

Colchicine: A Promising Drug in Clinical Translation, A Minireview Focused on Cardiovascular Diseases

Benoît Lattuca, Florence Leclercq, Jean-Christophe Macia, Richard Gervasoni, Thien-Tri Cung, Jean-Luc Pasquié, François Massin, Stéphane Cade, Frédéric Cransac, Mariama Akodad, François Roubille

Benoît Lattuca, Florence Leclercq, Jean-Christophe Macia, Richard Gervasoni, Thien-Tri Cung, Jean-Luc Pasquié, François Massin, Stéphane Cade, Frédéric Cransac, Mariama Akodad, François Roubille, Department of Cardiology, Hôpital Arnaud de Villeneuve, CHU de Montpellier, UFR de Médecine, Université Montpellier 1, 371, avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 05, France

Correspondence to: François Roubille, Department of Cardiology, Hôpital Arnaud de Villeneuve, CHU de Montpellier, UFR de Médecine, Université Montpellier 1, 371, avenue du Doyen Gaston Giraud, 34295 Montpellier cedex 05, France

Email: francois.roubille@gmail.com

Telephone: +33-467335953

Fax: +33-467336230

Received: November 11, 2014

Revised: December 3, 2014

Accepted: December 8, 2014

Published online: June 10, 2015

ABSTRACT

Colchicine is a venerable drug used for centuries for rheumatic diseases with potential pleiotropic anti-inflammatory effects. One of the main concerns remains the tolerability especially digestive side effects, but this aspect has been improved by many pharmacological improvements. Nowadays, colchicine is a promising drug for cancer therapy and cardiovascular diseases with several studies currently going on, an improved therapeutic window and a wider range of translations in cardioprotection but also in atrial fibrillation, ischemic cardiopathy or pericarditis.

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Key words: Colchicine; Cardiovascular Disease; Heart; Heart Failure; Acute Coronary Syndromes; Cancer; Colchicine Derivatives

Lattuca B, Leclercq F, Macia JC, Gervasoni R, Cung TT, Pasquié JL,

Massin F, Cade S, Cransac F, Akodad M, Roubille F. Colchicine: A Promising Drug in Clinical Translation, A Minireview Focused on Cardiovascular Diseases. Osteoarthritis and Cardiovascular Diseases: is Meta-Inflammation the Missing Link. Journal of Cardiology and Therapy 2015; 2(3): 311-314 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/1201>

COLCHICINE IS A VENERABLE DRUG

Colchicine has been used for centuries for the treatment and prevention of gouty attacks and rheumatic complaints and is one of the oldest drugs still currently available as recently reviewed^[1]. The active compound was initially extracted from the plant autumn crocus^[2] but the active chemical compound was isolated only in 1820^[3]. In 1889, a large dose of tincture of Colchicum was injected in two dogs leading to the observation that anaphases was blocked during mitosis and providing the first cellular explanation of the activity of the “poison-drug”^[4]: this is functioning as a mitotic spindle poison. The structure of the active compound was elucidated only in 1955. Colchicine exerts its well-known effects including anti-cancer ones, first by blocking the tubules in the cell (spindle poison)^[1]. Secondly, it could exert pleiotropic anti-inflammatory effects. Colchicine could have also direct anti-inflammatory effects (reviewed in^[5]) by inhibiting key inflammatory signaling networks known as the inflammasome and proinflammatory cytokines. The crystals involved in the pathogeny of gout and chondrocalcinosis have been shown to engage the caspase-1-activating NALP3 inflammasome^[6], resulting in the production of active interleukin-1 β (IL-1 β) and IL-18. Moreover, impaired neutrophil influx is observed in an in vivo model of crystal-induced peritonitis in inflammasome-deficient mice or IL-1 β -receptor-deficient mice^[6]. Although the most important effect of colchicine in gouty inflammation is inhibition of neutrophil migration^[7], these data suggest an alternative mechanism for the effectiveness of colchicine through anti-inflammatory functions,

such as preventing the release of IL-1 β by the neutrophils^[8,9] independently from the impact on cell migration.

