# Colchicine

**40**

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## Abstract

Colchicine is an alkaloid which was originally extracted from bulbs of a plant called Colchicum autumnale (meadow saffron). Its active pharmacological component was isolated in 1820 and in 1833 the active ingredient was purified and named colchicine. It consists of three hexameric rings termed A, B, and C. It was first recommended for the treatment of gout by Alexander of Tralles in the sixth century AD. Later it has been employed for suggested and approved indications including primary biliary cirrhosis (PBC), alcohol induced hepatitis, psoriasis, Behçet disease, Sweet syndrome, scleroderma, sarcoidosis and amyloidosis. Perhaps the most effective results have been obtained in the prophylaxis of familial Mediterranean fever (FMF). Colchicine is absorbed in the jejunum and ileum and is trapped in the body tissues. It is metabolized in the liver and the intestine by cytochrome P (CYP) 450 3A4 and P-glycoprotein (PGY) 1. Colchicine is excreted mainly by the biliary system, intestines and the kidneys. It has a narrow therapeutic range, but with normal liver and kidney functions is relatively safe and can be used during pregnancy, nursing and in infants. The main mechanism of action of colchicine is probably through interaction with microtubules affecting leukocyte chemotaxis, thereby suppressing inflammation. The blood level of colchicine may be affected by concomitant drug administration and therefore, caution should be exercised when such medications are added.

## Abbreviations

| | |
|---|---|
| ABCB1 | ATP-binding cassette subfamily B member 1 |
| AGREE | Acute Gout Flare Receiving Colchicine Evaluation |
| ARDS | Adult respiratory distress syndrome |
| COPPS | COlchicine for the Prevention of the Post-pericardiotomy syndrome |
| CRP | C-reactive protein |
| DIC | Disseminated intravascular coagulation |
| ER | Extended release |
| EULAR | European League Against Rheumatism |
| FDA | Food and Drug Administration |
| FMF | Familial Mediterranean fever |
| GEF | Guanine nucleotide exchange factor |

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| HCC | Hepatic cell carcinoma |
|---|---|
| HPLC-MS | High performance liquid chroma-tography with mass spectrometry |
| IL | Interleukin |
| ILGF1 | Insulin-like growth factor 1 |
| IV | Intravenous |
| MDR1 | Multiple drug resistant 1 |
| MSU | Monosodium urate |
| NLRP3 | NOD receptor family pyrin 3 |
| NOD | Nucleotide-binding oligomerization domain |
| PAAND | Pyrin associated autoinflammatory disease with neutrophilic dermatosis |
| PBC | Primary biliary cirrhosis |
| PGY1 | P-glycoprotein 1 |
| PKN | Protein kinases |
| PRR | Pattern recognition receptor |
| RhoA | Rat sarcoma homolog gene family, member A |
| SAA | Serum amyloid A |
| TGF | Transforming growth factor |
| TNF | Tumor necrosis factor |

**Key Points**

- **Colchicine is an alkaloid which is used for familial Mediterranean fever (FMF), gout, Behçet disease and recently for unusual additional conditions such as cardiovascular diseases**
- **Colchicine is effective in suppression of inflammation by different mechanisms. However, inhibition of neutrophil chemotaxis seems to be its main anti-inflammatory effect**
- **Colchicine is a relatively safe medication for pregnant or nursing patients with FMF provided that their liver and kidney functions are intact**
- **Colchicine is metabolized by cytochrome 3A4 which can be inhibited by many drugs leading to colchicine intoxication when given concomitantly**
- **Colchicine intoxication is a life-threatening condition. Therefore, one should be extremely cautious in using the drug in patients with renal and/or liver disturbances**

## 40.1 Introduction and Historical Notes

Colchicine is an alkaloid which has been used for centuries for treating gout [1]. The source of its name is Colchis, a kingdom on the Black Sea in Western Georgia. Its history is related to Medea who was the daughter of Aeetes, ruler of Colchis. Aeetes kept the "golden fleece" under heavy guard. His daughter, Medea used to "harvest grasses and to extract harmful juices squeezed from twisted roots" [2]. Among the most potent products squeezed from these bulb-corms was the juice of *Colchicum autumnale*, the yellow crocus of Colchis. On his quest to fetch the "golden fleece" from Colchis, Jason met Medea and fell in love with her. The princess used her potions (most of which consisted of concentrated colchicine) to help Jason poison the warriors and dragons that stood guard over the fleece.

