of the cytoskeleton, provide structure, shape to eukaryotic cells and tracks for fast transport of cargoes, including viruses, among others [41]. An intact microtubule system is essential for the process of virion formation. Two key factors determine the efficiency of the virus assembly process: intracellular transport (microtubules function as tracks) and molecular interactions [42].

At higher concentrations colchicine may induce microtubule dissociation [43]. Whereas plasma concentration after single dosing of 0.6-mg colchicine is approximately 3 nmol/L, it has been shown to accumulate in neutrophils to 40 to 200 nmol/L, well above its K_i of 24 nmol/L for microtubule polymerization [44,45]. Disrupting the microtubular network by colchicine binding to free tubulin dimers, may inhibit the SARS-CoV-2 cell entry/endocytosis, the assembly and the exocytosis/spread of the new virions. All this can affect the replication machinery within the cell, similarly to other viruses as IAVs (Influenza A viruses), flaviviruses like Zika and Dengue, RSV (respiratory syncytial virus) [46,47]. Colchicine has been demonstrated to decrease Dengue and Zika replication by inhibiting tubulin polymerization [48]. Colchicine has a proven antiviral effect in RSV where the virus replication was inhibited significantly, the level of IL-6 and TNF- α and the phosphorylation of Stat3, COX-2, and p38 were decreased also significantly [47].

In addition, Molecular Docking Analysis of colchicine demonstrated that it targets the main SARS-CoV-2 protease (Mpro) and to a lesser extent the RNA-dependent RNA Polymerase (RdRp), thus preventing viral replication [49,50].

In leukocytes, colchicine prevents microtubule polymerization, microtubule-based inflammatory cell chemotaxis, reduces their adhesion, recruitment and activation, leading to inhibition of vesicle transport, cytokine secretion and generation of leukotrienes, phagocytosis, migration and division. All these data show the great potential of colchicine against viral infections and that its antiviral effect is greatly underestimated.

Colchicine Inhibits the NLRP3 Inflammasome in Higher Concentrations

NLRs (nucleotide-binding domain, leucine-rich repeat-containing), a family of receptors form multiprotein complex (inflammasome), together with the adaptor apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and pro-caspase-1. As a component of the innate immune system, the inflammasome plays an important role in the recognition of danger-associated signals and induces pro-inflammatory cytokines, most notably IL-1 β and IL-18 [7].

NLRP3 (formerly NALP3) inflammasome is by far the most thoroughly studied NLR [49]. The NLRP3 inflammasome is vital part of the innate immune system for antiviral host defense, and has been detected in various cell types including myeloid cells, lung epithelial cells and cardiac cells [52].

The most serious complication of COVID-19 is the CS, due to aberrant activation of the NLRP3 inflammasome, with subsequent vascular inflammation, endothelial dysfunction, coagulopathy and multi-organ damage [9,53–55]. SARS-CoV-2 can activate the NLRP3 inflammasome directly (through ORF8b, S and N proteins) or indirectly (via diverse cellular signaling mechanisms) [9,11]

Rodrigues et al. also investigated whether NLRP3 inflammasome activation correlated with disease severity and clinical outcomes. They showed positive associations of caspase-1 and/or IL-18 levels with C-reactive protein (CRP), LDH, IL-6, and ferritin [56], that in turn correlated with COVID-19 severity [57–62]

This is the rationale where colchicine, a well known NLRP3 inflammasome inhibitor at micromolar concentrations, has been repurposed for the treatment of COVID-19 [63].

Colchicine has a great potential to prevent the CS and the hyper-coagulation state by inhibiting the aberrant activation of NLRP3 inflammasome. Microtubules mediate assembly of the NLRP3 inflammasome [64], therefore inhibiting the microtubule assembly, colchicine disrupts NLRP3 inflammasome activation [65].

Thus, colchicine reduces the viral load because it has an antiviral effect, and by inhibiting the NLRP3 inflammasome it prevents the CS and thrombus formation.

Dosing Strategies

The Collapse of Low-Doses Colchicine Against COVID-19

A wide variety of scientific research, including clinical trials, on the effect of colchicine as a treatment against COVID-19 continue to this day to report conflicting results [4,8,12,13,66].

The WHO does not recommend the use of colchicine, but “forgets” to specify that this applies to low doses. And why does he not recommend the application of high doses of colchicine? The explanation is simple - no clinical studies have been conducted with high doses.