One of the main concerns remains the tolerability. This aspect can be improved by avoiding the use of loading doses and using weight-adjusted doses (i.e. 0.5 mg twice daily for patients \geq 70 kg, but only 0.5 mg daily for patients <70 kg) and the dosage should be adapted in case of concomitant administration with other medications^[10] or comorbidities such as renal impairment^[11,12] and advanced age^[13,14]. Nevertheless, its therapeutic window is narrow, and a high dosage can be life-threatening. Indeed, the treatment prescribed for one month (30 mg) could be lethal without any antidote (see for review^[1]). Chemical interactions are numerous, including some antibiotics or even statins as regards cardiovascular (CV) diseases, as recently confirmed^[15]. Improving its chemical properties in order to improve its pharmacodynamics is promising, all the more as colchicine has recently gained interest of the medical community for the treatment of various diseases, including cancer and cardiovascular diseases, two leaders of morbimortality worldwide.

CHEMICAL IMPROVEMENTS HAVE BEEN PROPOSED

As the therapeutic window is relatively narrow, several chemical improvements have been proposed to decrease its current toxicity. As colchicine has 3 different rings, various chemical modifications could induce chirality and planar changes in tridimensional conformation^[16]. Pharmacological parameters could also be modified including lipophilicity^[17]. Various *in vitro* assays can be proposed to pre-screen valuable compounds, such as the antitubulin assays for the initial evaluation of biological effects including potential antitumor impact^[18] and *in vivo* studies allow developing promising drugs. Among them, the 10-thiomethyl analogues of colchicine and derivatives have been reported to be less toxic and presenting a better therapeutic index. Among them, 3-demethylthiocolchicine has been presented as a broad-spectrum antitumor agent of considerable promise and possibly with a less toxicity^[19]. Indeed, 3-demethylcolchicine and 3-demethylthiocolchicine (3-demethyl-10-thiomethylcolchicine) and their glucosides have been shown to possess superior pharmacological properties, accompanied by decreased toxicity. In a mouse model of amyloidogenesis, 3-demethylthiocolchicine was equipotent to colchicine in the blockage of casein induced amyloidogenesis, but it was markedly less toxic^[20]. Thiocolchicine exerts its effect through interaction with tubulin at the same site as colchicine but probably with higher efficacy and affinity^[21] as well as the other derivative N-acetylcolchicinol O-methyl ether (NCME)^[22]. Finally, numerous derivatives have been proposed with a promising feature^[23,24] and some of more deeply modified derivatives have lost the tubulin interaction but are able of topoisomerase II inhibition^[25]. Similarly, some of the 7-O-substituted deacetamidothiocolchicine derivatives could exert stronger antiproliferative effect in some *in vitro* studies^[26]. Finally, colchicine derivatives have been also tested in conjugate-compounds^[27].

Obviously nearly all the studies on derivatives were led in *in vitro* models of cytotoxicity, since colchicine and its derivatives are known to bind to tubulin. Its effects were then mainly evaluated first as regards antiproliferative agent capacity, whereas their potential anti-inflammatory properties have not been specifically explored. Taken these numerous preclinical works together, the most promising agents

with therapeutic windows larger than colchicine could be good candidates for further developments.

This approach could help to propose candidates to further clinical translation, as colchicine, in spite of its present narrow therapeutic window is still under study and other large studies are planned.

COLCHICINE PROMISES FOR CANCER THERAPY AND CARDIOVASCULAR DISEASES

As briefly presented in the Table, several studies are currently going on with colchicine. With a better therapeutic window, both its anti-cancer (or derivatives^[28]) and anti-inflammatory effects are promising (Table 1). This venerable drug offers new benefits in pericardial diseases^[29-34] and might be of interest for other cardiovascular diseases (for recent review, see^[35] where the authors present the main biochemical characteristics, mechanism of action and side-effects of colchicine, as well as its promising role in cardiovascular medicine beyond pericardial disease). In various pathophysiologies involves in CV disease, when inflammation plays a role, colchicine could be a promising candidate. For instance, post-surgical atrial fibrillation is largely mediated by inflammatory response^[36] and colchicine could be of interest including after pulmonary vein isolation^[37]. For example, colchicine was suspected to exert anti-atherosclerotic actions demonstrated both by macroscopic and microscopic investigation of the aorta in rabbits^[38] and was proposed to reduce inflammation in patients with stable coronary disease^[39].

Beyond the classical anti-inflammatory effects summarized in the background section, the drug could efficiently depress the membrane addressing of high molecular mass molecules, especially the adhesion molecules^[7,40]. This mechanism is probably important. Theoretically, it could both exert non specific anti-inflammatory effects by inhibiting chemo attraction, but could also interfere with various cell-cell interactions depending on the very models and could underline pleiotropic effects (cellular proliferation, adhesion, migration, etc.).