The use of the bulb-like corms of Colchicum for gout traces back to 550 A.D., as the "hermo-dactyl (Iris)" recommended by the Byzantine physician, Alexander of Tralles (today—Aydin in Turkey) [3]. While the Greeks and Romans knew about the use of colchicine for gout, the drug wasn't available in pure form until the late nineteenth century. The active pharmacological component of the plant, colchicum, was isolated in 1820 and in 1833, P.L. Geiger purified the active ingredient, which he named colchicine [4].

In the nineteenth century, Alfred Garrod, Dyce Duckworth, and many others, reached a consensus that colchicine was relatively specific for the treatment of gout [5]. Pernice, an Italian pathologist, found that when therapeutic doses of colchicine were given to experimental animals, lesions were produced in the nuclei of gastric and intestinal cells as these cells were arrested in metaphase [6]. In 1967, Ed Taylor and Gary Borisy used tritiated colchicine to identify the target of colchicine in dividing and non-dividing cells [7]. The protein they identified was the dimeric building block of microtubules, subsequently given the name "tubulin" by Mohri [8]. We now know that the traffic of intracellular materials is carried over tracks formed by microtubules [9].

In the last 50 years, colchicine has been employed for an increasing number of diseases, in addition to gout, including familial Mediterranean fever (FMF), idiopathic recurrent pericarditis, Behçet disease, Sweet syndrome, systemic sclerosis, amyloidosis and hepatic cirrhosis [1] (Table 40.1). In acute gout, colchicine is effective in alleviating the acute attack and as a prophylactic medication. In Behçet disease, colchicine is effective mainly in the treatment of mucosal ulcers, especially in female genitalia. In systemic sclerosis, colchicine may decrease the stiffness of the skin whereas in amyloidosis it may result in regression of amyloid deposition loci where serum amyloid A (SAA) fibers are deposited [10, 11]. Since 1972, colchicine has gained popularity as being the main effective remedy for FMF [12]. In this disease, colchicine prevents the occurrence of the acute inflammatory episodes and the development of amyloidosis. However, colchicine is not effective in controlling acute attacks when administered once they occur.

**Table 40.1** Suggested and approved indications for colchicine use

| **Crystal-induced arthropathy** |
| --- |
| Gout |
| Pseudogout |
| **Liver diseases** |
| Primary biliary cirrhosis |
| Alcohol induced hepatitis |
| Prevention of hepatocellular carcinoma in cirrhosis |
| **Skin diseases** |
| Psoriasis |
| Scleroderma |
| Dermatitis herpetiformis |
| Bullous dermatosis |
| **Heart diseases** |
| Acute pericarditis |
| Chronic relapsing pericarditis |
| Prevention of coronary artery disease |
| Prevention of post-operative atrial fibrillation |
| **Miscellaneous** |
| Familial Mediterranean fever (FMF) |
| Behçet disease |
| Amyloidosis |
| Sweet syndrome |
| Sarcoidosis |

## 40.2 Chemistry and Pharmacology

- **Colchicine is an alkaloid which is absorbed in the jejunum and ileum and is trapped in the body tissues**
- **Colchicine is metabolized in the liver and the intestine by cytochrome P (CYP) 450 3A4 and P-glycoprotein (PGY) 1**
- **Colchicine is excreted mainly by the biliary system, intestine and the kidneys**
- **The half-life of colchicine is between 7 and 9 h following oral ingestion**
- **Caution should be exercised in patients with liver or kidney disease or damage**

Colchicine is a tricyclic, lipid—soluble alkaloid with the chemical formula; N-(5, 6, 7, 9, tetrahydro-l, 2,3,10, tetramethoxy-9 oxobenzo[a] hep-tain-7-yl) acetamide n (Fig. 40.1). Pharmacokinetic studies of colchicine are limited, and their results somewhat contradictory because of the different methods used for its measurement. Previously, most studies employed thin-layer chromatography, whereas recently a more sensitive radioimmunoassay and high performance liquid chromatography with mass spectrometry (HPLC- MS) has been used [13].

### 40.2.1 Absorption and Elimination

Colchicine can be administered by mouth as 0.5, 0.6 and in some localities 1 mg tablets. Until recently an intravenous (IV) formula was also available. However, in 2014, the United States Food and Drug Administration (FDA) withdrew approval following several cases of fatal toxicity [14]. Formerly, it was thought that colchicine is almost completely absorbed after oral administration. However, recent studies have shown that its bioavailability ranged from 24 to 88% [15]. The exact site of absorption is unknown, but the drug seems to reach the jejunum and ileum because dysfunction of these bowel regions is common in cases of chronic colchicine overdose [16].

