“La colchicina, quando la storia incontra il presente, illumina il futuro!”

Gloriosa superba

CONVEGNO

SCIENZA E RICERCA SULLE PIANTE AI TEMPI DEL COVID 19
SCIENCE AND RESEARCH ON BOTANICALS IN THE TIMES OF COVID -19

Mauro Lepore, MD-Endocrinologo- Acarpia Colchicina Scientific Advisor

Acarpia & Indena una collaborazione consolidata

BOTANICAL AND PHARMACOPOEIA DATA

General Information of the Herbal Substance	
Scientific Name	Gloriosa superba L.
Common Name	Glory Lily
Botanical Name	Liliaceae
Country of Origin	India
Cultivated/Wild	Cultivated
Vegetative Stage	Fructification
Harvesting Period	December- March
Part of Plant	Seed
Drying	Natural drying

The herbal substance is not derived from plants listed in CITES Appendix I,II or III.

Colchicine from Indena complies with the current European Pharmacopoeia and it is covered by the following Certificate of European Pharmacopoeia: CEP 2004-182 valid version

PRODUCTION OF ACTIVE INGREDIENT

Indena SpA

Production of Colchicine

Sites:

- **Indena SpA |Settala| Milano|Italy**
  Full process, control and batch release
  or
  Process final steps, control and batch release (in case of importation of the intermediate RAW COLCHICINE)

- **Indena India |Bangalore| Karnataka| India**
  RAW COLCHICINE

Both sites are AIFA and FDA approved

Sommario regolatorio

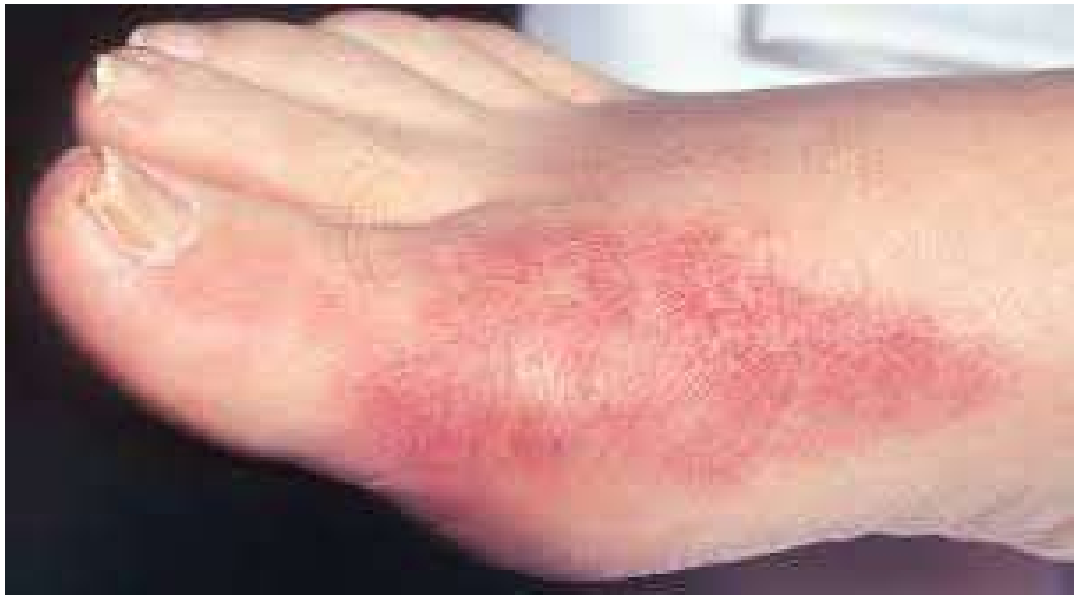
- **Colchicina Lirca** è stata registrata in Italia con procedura nazionale il **26 aprile 1955** per il trattamento **dell'attacco acuto di gotta e prevenzione dell'artrite gottosa ricorrente**

- Nel marzo **2017** è stata ottenuta l'indicazione " **Trattamento della pericardite acuta e della pericardite ricorrente "** . Acarpia è stata la prima ad ottenere questa indicazione in Europa

- Nel Febbraio **2020** la CTS AIFA ha espresso parere favorevole al rilascio di una nuova indicazione : "**Prevenzione dell'attacco di Febbre Mediterranea Familiare e dell'amiloidosi secondaria a Febbre Mediterranea Familiare nell'adulto e nell'adolescente**"

- Acarpia è fortemente impegnata nella ricerca e sviluppo di nuove indicazioni terapeutiche per la colchicina e numerosi studi clinici sono in corso

L’utilizzo clinico storico della colchicina:
La GOTTA



Il meccanismo d'azione della colchicina

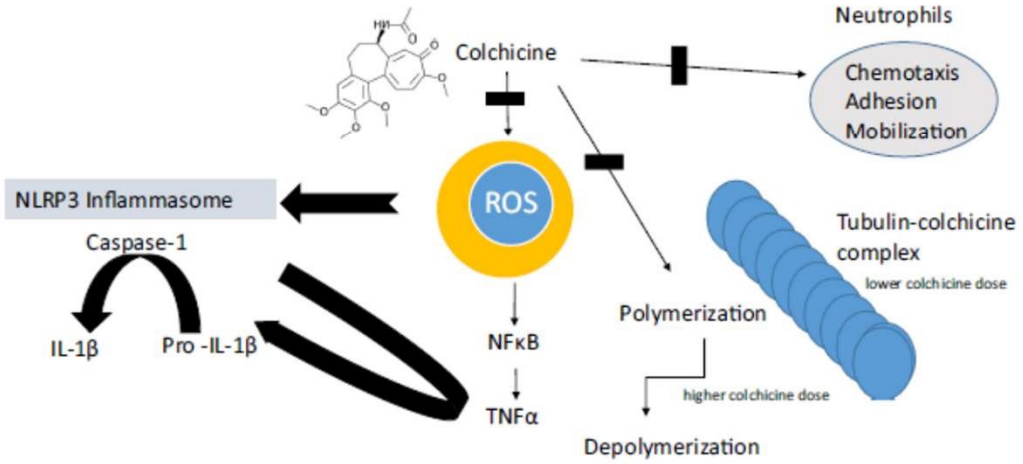


Fig. 1 Colchicine is anti-inflammatory

Published online: 18 July 2020

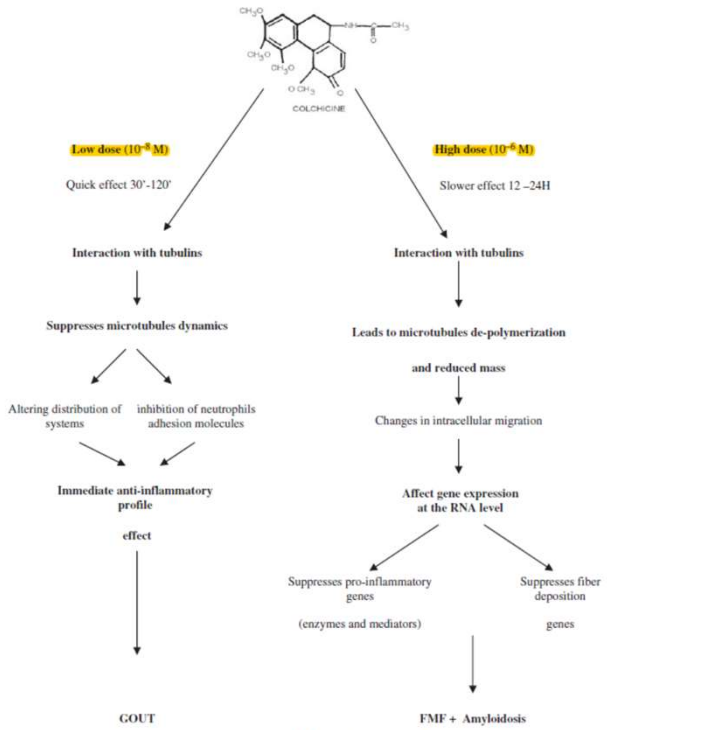


FIG. 3. A model of the mechanism of action of colchicine. The left arm shows the relatively quick effect of low concentration of colchicine through suppression of microtubules dynamics. The right arm depicts the effect of higher concentrations of colchicine through microtubules depolymerization and mass reduction. The latter activity requires 12–24 h.