Recently, a clinical trial supported this proposition, as colchicine was shown to be efficient to prevent restenosis after stent implantation^[41]. The favorable effect of colchicine against restenosis could be explained by (1) its ability to disrupt the mitotic spindle by inhibiting the self-assembly of microtubules; (2) its potent anti-inflammatory effect including the inhibition of neutrophils and macrophages; (3) the inhibition of the expression of cytokines (all of these aspects have been developed above); all of these processes have been largely involved in the pathophysiology of cellular hyperplasia and neointima formation leading to restenosis.

Beyond cell proliferation, pleiotropic effects could be useful in clinical settings. In patients with acute coronary syndromes, an important clinical proof-of-concept study, the LoDoCo study demonstrated a large effect of colchicine^[42]. This prospective randomized observer-blinded clinical trial studied the effect of colchicine 0.5 mg per day in 532 patients with stable coronary disease and optimal medical treatment. They were randomly assigned to colchicine or no colchicine. The primary outcome (composite incidence of acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) occurred in 15 of 282 patients (5.3%) who received colchicine versus 40 of 250 patients (16.0%) without colchicine (hazard ratio: 0.33; $p < 0.001$; number needed to treat: 11). Very few patients withdrew within 30 days due to intestinal intolerance (32 patients; 11%). These results have to be confirmed in a large multicenter study: a cheap widely available compound could have a large impact on public health.

Table 1 Ongoing clinical trials with colchicine.

Field	Pathology	Country	Number of patients	Dose of colchicin (orally)	Primary endpoint	Number in clinicaltrials.gov
Cancer	Castrate-resistant prostate cancer (after failure of taxotere-based chemotherapy)	USA	40	0.6 mg BID to a maximum of 1.2 mg BID	PSA response rate	NCT01481233
	Palliative management of hepatocellular carcinoma	Taiwan	60	1 mg three times once daily Continued during 4 days and stop for 3 days (and repeat as long as possible)	Overall survival	NCT01935700
	STEMI	Greece	75	2 mg loading dose; 0.5 mg BID for 5 days. Versus placebo	Infarct size on MRI	NCT01936285
Cardiovascular diseases	Acute coronary syndrome	Italy	500	0.5 mg once daily for 24 months. Versus placebo	Clinical outcomes at 2 years	NCT01906749
	PCI	USA	400 2 arms	1.2 mg 1 to 2 hours prior PCI, followed by 0.6 mg one hour later Versus placebo	IL6 level 30 minutes to one hour after the procedure	NCT01709981
	Atrial fibrillation Chronic/ablation	USA	60 3 arms	0.6 mg BID Versus placebo	CRP one month	NCT01755949
	Post-pericardiotomy syndrome	Italy	360	0.5 mg BID or colchicine 0.5 mg (<70kg) 48 to 72 hours before surgery till 1 months after surgery Versus placebo	Clinical outcomes 3 months	NCT01552187
	Post operative pericardial effusion	France	199	1 mg once daily during 14 days Versus placebo	change in effusion grade at day 14	NCT01266694
Others	Diabetic nephropathy	Israel	12	2 mg once daily for six months		NCT01005121
	Calcific tendonitis		80			NCT00983177

BID: bis in die; PCI: primary coronary intervention; STEMI: ST-elevation myocardial infarction.

CONCLUSION

Many biologics, immunomodulatory or anti-oxidative strategies have been proposed in various settings of cardioprotection^[43-45]. By contrast with most of these expensive approaches, colchicine is cheap and easy to obtain worldwide. Furthermore, this venerable drug appears as a good candidate to offer cardioprotection in various clinical settings, especially in chronic heart failure, in acute coronary syndromes involving or not ischemia-reperfusion injuries. Whether its promises could be held in clinical translation is currently challenged in several clinical trials.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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- Peer reviewers:** Ying-Fu Chen, Division of Cardiovascular Surgery, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, 100 Shih-Chuan 1st Rd, Kaohsiung, 80708 Taiwan; Anel Gómez García. PhD., Clinic Research Division, Biomedical Research Center of Michoacan, Instituto Mexicano del Seguro Social, Morelia, Michoacán, Mexico; Diego Fernando Dávila, Instituto de Investigaciones Cardiovasculares, Hospital Universitario de Los Andes. Ave. 16 de Septiembre, Universidad de Los Andes. Mérida, Venezuela, Apartado Postal 590, Mérida, Venezuela.