The plasma membrane-localized multidrug transporter P-glycoprotein 1 (PGY 1) [also known

**Fig. 40.1** Chemical structure of colchicine
CHsO~H CH2C) k~ /2O ′~OCH3
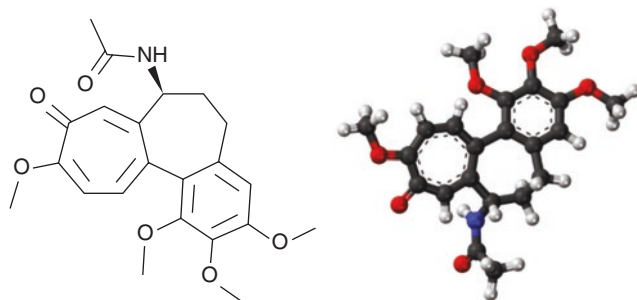


as ATP-binding cassette subfamily B member 1 (ABCB1), multiple drug resistant 1 (MDR1), and CD243] transports multiple classes of substrates across cell membranes [17, 18]. Altered intestinal PGY1 expression can change the absorption of drugs transported by this peptide, including colchicine. Therefore, PGY-1 is critical in the regulation of its bioavailability and plasma concentrations, which can lead to sub-optimal therapeutic effects or, alternatively, to drug toxicity [19, 20]. Also, PGY 1 clearly participates in the removal of drug metabolites through bile, the intestinal lumen, and urine [17–20].

Colchicine is predominantly eliminated by biliary excretion and through the stool, with gastrointestinal tract lining cell turnover playing a variable role in this process [17, 18, 21]. Normally, a lesser, but significant role in colchicine metabolism (~20%) is played by enteric and hepatic cytochrome P450 3A4 (CYP450 3A4), which catalyzes the demethylation of colchicine to 2 and 3 demethylcolchicine, which are inactive metabolites [21]. Renal elimination has been estimated to be responsible for 10–20% of drug disposition in normal subjects. However, CYP3A4 and renal disposition of colchicine can be significantly impacted by certain drug–drug interactions that affect PGY-1 (ABCB1), as well as hepatobiliary dysfunction and aging [21, 22].

The bioavailability of oral colchicine tablets is comparable in the young and elderly, but colchicine pharmacokinetics differ markedly, with volume of distribution at steady state ($V$ss) and total body clearance significantly reduced in the elderly, and the plasma $C$max significantly higher at equivalent colchicine doses [22].

Over the last decade, several single nucleotide polymorphisms of PGY 1 (ABCB1) were identified with the potential to influence expression and quantitative transporter function [23]. For instance, 5–10% of patients diagnosed with FMF do not respond to treatment with colchicine. Compared with non-responders (who usually have more severe disease)**,** treatment responders had a twofold greater concentration of colchicine in mononuclear cells, which was attributed to a potential genetic effect independent of *MEFV* mutations [23, 24]. Specifically, the distribution of ABCB1 3435 C and T-genotypes was significantly different between colchicine-responders and non-responders, with the 3435C allele significantly increasing the risk of resistance to colchicine, whereas in patients with the 3435T genotype a decreased colchicine dose was needed to obtain an adequate response [23].

### 40.2.2 Pharmacokinetic Studies of Colchicine

Wallace and Ertel [25] were pioneers in studying the pharmacokinetics of colchicine. They found that after IV administration of 1 mg of the drug to healthy volunteers, the peak plasma concentration averaged 0.32 + 1.17 μg/100 mL. After IV administration of 2.0 mg of colchicine, a rapid drop of plasma levels occurred during the first 10 min, followed by a logarithmic decline [26]. The rapidity of colchicine disappearance from the plasma and its persistent excretion days after drug ingestion suggest that it is trapped in body tissues for a prolonged period. Indeed, the

apparent volume of distribution calculated for orally administered colchicine was $4.25 \pm 2.90$ L/kg, indicating intensive tissue binding of the drug [27]. An example for such binding is the detection of colchicine in leukocytes 10 days after a single IV dose [28]. Furthermore, it was shown that in plasma 40% of the colchicine is bound to albumin [29]. After oral administration of colchicine, the Tmax (the time needed to reach peak plasma levels) is 1–3 h [14]. However, maximal anti-inflammatory effects develop over 24–48 h based upon intra-leukocytes accumulation of the drug [30].