Metabolismo ed escrezione della colchicina – ricircolo enteroepatico

RHEUMATOLOGY

Rheumatology 2018;57:i4–i11
doi:10.1093/rheumatology/kex453

Update on colchicine, 2017

Anastasia Slobodnick[1,2], Binita Shah[2,3], Svetlana Krasnokutsky[1,2] and Michael H. Pillinger[1,2]

Abstract

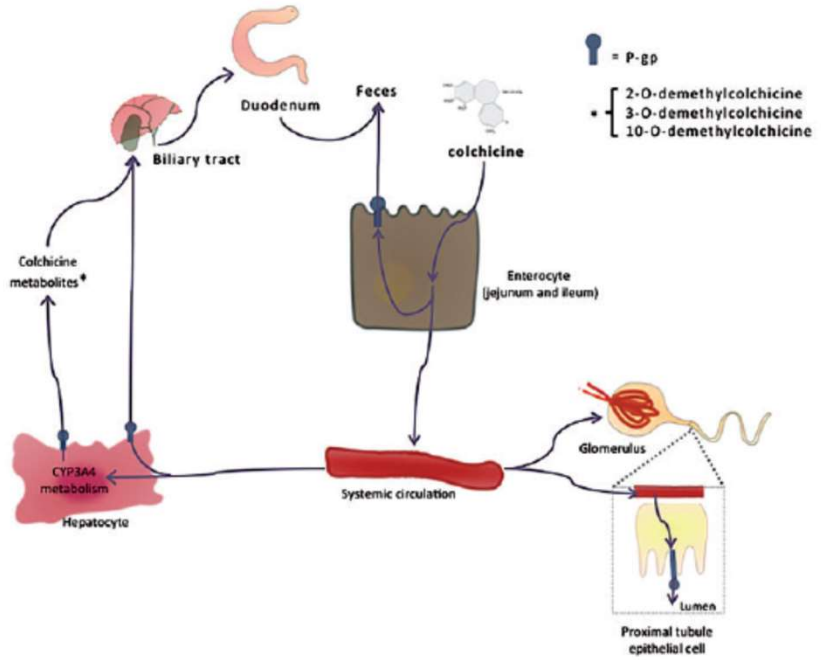
Colchicine is an ancient medication that is currently approved for the treatment of gout and FMF. However, colchicine has a wide range of anti-inflammatory activities, and studies indicate that it may be beneficial in a variety of other conditions. This paper reviews the evidence for the well-established use of colchicine in gout, as well as several other rheumatic diseases. In addition, we highlight the potential benefit of colchicine in cardiac disease, including coronary artery disease in patients both with and without gout.

Key words: colchicine, gout, cardiovascular disease, inflammation

Rheumatology key messages

- Colchicine's mechanisms of action are multiple, and more complex than previously appreciated.
- In rheumatic disease, colchicine is most useful for conditions driven by macrophages and neutrophils.
- Colchicine's anti-inflammatory effects hold promise for prevention/management of cardiovascular conditions, including acute coronary syndromes.

FIG. 1 Major mechanisms of colchicine metabolism and excretion



Colchicine is initially absorbed in the jejunum and ileum. P-Glycoprotein (P-gp) on the apical surface of enterocytes secretes a fraction of unchanged colchicine back into the lumen, from which it can be excreted. The remainder enters the systemic circulation and passes through the kidneys, where unchanged colchicine is excreted through glomerular filtration as well as through direct renal P-gp secretion into the proximal tubule. Within hepatocytes, colchicine undergoes demethylation into three distinct metabolites through the action of CYP3A4. These metabolites, along with a portion of unchanged colchicine, are secreted into the bile via hepatic P-gp, and thence into the duodenum for potential excretion.

I principali effetti collaterali - profilo di sicurezza

Stewart *et al. Arthritis Research & Therapy* (2020) 22:28
https://doi.org/10.1186/s13075-020-2120-7

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials

Sarah Stewart[1], Kevin Chih Kai Yang[2], Kate Atkins[1], Nicola Dalbeth[1] and Philip C. Robinson[2,3*]

La Colchicina aumenta la frequenza di disturbi gastrointestinali e diarrea, facilmente gestibili con aggiustamento della dose in base alla risposta clinica del paziente; è farmaco generalmente ben tollerato alle dosi terapeutiche consigliate dal medico nel range da 0,5mg fino a 3mg /die previsto nella attuale scheda tecnica e per le indicazioni approvate

Abstract

Background: Colchicine is a widely used drug to treat inflammatory diseases. Due to its long historical use in medicine, controlled clinical trials have been small and there remains some caution with the use of this drug in patients with co-morbidities. The aim of the study is to systematically examine the side effect profile of colchicine in controlled clinical trials across all published indications.

Methods: A systematic review was conducted in accordance with PRISMA methodology. The Cochrane Library, MEDLINE and EMBASE were searched for double-blind controlled trials of oral colchicine in adult patients that reported adverse event data. Meta-analyses were used to determine the relative risk (RR) of adverse events in colchicine users compared to comparator groups.

Results: A total of 4915 studies were initially identified and after exclusions, 35 randomised controlled trials with placebo ($n = 30$) or active comparators ($n = 5$) were included. The most common diseases studied were gout, liver cirrhosis and pericarditis. There were a total of 8659 pooled participants, 4225 participants were randomised to receive colchicine, 3956 to placebo and 411 to an active comparator. Diarrhoea was reported in 17.9% of colchicine users versus 13.1% in comparator groups (RR 2.4, 95% confidence interval (CI) 1.6, 3.7). Any gastrointestinal event was reported in 17.6% of colchicine users and 13.1% of comparators (RR 1.7, 95% CI 1.3, 2.3). Adverse liver events were reported in 1.9% of colchicine users versus 1.1% in the comparator groups (RR 1.6, 95% CI 0.9, 3.0). Muscle events were reported in 4.2% of colchicine users and 3.3% in the comparator groups (RR 1.3, 95% CI 0.8, 1.9). Haematology events were reported in 0.6% of colchicine users and 0.4% of comparator groups (RR 1.34 (0.64, 2.82). No study reported neuropathy events. Other sensory events were reported in 1.1% of colchicine users and 1.5% of comparator groups (RR 1.4, 95% CI 0.3, 6.7). Infectious events were reported in 0.4% of colchicine users and 2.1% of comparator groups (RR 1.0, 95% CI 0.7, 1.5). No study reported death as an adverse event.

Conclusion: Colchicine increases the rate of diarrhoea and gastrointestinal adverse events but does not increase the rate of liver, sensory, muscle, infectious or haematology adverse events or death.

Keywords: Colchicine, Gout, Diarrhoea, Nausea

La Storia ed il Presente : tra indicazioni d'uso…..

- Attacco acuto di artrite gottosa, trattamento profilattico dell'artrite gottosa ricorrente
- Trattamento della pericardite acuta e della pericardite ricorrente – **indicazione d'uso completamente ed originale sviluppata in Italia da Acarpia mediante specifico piano di ricerca clinica e presente nelle linee guida ESC**
- Trattamento cronico per la prevenzione degli attacchi acuti di Febbe Mediterranea Familiare (FMF) e prevenzione secondaria amiloidosi della FMF

….usi Off Label consolidati ed in fase avanzata di studio

- Malattia di Behçet – Eular 2018 linee guida
- Artrite da cristalli di calcio pirofosfato (Pseudogotta) e profilassi (Das 2002- Alvarellos 1986- Rheumatol 1986 Aug 13(4):804-5, Eular Zhang 2011)
- Prevenzione Sindrome Postpericardiotomia (Imazio 2010 – Imazio 2014)
- Sweet Sindrome (dermatosi neutrofila febbrile acuta)-Maillard 1999- Nestor 2017- Suehisa 1981-Suehisa 1983
- Vasculite, piccoli vasi cutanei (idiopatica) Callen 1985 – Callen 1987
- Sindrome Metabolica, Diabete ed Obesità – Luglio 2019, 21(7):1642-1651.Doi:10.1111/dom 13702

La prossima nuova indicazione d'uso supportata da solida EBM : prevenzione secondaria Post - Infarto

Colchicina e prevenzione cardiovascolare: inibizione dell'aterosclerosi associata ad infiammazione