Of all clinical trials with colchicine, only one gave two different doses – low (1.6 mg) and high (4.8 for 6 hours), but this was for the treatment of a gout attack. Since it is concluded that there is no difference in the effects between low and high dose colchicine, it is appropriate to use the low dose. Thus the incidence of diarrhea will drop from 76.9% to 23 % [67]. Low-dose colchicine is automatically used to fight COVID-19, even though it is a different disease. It is incredible and inexplicable that despite the fact that colchicine accumulates in white blood cells, where the CS is generated, and has the capacity to inhibit the NLRP3 inflammasome, no one has repeated the 2010 year low- and high-dose colchicine clinical trial [4,11].

Moreover, the high dose of 4.8 mg in 6 hours is even higher than our maximum loading dose of 5 mg in 24 hours. Most importantly, however, aside from the increased incidence of diarrhea, these colchicine concentrations are absolutely safe. In a number of cases, high loading doses of colchicine have been used (4 mg - 6.7 mg) [67–70]. No life-threatening side effects are described, with the most common being diarrhea. Patients treated with our regimen suffered diarrhea with frequency comparable to that in the literature [67,68]

Our Dosage Strategy

Our dosage strategy is detailed in our other publications [4,11,16,17,70,71]. In short, the NLRP3 inflammasome inhibition has been assessed at colchicine concentrations 10-to 100-fold higher than those achieved in serum [72]. However, colchicine has the remarkable ability to accumulate intensively in leukocytes, where the CS is generated [67,73,74]. Our assumption was that a safe increase in colchicine doses to reach micromolar concentrations in leukocytes will result in NLRP3 inflammasome/CS inhibition [4].

Does Colchicine Have an Immunosuppressive Effect?

There is no conclusive opinion about the immunosuppressive effect of colchicine in the literature. Most of the publications imply that used at standard doses, colchicine shows no immunosuppressive effect [75] and does not cause any significant risk of infection. This is a serious advantage of colchicine over glucocorticoids such as dexamethasone [76]. This is very important for the treatment of the first (viral) phase of COVID-19 infection, because the non-administration of immunosuppressants or glucocorticoids (which are well-known to increase the risk of infections) may be useful to avoid a decrease of the immune system [77].

According to others, colchicine as an immunosuppressive drug [78], weakens the immune system, rendering the patient prone to pneumonia infection [79,80].

Our data strongly support the opinion that colchicine does not have an immunosuppressive effect, since all unvaccinated patients treated with colchicine according to our scheme produce anti-SARS-CoV-2 antibodies.

Why Didn't We Try to Do a Randomized Clinical Trial - Ethical Considerations

Randomized clinical trials (RCTs) are the gold standard of clinical trial design. This randomization is normally performed by a computer. We firmly decided not to conduct such during the COVID-19 epidemics for the following reasons: In the spring of 2020, we were convinced of the amazing effect of high doses of colchicine in the treatment of outpatients and inpatients. We have published some of the most characteristic and severe cases [71,81–84]. Particularly interesting are the four cases of accidental overdoses of colchicine, which led to rapid recovery of the COVID-19 patients [84,85].

All of us, our families, friends, and patients with COVID-19 have been treated with the high-dose colchicine regimen. Our ethics do not allow us to put every person randomly assigned to either a treatment arm or a control arm (RCT); or the patient not knowing which group he is in (blint RCT) or neither the participant nor the researcher to know which group the participant is in (double blint RCT). How do we let the computer "to decide" whether your mother or father, sister or brother will live, deteriorate or die to make the results look more scientific?

As we have already commented [4] the large-scale, randomized, controlled RECOVERY trial, pretending to be "an exceptional study that is leading the global fight against COVID-19" analysed 2178 reported deaths among 11162 randomized patients treated with low dose colchicine [10]. The WHO automatically complies with the conclusions of these clinical trials and gives "Strong recommendation against" the use of colchicine for COVID-19 treatment [86]. The conclusion "overall result is negative", applies only for low-dose colchicine. If high doses of colchicine had been tested, the deaths in this RCT would have been about 5 times less. Because of this fundamental omission, in our view, the opportunity to save millions of human lives was missed [4].

Conclusion:

Our experience with a number of severe cases of COVID-19, high-dose colchicine led us to the following conclusions:

1. Already at the beginning of COVID-19, high doses of colchicine should be administered because of its antiviral effect, and inhibition of the NLRP3 inflammasome leading to prevention of the CS and thrombus formation.
2. Outpatients' high-dose colchicine treatment practically prevents hospitalizations.
3. Total colchicine uptake analysis demonstrates reverse relationship with hospitalization.
4. The period of colchicine uptake analysis demonstrates reverse relationship with hospitalization and post-COVID-19 symptomatics.

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