Initial studies reported terminal elimination half-life time ($T_{1/2}$) from 19 min (after IV administration) to 16 h (after oral ingestion) [31]. In an additional study, the mean $T_{1/2}$ was 9.3 h, similar to findings in patients with FMF without renal or liver disease ($T_{1/2}$ of about $9 \pm 4$ h) [27, 32]. In a study in which we evaluated the pharmacokinetics of colchicine in patients with FMF with and without renal or liver disease, we found that colchicine clearance was significantly impaired in those with kidney or liver failure [27]. The $T_{1/2}$ of colchicine in patients with severe renal failure was two- to threefold longer and in a patient with both renal failure and cirrhosis tenfold longer than in patients with normal renal and liver function. Leighton et al. [33] reported similar results in patients with liver cirrhosis. These findings suggest that patients with either liver or renal disease should be closely monitored even when treated with conventional doses of colchicine.

## 40.3 Biological Effects

- **Colchicine binds non-polymerized tubulin forming a tubulin-colchicine complex**
- **Heterodimers of α- and β-tubulin form microtubules that can elongate and contract as filaments**
- **Colchicine, can bind the tubulin molecule and inhibit its polymerization into microtubules in vitro**
- **Since microtubules are involved in cell division, in signal transduction, regulation of gene expression and cell migration, colchicine can inhibits these functions and especially neutrophil chemotaxis**

Older studies claimed that most of the effects of colchicine at the cellular level are attributed to its interaction with tubulin, the main building block of microtubules [34]. Colchicine binds in an equimolar and poorly reversible manner to soluble non-polymerized tubulin with high activation energy, forming a tubulin-colchicine complex [21, 30, 34]. Heterodimers of α- and β-tubulin form dynamic polymers termed microtubules that can elongate and contract as filaments, to change the structure and function of the cytoskeleton, exemplified by the interphase microtubule network and the mitotic spindle. Microtubules are involved not only in cell division, but also in signal transduction, regulation of gene expression, migration, and secretion [35].

Microtubules are widely distributed in organelles present in nerve cells, ciliated cells, leukocytes, and sperm tails. It was shown that tropolone methyl ester, which is a precise analog of the ring C of colchicine, can bind the tubulin molecule and inhibit its polymerization into microtubules in vitro. Furthermore, mescaline, which is an analog of the methoxyphenyl moiety of ring A of colchicine, also may inhibit microtubular assembly [34]. These data suggest that the action of colchicine is dependent on its two rings which bind microtubules, inhibiting the movement of intracellular granules, thereby disturbing the secretion of various components to the cell exterior.

Colchicine has an inhibitory effect on several leukocyte functions such as adhesiveness, ameboid motility, mobilization and degranulation of lysosomes [1]. However, the most potent effect of colchicine is on leukocyte chemotaxis [36]. Of all the effects of colchicine, only the inhibition of chemotaxis was shown to occur at concentrations as low as $1 \times 10^{-8}$ mol/L. A higher dose is necessary to inhibit other effects. It was suggested that the primary anti-inflammatory effect of colchicine is derived from its potent inhibitory effect on leukocytes chemotaxis [37]. However, additional

studies have shown that colchicine decreases the expression of adhesion molecules on neutrophil membranes, leading to significant inhibition in migration and interaction with endothelial cells [38]. Other investigators have shown that colchicine may modulate cytokine production by polymorphonuclear cells.

Several studies have shown a relatively high concentration of colchicine in leukocytes explaining its potential effect on these cells [24, 30]. However, the cause for the special "affinity" of colchicine to leukocytes was unclear. We and other investigators, have shown that granulocytes have low activity of the PGY1 efflux pump and therefore when colchicine enters these cells it accumulates in their cytoplasm [39, 40]. Conversely, lymphocytes and mononuclear cells have a higher activity level of PGY1. Therefore, some of the colchicine entering these cells is effluxed, explaining why the level of colchicine in granulocytes exceeds that of lymphocytes and monocytes.

## 40.4 Anti–Inflammatory Mechanisms of Colchicine

- **The anti-inflammatory mechanisms of colchicine may involve activation of the rat sarcoma homolog gene family, member A (Rho A) protein, direct interaction with the *MEFV* gene or pyrin, the protein product of the gene**
- **Colchicine interacts with tubulin thereby affecting chemotaxis and modulating adhesion molecules on the membrane of leukocytes**
- **Changes in neutrophils elasticity and relaxation caused by colchicine are the most effective steps in inhibiting neutrophil chemotaxis**
- **The anti-fibrotic action of colchicine may explain its role in preventing amyloidosis**

Several mechanisms have been ascribed to the therapeutic action of colchicine (Table 40.2). Bessis and Gorius discovered that colchicine disrupts microtubules in a dose-dependent fashion [41]. Colchicine does not enhance microtubule dissolution but abrogates the process of microtu-