Atherosclerosis
journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation

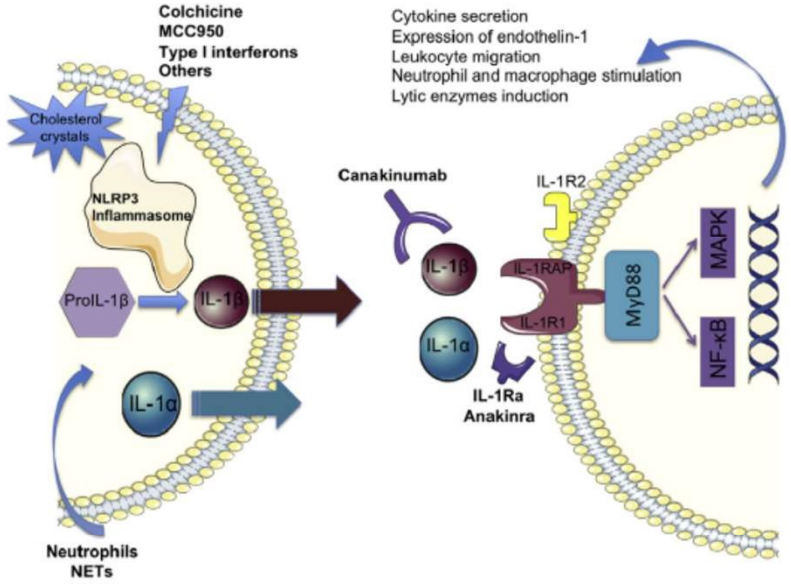


Fig. 1. Interleukin 1α and β activity, natural regulators and inhibitors.
The interleukin 1 is a complex system. While IL-1α acts immediately upon activation, IL-1β requires conversion of its precursor into the active molecule by the NLRP3 inflammasome. Both IL-1α and IL-1β act on the IL-1R1/IL-1RAP complex to activate NF-κB and MAPK signalling. This results in a series of pro-atherogenic effects. These effects can be inhibited by acting on the NLRP3 inflammasome (diminishing IL-1β and IL-18 levels) or by modulating the interaction with the IL-1R1/IL-1RAP complex (i.e. canakinumab, anakinra). IL-1Ra and IL-1R2 are natural regulators of IL-1 activity.

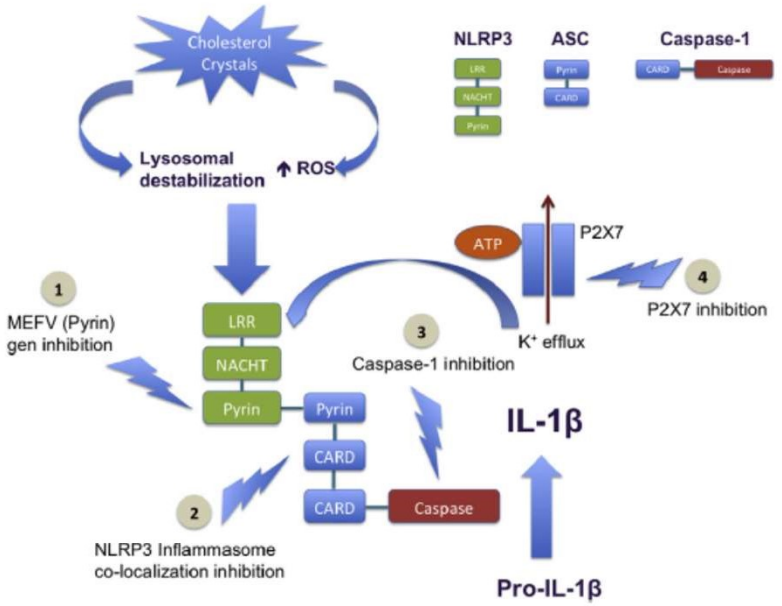


Fig. 2. Colchicine inhibition of the NLRP3 inflammasome.
At least four purported mechanisms of inhibition of the NLRP3 inflammasome by colchicine have been described. 1) Inhibition of MEFV gene resulting in Pyrin (receptor) inhibition; 2) inhibition of inflammasome cytoplasmic co-localization due to tubulin interference; 3) direct caspase-1 blockage; 4) inhibition of P2X7-mediated pore formation resulting in decreased K+ efflux. The final result is inhibition of active form IL-1β (and probably IL-18) production.

Sviluppo in ambito cardiovascolare: prevenzione secondaria Post Infarto dalle evidenze preliminari allo studio COLCOT

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Colchicine Acutely Suppresses Local Cardiac Production of Inflammatory Cytokines in Patients With an Acute Coronary Syndrome

Gonzalo J. Martínez, MD;* Stacy Robertson, PhD;* Jennifer Barraclough, MBBS; Qiong Xia, BSc; Ziad Mallat, MD, PhD; Christina Bursill, PhD; David S. Celermajer, MBBS, PhD, DSc; Sanjay Patel, MBBS, PhD

Conclusions—ACS patients exhibit increased local cardiac production of inflammatory cytokines. Short-term colchicine administration rapidly and significantly reduces levels of these cytokines. (*J Am Heart Assoc.* 2015;4:e002128 doi: 10.1161/JAHA.115.002128)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 26, 2019 VOL. 381 NO. 26

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., Petr Ostadal, M.D., Ph.D., Wolfgang Koenig, M.D., Denis Angoulvant, M.D., Jean C. Grégoire, M.D., Marc-André Lavoie, M.D., Marie-Pierre Dubé, Ph.D., David Rhainds, Ph.D., Mylène Provencher, Ph.D., Lucie Blondeau, M.Sc., Andreas Orfanos, M.B., B.Ch., Philippe L. L'Allier, M.D., Marie-Claude Guertin, Ph.D., and François Roubille, M.D., Ph.D.

RESULTS

A total of 4745 patients were enrolled; 2366 patients were assigned to the colchicine group, and 2379 to the placebo group. Patients were followed for a median of 22.6 months. The primary end point occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02). The hazard ratios were 0.84 (95% CI, 0.46 to 1.52) for death from cardiovascular causes, 0.83 (95% CI, 0.25 to 2.73) for resuscitated cardiac arrest, 0.91 (95% CI, 0.68 to 1.21) for myocardial infarction, 0.26 (95% CI, 0.10 to 0.70) for stroke, and 0.50 (95% CI, 0.31 to 0.81) for urgent hospitalization for angina leading to coronary revascularization. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P=0.35). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group and in 0.4% of those in the placebo group (P=0.03).

CONCLUSIONS

Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo. (Funded by the Government of Quebec and others; COLCOT ClinicalTrials.gov number, NCT02551094.)

In prevenzione secondaria post infarto la dose utilizzata è stata 0,5mg /die

ACARPIA

Prevenzione secondaria post infarto del miocardio: LoDoCo 2

The NEW ENGLAND JOURNAL of MEDICINE

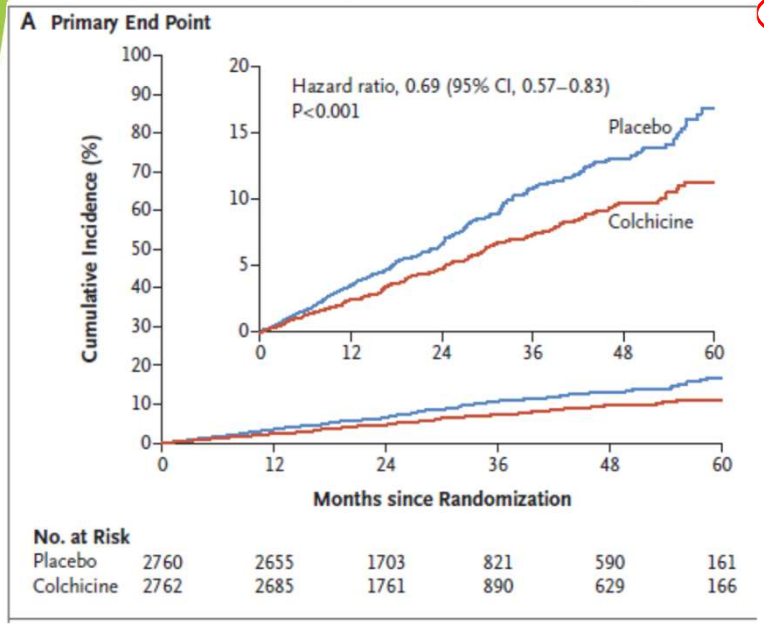
This article was published on August 31, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2021372

ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, J.W. Eikelboom, A. Schut, T.S.J. Opstal, S.H.K. The, X.-F. Xu, M.A. Ireland, T. Lenderink, D. Latchem, P. Hoogslag, A. Jerzewski, P. Nierop, A. Whelan, R. Hendriks, H. Swart, J. Schaap, A.F.M. Kuijper, M.W.J. van Hessen, P. Saklani, I. Tan, A.G. Thompson, A. Morton, C. Judkins, W.A. Bax, M. Dirksen, M.M.W. Alings, G.J. Hankey, C.A. Budgeon, J.G.P. Tijssen, J.H. Cornel, and P.L. Thompson, for the LoDoCo2 Trial Investigators*



METHODS

In a randomized, controlled, double-blind trial, we assigned patients with chronic coronary disease to receive 0.5 mg of colchicine once daily or matching placebo. The primary end point was a composite of cardiovascular death, spontaneous (non-procedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. The key secondary end point was a composite of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke.