**Table 40.2** Biologic effects of colchicine

| |
|---|
| Abrogates the microtubule self-assembly by forming complex with tubulin |
| Reduces the generation of tumor necrosis factor (TNF)-α by macrophages |
| Abrogates E-selectin-mediated adhesiveness of endothelium to neutrophils |
| Alters distribution of adhesion molecules on endothelial cells |
| May suppress phospholipase A2 activation (at high concentrations) |
| May inhibit lysosomal enzyme release, and phagocytosis |
| Raises *MEFV* gene expression in a cell line of peritoneal fibroblasts |
| May modulate the expression of numerous genes in endothelial cells |
| Suppresses the activation of caspase-1 |
| May inhibit superoxide production by neutrophils |
| Leads to release of guanine nucleotide exchange factor (GEF)-H1 factor thereby activating rat sarcoma homolog gene family, member A (RhoA) |
| Reduces neutrophils elasticity and relaxation inhibiting chemotaxis |
| Inhibits liver fibrosis by inducing stellate cell apoptosis |
| Inhibits anti-transforming growth factor (TGF)-β1 activity |

bule self-assembly by forming tubulin-colchicine complexes [42, 43]. Colchicine reduces the generation of tumor necrosis factor (TNF)-α by macrophages and its receptors on endothelial cells [44, 45]. Colchicine also has been shown to interfere with the interaction of neutrophils and the vascular endothelium by abrogating their binding to adhesion molecules. Colchicine abrogates the E-selectin-mediated adhesiveness of the cytokine-stimulated vascular endothelium to neutrophils. It also alters the distribution of the adhesion molecules on the surface of endothelial cells and neutrophils, significantly reducing their interaction [46]. In addition, at high concentrations colchicine suppresses phospholipase $A_2$ activation, lysosomal enzyme release and phagocytosis [47]. Conversely, colchicine does not exert its anti-inflammatory effect through inhibition of cyclooxygenases [48].

In 1997, the gene likely to cause FMF was isolated and cloned [49, 50]. Following the isolation of the *MEFV* gene and the finding that it is fully expressed in neutrophils, a question was raised regarding the possibility of a direct effect of col-

chicine on the gene or its protein. In a study where we tested this hypothesis, we showed that colchicine did not up-regulate the expression of *MEFV* gene in neutrophils [51]. However, colchicine increased the *MEFV* gene expression in a primary cell line of peritoneal fibroblasts. The exact significance of this finding is unknown. Nevertheless, it should be borne in mind that peritoneal cells comprise an important target in the acute attack of FMF (peritonitis), suggesting a potential local effect of colchicine.

A few studies suggested that colchicine modulation of pyrin expression and interaction with pyrin in the cytosol contributed to its efficacy in FMF [52, 53]. At relatively high concentrations, colchicine also modulates the expression of numerous genes in cultured endothelial cells, with a significant delay in the onset of action [54]. This may explain the observation that initiation of colchicine treatment during acute attacks of FMF does not effectively terminate them.

Colchicine has recently been shown to suppress the activation of caspase-1, the enzymatic component of the nucleotide-binding oligomerization domain (NOD) receptor family pyrin 3 (NLRP3) inflammasome. Caspase-1 suppression blocks conversion of pro-interleukin (IL)-1β to active IL-1β, leading to secondary reduction in cytokines such as TNF-α and IL-6. The effect of colchicine on this process may be upstream of the inflammasome, rather than a direct effect [55]. To date, inflammasome inhibition has been assessed at colchicine concentrations 10 to 100-fold higher than that achieved in the serum. Whether colchicine inhibits caspase-1 at physiologic concentrations, or whether colchicine accumulation in leukocytes is sufficient to block the inflammasome, remains to be determined.

Another mechanism by which colchicine may suppress inflammation is by inhibition of superoxide production by neutrophils. Chia et al. demonstrated that colchicine inhibits monosodium urate (MSU)-induced superoxide production by murine peritoneal macrophages in vivo at doses 100 times lower than that required to inhibit neutrophil infiltration [56]. This suggests that superoxide anion production is more sensitive to suppression by colchicine than microtubule formation involved in cell migration.