RESULTS

A total of 5522 patients underwent randomization; 2762 were assigned to the colchicine group and 2760 to the placebo group. The median duration of follow-up was 28.6 months. A primary end-point event occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group (incidence, 2.5 vs. 3.6 events per 100 person-years; hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001). A key secondary end-point event occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group (incidence, 1.5 vs. 2.1 events per 100 person-years; hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P=0.007). The incidence rates of spontaneous myocardial infarction or ischemia-driven coronary revascularization (composite end point), cardiovascular death or spontaneous myocardial infarction (composite end point), ischemia-driven coronary revascularization, and spontaneous myocardial infarction were also significantly lower with colchicine than with placebo. The incidence of death from noncardiovascular causes was higher in the colchicine group than in the placebo group (incidence, 0.7 vs. 0.5 events per 100 person-years; hazard ratio, 1.51; 95% CI, 0.99 to 2.31).

CONCLUSIONS

In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo. (Funded by the National Health Medical Research Council of Australia and others; LoDoCo2 Australian New Zealand Clinical Trials Registry number, ACTRN12614000093684.)

Dose utilizzata 0,5mg/die

Diabete/Obesità/sindrome Metabolica - un potenziale meccanismo d'azione utile anche per combattere la Covid19

Abstract

Objective Recent clinical trials have demonstrated that colchicine may have metabolic and cardiovascular and benefits in at-risk patients; however, the mechanisms through which colchicine may improve outcomes are still unclear. We sought to examine colchicine's effects on circulating inflammatory and metabolic molecules in adults with obesity and metabolic syndrome (MetS).

Methods Blood samples were collected pre- and post-intervention during a double-blind randomized controlled trial in which 40 adults with obesity and MetS were randomized to colchicine 0.6 mg or placebo twice-daily for 3 months. Serum samples were analyzed for 1305 circulating factors using the SomaScan Platform. The Benjamini–Hochberg procedure was used to adjust the false discovery rate (FDR) for multiple testing.

Results At baseline, age (48.0 ± 13.8 vs. 44.7 ± 10.3 years) and BMI (39.8 ± 6.4 vs. 41.8 ± 8.2 kg/m^2) were not different between groups. After controlling for the FDR, 34 molecules were significantly changed by colchicine. Colchicine decreased concentrations of multiple inflammatory molecules, including C-reactive protein, interleukin 6, and resistin, in addition to vascular-related proteins (e.g., oxidized low-density lipoprotein receptor, phosphodiesterase 5A). Conversely, relative to placebo, colchicine significantly increased concentrations of eight molecules including secreted factors associated with metabolism and anti-thrombosis.

Conclusions In adults with obesity, colchicine significantly affected concentrations of proteins involved in the innate immune system, endothelial function and atherosclerosis, uncovering new mechanisms behind its cardiometabolic effects. Further research is warranted to investigate whether colchicine's IL-6 suppressive effects may be beneficial in COVID-19.

https://doi.org/10.1038/s41366-020-0598-3

BRIEF COMMUNICATION

Clinical Research

Colchicine's effects on metabolic and inflammatory molecules in adults with obesity and metabolic syndrome: results from a pilot randomized controlled trial

Andrew P. Demidowich[1,2,3,5] · Jordan A. Levine[1] · Richard Apps[4] · Foo K. Cheung[4] · Jinguo Chen[4] · Giovanna Fantoni[4] · CHI Consortium · Tushar P. Patel[1] · Jack A. Yanovski[1]

Received: 23 March 2020 / Revised: 3 May 2020 / Accepted: 7 May 2020

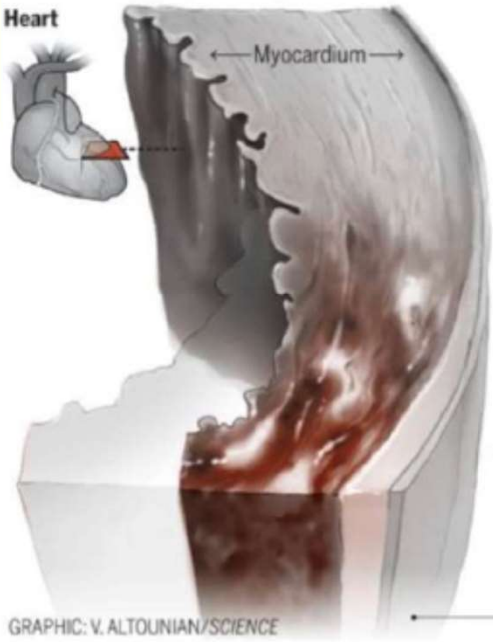
Covid 19 e complicanze cardiopolmonari

Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19)

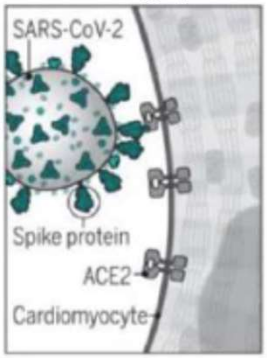
Chaomin Wu[1,2*], Xianglin Hu[2*], Jianxin Song[3*], Chunling Du[1*], Jie Xu[4], Dong Yang[2], Dechang Chen[5], Ming Zhong[6], Jinjun Jiang[2], Weining Xiong[7], Ke Lang[2], Yuye Zhang[2], Guohua Shi[8], Lei Xu[9], Yuanlin Song[1,2,10,11†], Xin Zhou[12†], Ming Wei[13†], Junhua Zheng[13,14†].; The first batch of medical teams from Shanghai to support Hubei, China and study group.

Damaging the heart

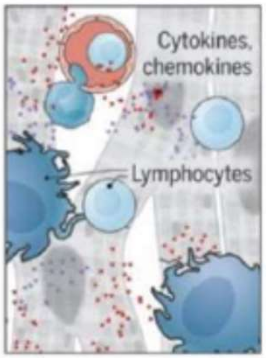
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has the potential to directly and indirectly induce cardiac damage.



GRAPHIC: V. ALTOUNIAN/*SCIENCE*



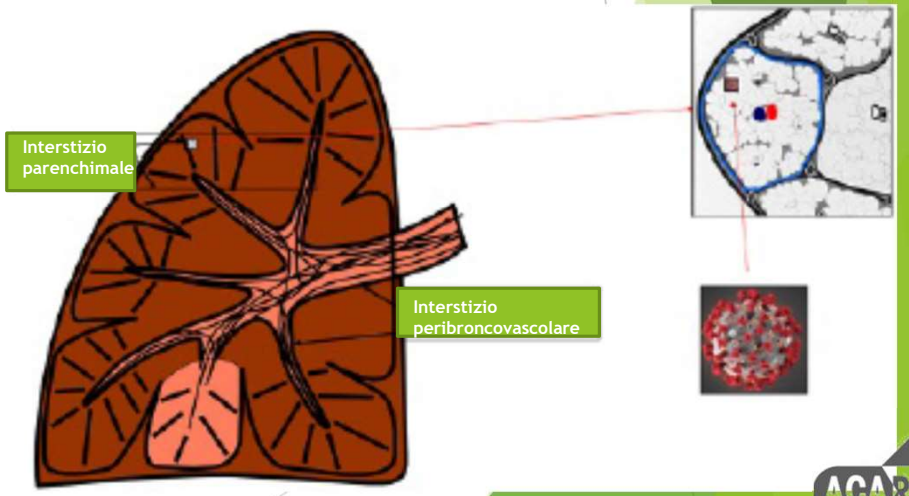
SARS-CoV-2 can **directly infect** cardiomyocytes, attaching to angiotensin-converting enzyme 2 (ACE2) through its spike protein and entering the cells by fusing viral and cellular membranes.



SARS-CoV-2 infection can **indirectly damage** cardiomyocytes through systemic inflammatory responses and diminished blood supply (e.g., from blood clots and endothelitis, not shown).

Complications

Damaged cardiomyocytes, necrosis, and cardiogenic shock can result from direct and/or indirect effects of SARS-CoV-2 infection. This can lead to scarring and thinning of the myocardium, myocarditis, cardiomyopathy, arrhythmias, and potentially cardiac arrest.



Razionale per lo sviluppo di protocolli di trattamento clinico precoce in corso di Covid 19

mayo
Mayo Clinic Proceedings
March 1997
Volume 72
Number 3

Colchicine Versus Prednisone as Treatment of Usual Interstitial Pneumonia

William W. Douglas, M.D., Jay H. Ryu, M.D., Julie A. Bjoraker, M.D., Darrell R. Schroeder, M.S., Jeffrey L. Myers, M.D., Henry D. Tazelaar, M.D., Stephen J. Swensen, M.D., Paul D. Scanlon, M.D., Steve G. Peters, M.D., and Richard A. DeRemee, M.D.*

I cortisonici e la colchicina nelle polmoniti interstiziali sono studiati dal 1997…

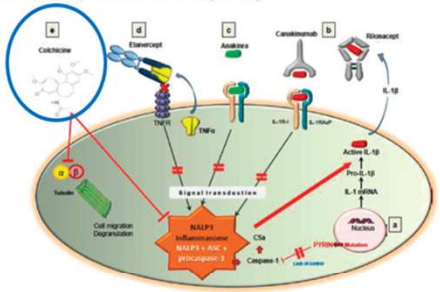
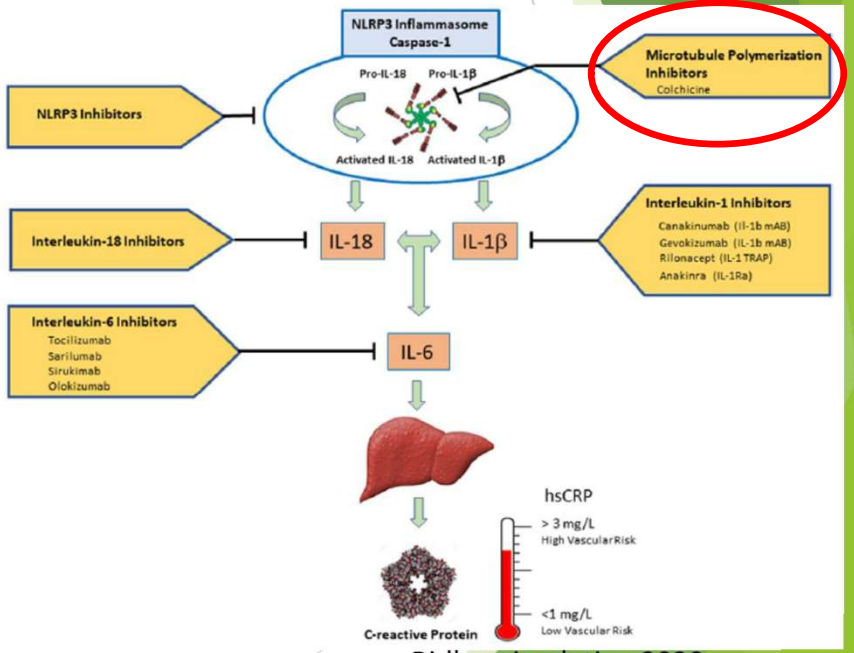


Figure 2. Treatment with cochicine, TNF blo…e.g., Etanercept) or IL-1β blockade (e.g., Anakinra, Canakinumab, Rilonacept) can lead to inactiv… of the NALP3 inflammasome (Figure was originally published by Wang DQH *et al.* and cited with …mission in this paper as reference [18]). Abbreviation: C5a, Complement protein fragment C5a.

Int. J. Mol. Sci. **2016**, *17*, 725

…i coronavirus attivano l'inflammasome… La colchicina inibisce l'attivazione dello inflammasome….



Ridker circulation 2020

Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome

J.L. Nieto-Torres et al. / Virology 485 (2015) 330–339

Gli studi clinici nella Covid19 - il contributo italiano

Review article

The anti-viral facet of anti-rheumatic drugs: Lessons from COVID-19

Carlo Perricone[a], Paola Triggianese[b], Elena Bartoloni[a], Giacomo Cafaro[a], Angelo F. Bonifacio[a], Roberto Bursi[a], Roberto Perricone[b], Roberto Gerli[a,*]

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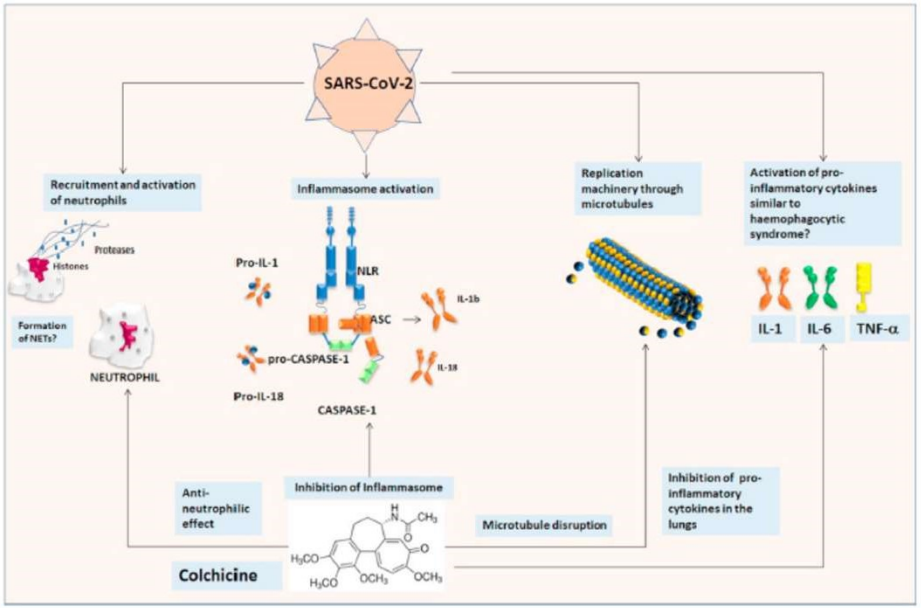

Review article

I.F.C. Italian Federation of Cardiology

Anti-inflammatory therapies for pericardial diseases in the COVID-19 pandemic: safety and potentiality

Massimo Imazio[a], Antonio Brucato[b], George Lazaros[c], Alessandro Andreis[a], Mirko Scarsi[d], Allan Klein[e,*], Gaetano Maria De Ferrari[a,*] and Yehuda Adler[f,*]

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Letter to the Editor

Treating COVID-19 with colchicine in community healthcare setting

Emanuel Della-Torre[a,b,*], Fabrizio Della-Torre[c], Marija Kusanovic[d], Raffaella Scotti[e], Giuseppe Alvise Ramirez[a,b], Lorenzo Dagna[a,b], Moreno Tresoldi[e]

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ACARPIA

AIFA: Sperimentazioni cliniche - COVID-19

Nell'ambito dell'emergenza epidemiologica del Coronavirus all'AIFA è stato affidato il compito di valutare tutte le sperimentazioni cliniche sui medicinali per pazienti con COVID-19 (Decreto Legge Cura Italia Art. 17). In questa sezione sono disponibili le informazioni aggiornate sulle sperimentazioni in corso e i relativi documenti.

Di seguito le sperimentazioni già autorizzate (data autorizzazione, nome dello studio e del farmaco in sperimentazione, promotore):

- 22/04/2020 - **BARCIVID** – Studio sull'utilizzo di baricitinib
- 22/04/2020 - **INHIXACOVID** – Studio sull'utilizzo di enoxaparina
- 20/04/2020 - **ColCOVID** – Studio sull'utilizzo di colchicina
- 11/04/2020 - **COLVID-19** – Studio randomizzato sull'utilizzo di colchicina
- 09/04/2020 - **SOLIDARITY** – Studio randomizzato OMS
- 08/04/2020 - **Hydro-Stop - somministrazione precoce di idrossiclorochina** - ASUR-AV5 Ascoli Piceno
- 30/03/2020 - **Tocilizumab 2020-001154-22 (tocilizumab)** - F. Hoffmann-La Roche Ltd. -
- 27/03/2020 - **RCT-TCZ-COVID-19 (tocilizumab)** - AUSL – IRCSS di Reggio Emilia
- 26/03/2020 - **Sarilumab COVID-19 (sarilumab)** - Sanofi-Aventis Recherche & Développement
- 25/03/2020 - **Sobi.IMMUNO-101 (emapalumab/ anakinra)** - SOBI
- 22/03/2020 - **TOCIVID-19 (tocilizumab)** - Istituto Nazionale Tumori, IRCSS, Fondazione G. Pascale di Napoli
- 11/03/2020 - **GS-US-540-5773 (remdesivir)** - Gilead
- 11/03/2020 - **GS-US-540-5774 (remdesivir)** - Gilead

Sono 22 (*3* sono stati autorizzati da AIFA in Italia) gli studi clinici in corso nel Mondo e registrati in Clin.GOV : dalla profilassi studio COLCORONA al trattamento delle complicanze cardiopolmonari da Covid 19 !