## 40.5 How Does Colchicine Prevent Attacks of FMF?

- **Rat sarcoma homolog gene family, member A (Rho A) protein is a peptide which controls the action of GTPases thereby affects tubulin dynamics**
- **Pyrin is a specific immune sensor (pattern recognition receptor—PRR) for bacterial modifications of Rho and GTPases**
- **Activation of RhoA inhibits pyrin activity while inactivation of RhoA causes over activation of pyrin resulting in increased production of interleukin (IL)-1, thereby enhancing inflammation**
- **Colchicine may activate RhoA by guanine nucleotide exchange factor (GEF)-H1, thereby suppressing pyrin activity and inflammation**
- **Colchicine also disrupts microtubules structure reducing neutrophils membrane elasticity and relaxation, thereby preventing their extravasation from the blood vessels to the inflammatory site**

To understand this process, we first need to explain the cellular role of pyrin. Pyrin is the protein encoded by the *MEFV* gene, which is mutated in FMF (see Chap. 16). Rat sarcoma homolog gene family, member A (Rho A) protein is an intra-cellular peptide which controls the action of GTPases. GTPases are important enzymes in regulation of actin and tubulin dynamics. Actin-tubulin interaction has a major role in the motility and chemotaxis of neutrophils [37, 42–44].

Bacterial toxins such as that of Clostridium may modify the effect of Rho on GTPases, thereby inhibiting actin activity and leukocytes chemotaxis. Xu et al. found that pyrin is a specific immune sensor (pattern recognition receptor—PRR) for bacterial modifications of Rho and GTPases [57]. Pyrin does not directly recognize Rho modification, but probably senses events downstream of Rho modification. Xu et al. showed that activation of RhoA inhibits pyrin activity while inactivation of RhoA causes over activation of pyrin resulting in increased production of IL-1, thereby enhancing inflammation. Clostridium toxin inactivates RhoA thereby leading to less production or recruitment of
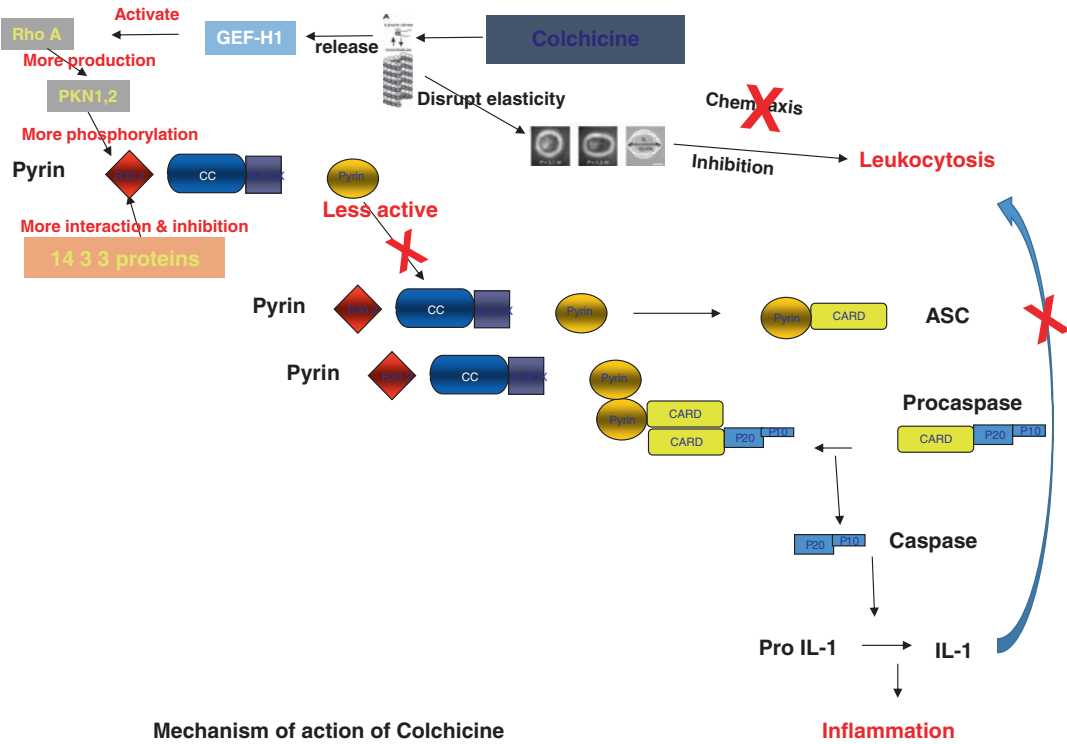
**Fig. 40.2** Schematic illustration of the inflammatory cascade of the pyrin inflammasome and the putative role of colchicine in inhibiting this process (see text)

protein kinases (PKNs) and thereby less phosphorylation of pyrin [57]. 14 3 3** peptides (**the name reflect the migration pattern on 2D DEAE gel of these acidic proteins family) are group of proteins which interact with phosphorylated pyrin [58]. Decreased phosphorylation of pyrin leads to less interaction and reduced binding by 14 3 3 peptides. This increases the amount of free pyrin which can recruit apoptosis-associated speck-like protein containing a CARD (ASC) and procaspase −1 to construct the pyrin inflammasome, leading to increased secretion of IL-1β and an enhanced inflammatory process (Fig. 40.2).