COLCHICINE IN COVID-19, PILOT STUDY AIFA APPROVED
First study on April 11th2020

This project was written at the time of the coronavirus pandemic in Italy.

Study population: patients with covid-19 pneumonia with oxygen deficiency who need hospitalization assistance

In clinical study Colchicina Lirca 0,5 mg is given to patiens three times a day.

Scientific Commitee: Roberto *Gerli, Massimo Andreoni, Venerino Poletti*
Promoter Name: department of medicine, Hospital of Perugia

Agenzia Italiana del Farmaco
AIFA

6.1. Treatments Administered
Study Treatment Name:
Colchicine
Dosage formulation:
Colchicina LIRCA
1 mg Unit dose
strength(s)/Dosage level(s):
Colchicine up to 2 mg/day
Such dose is same approved by EULAR for the treatment of Gout and FMF
Route of Administration orally
Dosing instructions:
Packaging and Labeling

ACARPIA

Lo studio in Parma- Prof U Maggiore monocentrico

COVID-19 in Kidney Transplant Recipients

Ilaria Gandolfini, MD[1], Marco Delsante, MD[1], Enrico Fiaccadori, MD, PhD[1], Gianluigi Zaza, MD, PhD[2], Lucio Manenti, MD[1], Anna Degli Antoni, MD[3], Licia Peruzzi, MD[4], Leonardo V. Riella, MD, PhD[5], Paolo Cravedi, MD, PhD[6], Umberto Maggiore, MD[1]

La prima pubblicazione italiana sull'uso della colchicina in Covid 19 : si tratta di due casi descritti

Il Protocollo in corso di realizzazione

EudraCT Number: 2020-001258-23

Protocol Title

"COLCHICINE TO COUNTERACT INFLAMMATORY RESPONSE IN COVID-19 PNEUMONIA"

Protocol Number: 1.0

Investigational Compound: colchicine

Short Title: ColCOVID-19

Promoter Name and Legal Registered Address: Azienda Ospedaliero-Universitaria di Parma, Via Gramsci 14, 43126 Parma, Italy

Scientific Committee

Umberto Maggiore[1,4]

1. SYNOPSIS

Rationale

There is currently no approved treatment available for COVID-19 infection. The use of antiviral drugs Lopinavir, Ritonavir, Darunavir gave It has multiple drug-to-drug interactions with many commonly used drugs in clinical practice; thus, its clinical safety is not determined.

The recommendation for using CLC as treatment of COVID-19 is based on the hypothesis that colchicine controls the cytokine storm occurring during COVID-19 infection by modulating NLRP3 inflamma some activity.

Colchicine (CLC) is an old, low cost and easily available drug with an acceptable known clinical tolerability and safety profiles.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the clinical efficacy of colchicine relative to the control arm in adult patients hospitalized for COVID-19 with pneumonia and clinically stable conditions	Time to clinical improvement: defined as time from randomization to an improvement of two points from the status at randomization on a seven-category ordinary scale or live discharge from the hospital (whatever comes first) as recommended by Coronavirus Disease (COVID – 2019) R&D Geneva World Health Organization http://www.who.int/

Lo Studio Choice - profilassi domiciliare

EudraCT Number: 2020-001806-42
Protocol Title: **"ColcHicine in patients with COVID-19: a home CarE study"**
Protocol Number: 1
Amendment Number: [amendment number]
Investigational Compounds: **colchicine**
Short Title: **Colchicine in COVID-19**

Promoter Name and Legal Registered Address:
Società Italiana di Reumatologia (SIR), via Turati 40, 20121 Milano (MI)
Società Italiana di Medicina Generale e delle Cure Primarie (SIMG) Via del Sansovino 179, 5014
Firenze (FI)

Scientific Committee
Principal Investigators
Roberto Gerli[1]
Claudio Cricelli[2]

1.2 Objectives and endpoints

Primary	
To evaluate the efficacy of colchicine by describing:	
1. Rate of hospitalization (30 days)	a. Need for hospitalization (at 30 days after randomization)

1.4 Treatment and Duration

Participants in arm 1 will receive current care from day 1 to day 30 plus colchicine 0.5 mg every 8 hours from day 1 to day 7, then colchicine 0.5 mg every 12 hours from day 8 to day 30.
Participants in arm 2 will receive current care from day 1 to day 30.
Colchicine may be lowered at 0.5 mg every 12 hours during the first week or at 0.5 mg every 24 hours during the entire month of treatment in case of gastrointestinal symptom appearance at discretion of the Investigator. Colchicine may cause gastrointestinal side effects, particularly diarrhea, in about 9.6% of patients that usually do not require treatment discontinuation.
The maximum dose is the same approved by EULAR for the treatment of Gout and FMF.
Treatment can be withdrawn in both arms in case of clinical remission (disappearance of symptoms and two consecutive negative swabs at 24 hours) occurring prior of the 30 days after randomization.

ARM 1.

ARM 2.

Le prime evidenze pubblicate : lo studio Grecco-19

JAMA Network Open

Original Investigation | Infectious Diseases

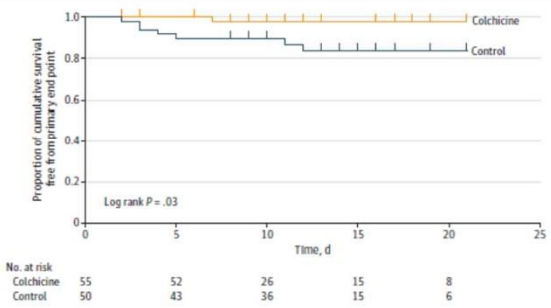
Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019
The GRECCO-19 Randomized Clinical Trial

Spyridon G. Deftereos, MD, PhD; Georgios Giannopoulos, MD, PhD; Dimitrios A. Vrachatis, MD, MSc, PhD; Gerasimos D. Siasos, MD, MSc, PhD; Sotiria G. Giotaki, M Panagiotis Gargalianos, MD, PhD; Simeon Metallidis, MD, PhD; George Sianos, MD, PhD; Stefanos Baltagiannis, MD, MSc; Periklis Panagopoulos, MD, PhD; Konstantinos Dolianitis, MD, MSc; Efthalia Randou, MD; Konstantinos Syrigos, MD, PhD; Anastasia Kotanidou, MD, PhD; Nikolaos G. Koulouris, MD, PhD; Haralampos Milionis, MD, PhD; Nikolaos Sipsas, MD, PhD; Charalampos Gogos, MD, PhD; George Tsoukalas, MD, PhD; Christoforos D. Olympios, MD, PhD; Eleftheria Tsagalou, MD, PhD; Ilias Migdalis, MD, PhD; Styliani Gerakari, MD; Christos Angelidis, MD; Dimitrios Alexopoulos, MD, PhD; Pericles Davlouros, MD, PhD; George Hahalis, MD, PhD; Ioannis Kanonidis, MD, PhD; Demosthenes Katritsis, MD, PhD; Theofilos Kolettis, MD, PhD; Antonios S. Manolis, MD, PhD; Lampros Michalis, MD, PhD; Katerina K. Naka, MD, PhD; Vlasios N. Pyrgakis, MD, PhD; Konstantinos P. Toutouzas, MD, PhD; Filippos Triposkiadis, MD, PhD; Konstantinos Tsioufis, MD, PhD; Emmanouil Vavouranakis, MD, PhD; Luis Martinèz-Dolz, MD, PhD; Bernhard Reimers, MD; Giulio G. Stefanini, MD, MSc, PhD; Michael Cleman, MD, PhD; John Goudevenos, MD, PhD; Sotirios Tsiodras, MD, PhD; Dimitrios Tousoulis, MD, PhD; Efstathios Iliodromitis, MD, PhD; Roxana Mehran, MD, PhD; George Dangas, MD, PhD; Christodoulos Stefanadis, MD, PhD; on behalf of the GRECCO-19 investigators

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, participants who received colchicine had statistically significantly improved time to clinical deterioration. There were no significant differences in high-sensitivity cardiac troponin or C-reactive protein levels. These findings should be interpreted with caution.

JAMA Network Open. 2020;3(6):e2013136. doi:10.1001/jamanetworkopen.2020.13136

Figure 2. Kaplan-Meier Curves for Survival From the Primary Clinical End Point



0.11 (95% CI, 0.01-0.96; *P* = .046). Kaplan-Meier event-free survival curves are depicted in **Figure 2**. Cumulative event-free 10-day survival was 83% vs 97% in the control and colchicine groups, respectively (Gehan statistic, 4.9; *P* = .03). Of the 7 patients who met the primary clinical end point

Treatment

CLINICAL SCIENCE

Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome

Mirko Scarsi,[1,2] Silvia Piantoni,[3,4] Enrico Colombo,[1,2] Paolo Airó,[4] Donata Richini,[1,2] Marco Miclini,[1,2] Valeria Bertasi,[2,5] Marta Bianchi,[2,5] Damiano Bottone,[2,6] Patrizia Civelli,[2,5] Maria-Sofia Cotelli,[2,5] Ezio Damiolini,[2,6] Gloria Galbassini,[1,2] Diego Gatta,[2,6] Maria-Laura Ghirardelli,[1,2] Roberto Magri,[2,6] Paola Malamani,[1,2] Monia Mendeni,[1,2] Stefano Molinari,[1,2] Andrea Morotti,[2,5] Luisa Salada,[2,6] Marinella Turla,[2,5] Angiola Vender,[7] Angela Tincani,[3,4] Antonio Brucato,[8] Franco Franceschini,[3,4] Roberto Furloni,[1,2] Laura Andreoli[3,4]

ABSTRACT

Objectives The outbreak of COVID-19 posed the issue of urgently identifying treatment strategies. Colchicine was considered for this purpose based on well-recognised anti-inflammatory effects and potential antiviral properties. In the present study, colchicine was proposed to patients with COVID-19, and its effects compared with 'standard-of-care' (SoC).

Methods In the public hospital of Esine, northern Italy, 140 consecutive inpatients, with virologically and radiographically confirmed COVID-19 admitted in the period 5–19 March 2020, were treated with 'SoC' (hydroxychloroquine and/or intravenous dexamethasone; and/or lopinavir/ritonavir). They were compared with 122 consecutive inpatients, admitted between 19 March and 5 April 2020, treated with colchicine (1 mg/day) and SoC (antiviral drugs were stopped before colchicine, due to potential interaction).

Results Patients treated with colchicine had a better survival rate as compared with SoC at 21 days of follow-up (84.2% (SE=3.3%) *vs* 63.6% (SE=4.1%), p=0.001). Cox proportional hazards regression survival analysis showed that a lower risk of death was independently associated with colchicine treatment (HR=0.151 (95% CI 0.062 to 0.368), p<0.0001), whereas older age, worse PaO2/FiO2, and higher serum levels of ferritin at entry were associated with a higher risk.

Conclusion This proof-of-concept study may support the rationale of use of colchicine for the treatment of COVID-19. Efficacy and safety must be determined in controlled clinical trials.

Lo studio proof of concept italiano!

ACARPIA

Lo studio Brasiliano

Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial

Maria IF Lopes[1], Letícia P Bonjorno[1], Marcela C Giannini[1], Natália B Amaral[1], Maíra N Benatti[1], Uebe C Rezek[1], Laerte L Emrich Filho[1], Betânia AA Sousa[1], Sérgio CL Almeida[1], Rodrigo Luppino-Assad[1], Flávio P Veras[2], Ayda Schneider[2], Tamara S Rodrigues[3], Luiz OS Leiria[2], Larissa D Cunha[3], José C Alves-Filho[2], Thiago M Cunha[2], Eurico Arruda[3], Carlos H Miranda[4], Antonio Pazin-Filho[4], Maria A Martins[5], Marcos C Borges[4], Benedito AL Fonseca[1], Valdes R Bollela[1], Cristina M Del-Ben[6], Fernando Q Cunha[2], Dario S Zamboni[3], Rodrigo C Santana[1], Fernando C Vilar[1], Paulo Louzada-Junior[1], Renê DR Oliveira[1]

Departments of [1]Internal Medicine, [2]Pharmacology, [3]Cell Biology, [4]Emergency Medicine, [5]Surgery and Anatomy and [6]Neuroscience and Behavior Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil.

450 ms. **Results.** Thirty-five patients (18 for Placebo and 17 for Colchicine) completed the study. Both groups were comparable in terms of demographic, clinical and laboratory data at baseline. Median (and interquartile range) time of need for supplemental oxygen was 3.0 (1.5-6.5) days for the Colchicine group and 7.0 (3.0-8.5) days for Placebo group ($p = 0.02$). Median (IQR) time of hospitalization was 6.0 (4.0-8.5) days for the Colchicine group and 8.5 (5.5-11.0) days for Placebo group ($p = 0.03$). At day 2, 53% vs 83% of patients maintained the need for supplemental oxygen, while at day 7 the values were 6% vs 39%, in the Colchicine and Placebo groups, respectively (log rank; $p = 0.01$). Hospitalization was maintained for 53% vs 78% of patients at day 5 and 6% vs 17% at day 10, for the Colchicine and Placebo groups, respectively (log rank; $p = 0.01$). One patient per group needed admission to ICU. No recruited patient died. At day 4, patients of Colchicine group presented significant reduction of serum C-reactive protein compared to baseline ($p < 0.001$). The majority of adverse events were mild and did not lead to patient withdrawal. Diarrhea was more frequent in the Colchicine group ($p = 0.17$). Cardiac adverse events were absent. **Discussion.** The use of colchicine reduced the length of both, supplemental oxygen therapy and hospitalization. Shortly less than half of the patients of the Colchicine group stopped receiving supplemental oxygen until day 2. Clinical improvement was in parallel with a reduction on serum levels of C-reactive protein. The drug was safe and well tolerated. Colchicine may be considered a beneficial and not expensive option for COVID-

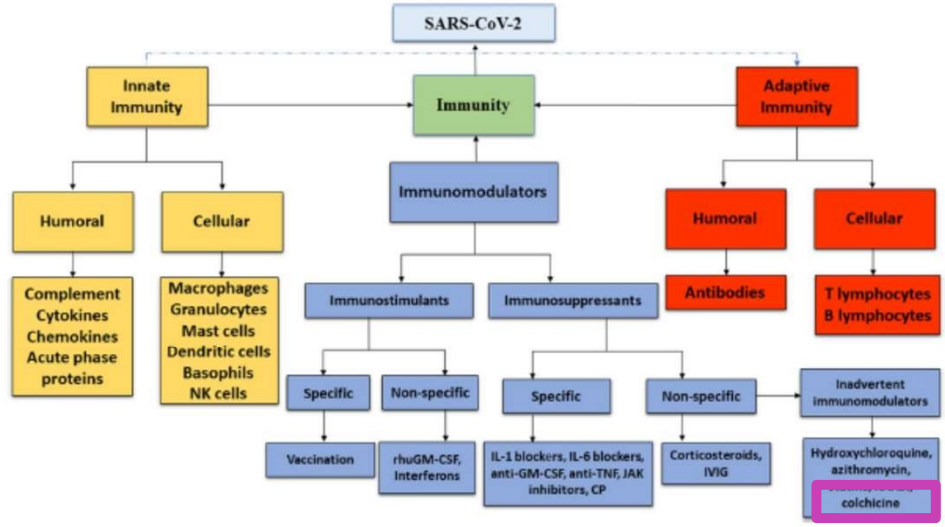
Dove si colloca la colchicina nella strategia di trattamento della Covid 19?