Colchicine may also suppress inflammation in FMF by the following mechanism. It binds to tubulin and depolymerizes microtubules, resulting in the release of the RhoA activator, guanine nucleotide exchange factor (GEF)-H1, which is inactive when bound to microtubules [59, 60]. Thus, colchicine indirectly activates RhoA. Activation of this protein results in enhancement of pyrin phosphorylation, thereby higher binding by the 14 3 3 pep-

tides and hence, less free pyrin is available for constructing the inflammasome, required for secreting inflammatory cytokines, including IL-1.

In a recent study, we looked more closely to the mechanistic features of the effect of colchicine on the neutrophil membrane [61]. We found that colchicine disrupts the microtubules structure and reduces neutrophil elasticity and relaxation, thereby preventing their extravasation from the blood vessels to the site of inflammation. This may be the final and most effective step in inhibiting chemotaxis.

## 40.6 The Anti-Fibrotic Action of Colchicine

Colchicine has anti-fibrotic effects. In a rat model of hypertensive chronic kidney disease, colchicine inhibited renal fibrosis via inhibition of RhoA signaling and infiltration of inflammatory cells [62]. In another rat model, colchicine inhibited liver

fibrosis by inhibiting the activation of hepatic stellate cells and inducing stellate cell apoptosis [63]. In an encapsulating peritoneal sclerosis model, colchicine inhibited anti-transforming growth factor (TGF)-β1 activity [64].

## 40.7   The Safety Profile and Toxicity of Colchicine

- **Colchicine is a relatively safe medication but has a narrow therapeutic window**
- **The metabolism of colchicine is affected by the functions of cytochrome P (CYP) 3A4, P-glycoprotein (PGY) 1, the liver and the kidneys and by additional medications taken concomitantly**

Colchicine is a relatively safe medication but has a narrow therapeutic window [65, 66]. Colchicine is well tolerated when taken in age dependent doses that are less than 2 mg/day in children (up to 12 year old) and 3 mg/day in adults with normal liver and kidney function, when not taking concomitant drugs that may affect its pharmacokinetics. Nevertheless, therapeutic oral doses of colchicine (1–2 mg/day), may cause cramping, abdominal pain, hyperperistalsis, diarrhea and vomiting. These effects are usually mild and transient. When abdominal cramps persist, lowering colchicine dose may be effective. When diarrhea persists dividing the dose of colchicine (twice daily) may be helpful. In resistant cases, a short course of anti-diarrhea medications such as loperamide may be beneficial [67]. Decreasing use of lactose containing products or using lactase prior to their consumption may also reduce symptoms. Leukopenia is a very rare adverse event in therapeutic dose and neuromuscular complications may occur when renal functions are impaired or with use of concomitant drugs such as clarithromycin.

### 40.7.1   Colchicine Overdose

Colchicine overdose may lead to a cholera-like syndrome associated with dehydration, shock, multiple organ failure, alopecia, disseminated intravascular coagulation (DIC), seizures, coma and death [68].

Colchicine doses of 0.5–0.8 mg/kg are highly toxic, and doses of more than 0.8 mg/kg are typically lethal [69]. Cumulative doses of colchicine causing toxicity when administered intravenously were 18 mg given over 11 days, 10 mg in 5 days and even 8 mg given within 3 days. The lowest reported oral dose causing lethal colchicine toxicity was 7 mg given over 3 days to a 39-year old male [70].

The course of colchicine intoxication can be divided into three stages, with overlap between the stages. In the first stage, gastrointestinal symptoms dominate. There may be excessive fluid loss through diarrhea, leading to volume depletion and dehydration. This stage develops within 24–72 h following ingestion of the drug. The second stage is dominated by multi-organ failure which may include: bone marrow failure, renal insufficiency, adult respiratory distress syndrome (ARDS), arrhythmias, disseminated intravascular coagulation (DIC), neuromuscular disturbances and alopecia. This stage develops over 3–7 days. Patients surviving this stage may enter the third stage which is characterized by bone marrow recovery and rebound leukocytosis, resolution of organ failure and regrowth of hair.

Clinical management of colchicine intoxication is basically supportive. In a single case, treatment with F(ab) fragments of anti-colchicine antibodies was successful [71]. Unfortunately, these antibodies, raised in goats, are not currently available.