Drugs
https://doi.org/10.1007/s40265-020-01367-z

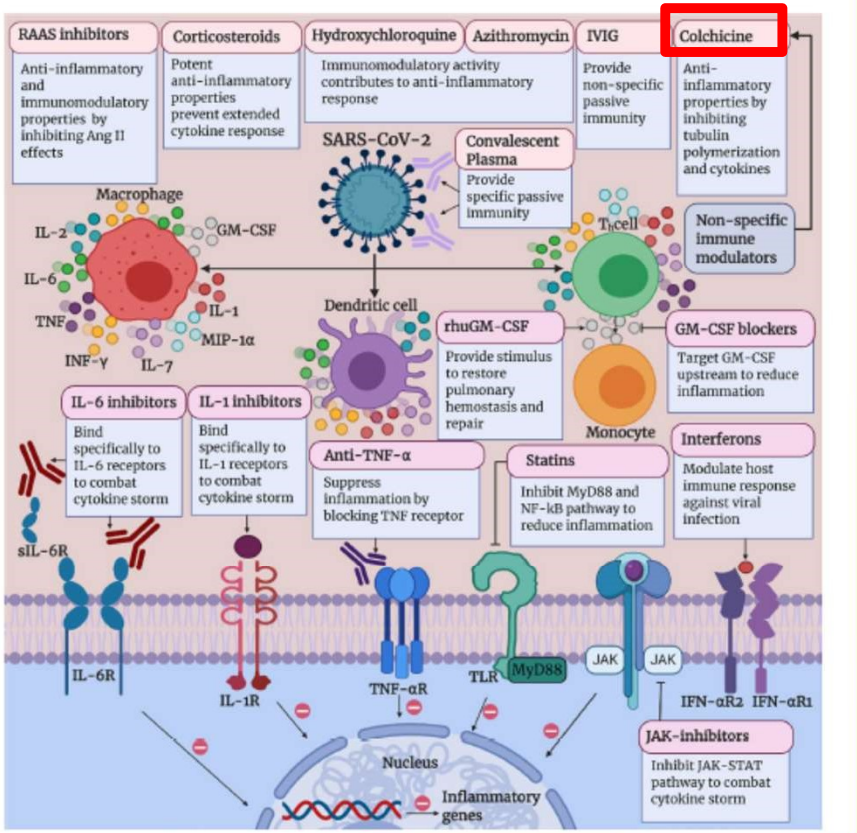
LEADING ARTICLE

Pharmaco-Immunomodulatory Therapy in COVID-19

John G. Rizk[1] · Kamyar Kalantar-Zadeh[2,3,4] · Mandeep R. Mehra[5] · Carl J. Lavie[6] · Youssef Rizk[7] · Donald N. Forthal[8,9]



Pharmaco-Immunomodulatory Therapy in COVID-19



IVIG: immunoglobuline da plasma di pazienti guariti o cocktail di anticorpi policlonali di sintesi

Meccanismi d'azione della Colchicina ed indicazioni terapeutiche - sommario

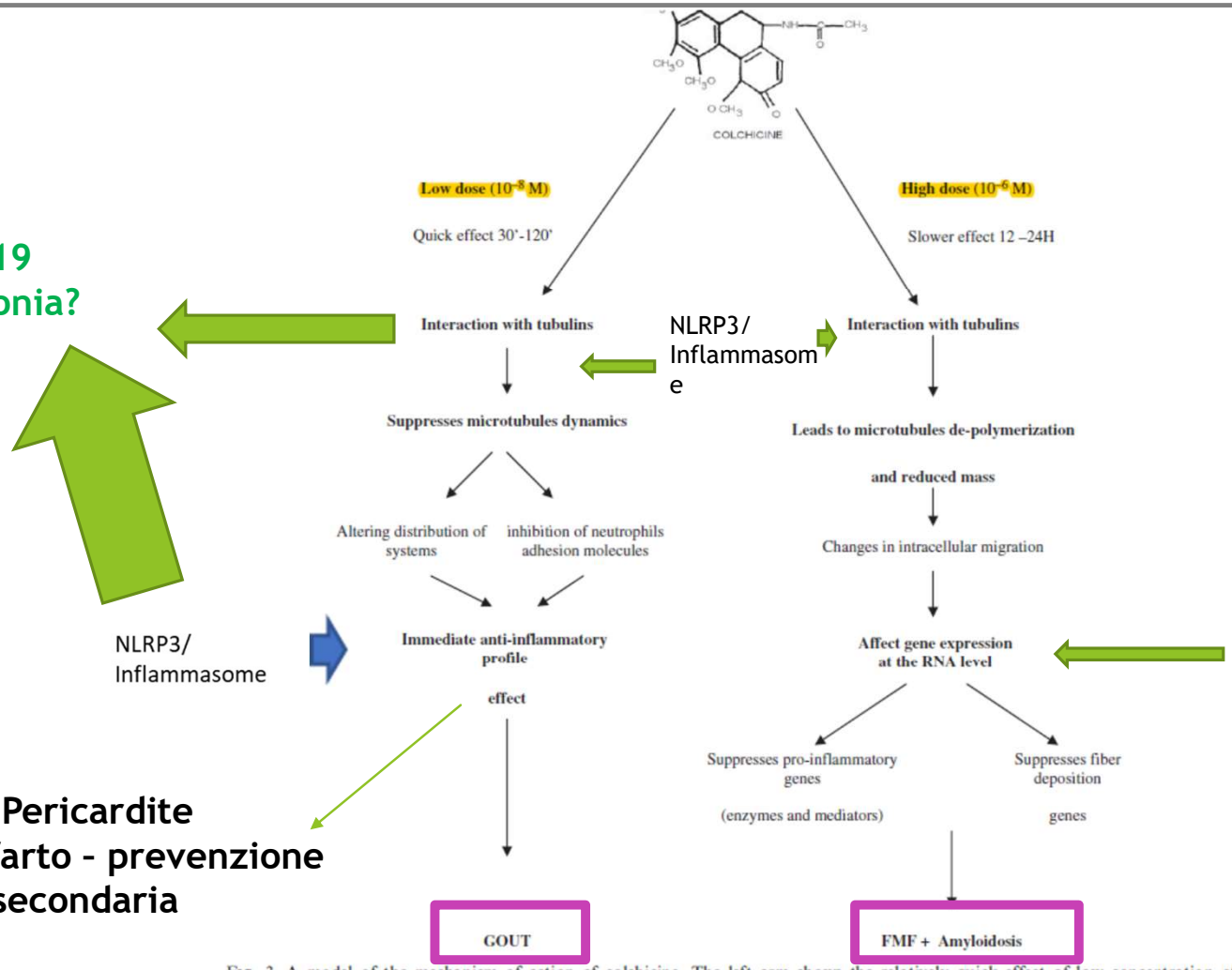


FIG. 3. A model of the mechanism of action of colchicine. The left arm shows the relatively quick effect of low concentration of colchicine through suppression of microtubules dynamics. The right arm depicts the effect of higher concentrations of colchicine through microtubules depolymerization and mass reduction. The latter activity requires 12–24 h.

COVID 19 pneumonia?

NLRP3/ Inflammasome

NLRP3/ Inflammasome

Alte dosi in cronico come nella FMF sono ben tollerate e sicure

- Pericardite
- Post infarto – prevenzione secondaria

La colchicina ….. Illumina il futuro!

Gloriosa superba

Dosaggi clinici raccomandati per indicazioni terapeutiche le più studiate

Gotta: da 2 a 3 cpr da 1 mg per i primi tre -4 giorni, per una settimana due cpr da 1 mg, poi per 3/4/5 mesi 1 cpr ogni due giorni.
In subacuto 1 o 2 cpr al giorno; come preventivo con dolore e lieve gonfiore da 1 a 2 cpr da 1 mg per uno o due giorni

Pericardite acuta e ricorrente: 0,5mgx2/die pazienti >70kg; 0,5mg una volta al giorno pazienti<70kg; trattamento da 3 a 6 mesi

Febbre Mediterranea Familiare: 1-1,5 mg /die negli adulti fino a max 3mg/die; nei bambini da 0,5 a 1 mg /die in età tra 5 e 10 anni; 1-1,5mg/die nei bambini dai 10 anni

Prevenzione secondaria post infarto : 0,5mg/die per durata di 28 mesi circa studio LoDoCo2

Gloriosa superba

« New friends may be poems but old friends are alphabets. Don’t forget the alphabets because you will need them to read the poems».
W Shakespeare

Nel buio della pandemia a volte siamo spinti a pensare oltre!

Veniamo quindi a noi, il tocilizumab in confronto alla colchicina ha il vantaggio di essere come tutti gli anticorpi monoclonali molto specifico sul bersaglio e quindi ha un profilo di sicurezza potenzialmente migliore, tuttavia interviene bloccando il recettore della IL 6 che è a valle del punto di attacco della colchicina sull’inflammasome (guardi la fig nel paper è molto didattica) che attivato porta al rilascio di IL6.
Quindi sicuramente il tocilizumab è un potentissimo immunosoppressore che blocca l’azione della IL6 e quindi nei processi infiammatori (come la polmonite da COVID 19 che è a tutti gli effetti una sindrome da eccessivo rilascio di IL6) ha una indubbia efficacia, invece la colchicina agendo a monte della cascata che porta al rilascio dell’IL6, se usata in maniera profilattica, ha tutta la potenziale capacità di bloccare il meccanismo che porta al rilascio della IL6 (come avviene nella FMF per intenderci) e quindi potrebbe essere utile anche nel trattamento preventivo della polmonite da COVID 19 in chi manifesta i sintomi inizialòi di questa complicanza che una volta sviluppata sembra rispondere bene al tocilizumab.

GRAZIE PER L'ATTENZIONE

Acarpia believes in scientific research to rediscover, in what has been, new potential for the future.

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