One of the problems of managing colchicine overdose is that it is not dialyzable using regular dialysis membranes. Recently, new high flux polysulfone membranes have been introduced to improve dialysis [72]. Many medications and substrates which were non-dialyzable with older membranes are now dialyzable. Colchicine is one of the medications of which steady state levels were reduced when given to patients with FMF on high flux dialysis [73]. However, our study showed that the rate of excretion of colchicine by these membranes is far less than the rate needed for effective treatment of colchicine intoxication.

## 40.8 Colchicine Drug-Drug Interaction

- **Cytochrome P (CYP)3A4 is the most abundant of the human P450 enzymes and metabolizes multiple structural classes of drugs including colchicine**
- **Macrolides, anti-fungal and anti human immunodeficiency virus (HIV) drugs may have specific inhibitory effect on CYP3A4, thereby increasing colchicine blood levels**
- **Taking these drugs concomitantly with colchicine requires a reduction of the dose of colchicine to prevent toxicity**
- **On the other hand, colchicine can alter absorption of other compounds or medications from the intestines**
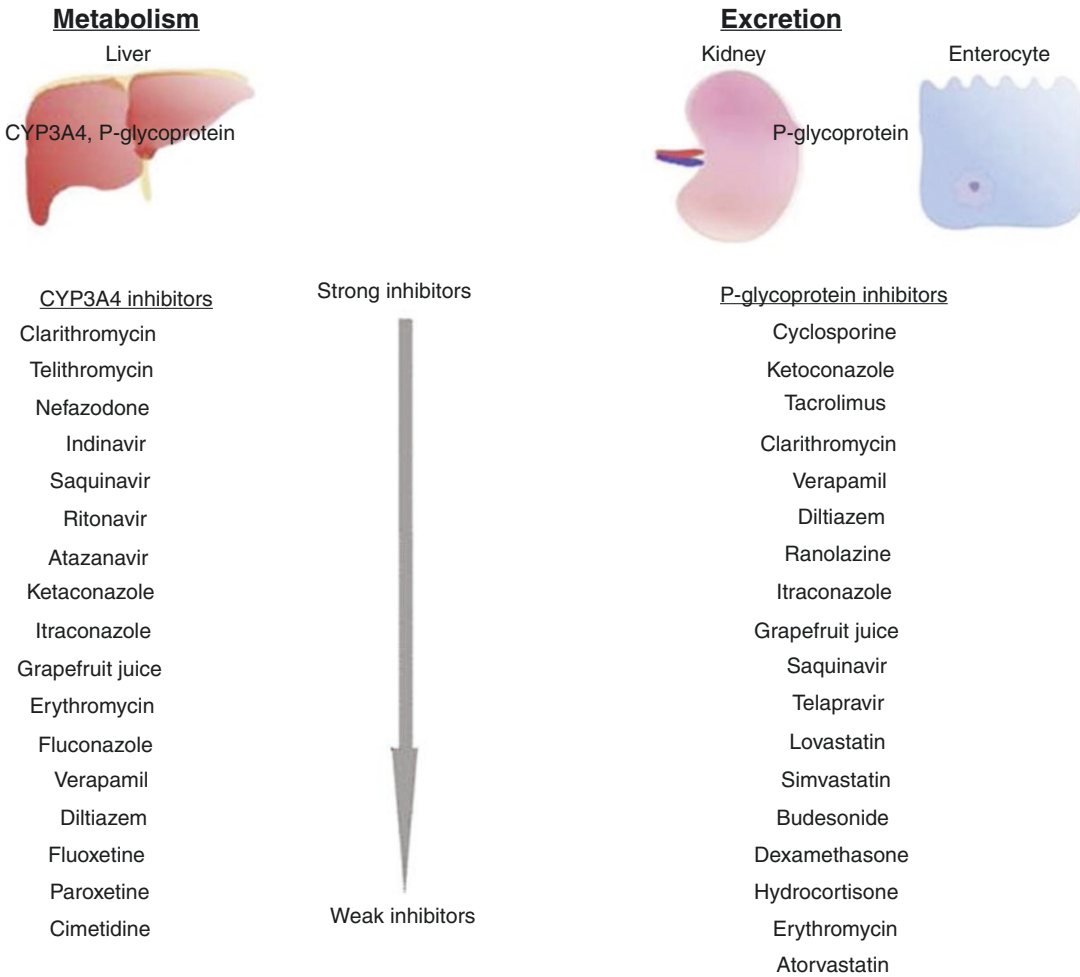
Drug–drug interactions have increasingly become apparent as a cause of colchicine toxicity in patients treated with "standard" daily prophylactic regimens. ABCB1 (PGY1) can undergo conformational changes with expression modulation thereby promoting clinically significant colchicine drug– drug interactions [16, 18, 20, 74]. Cyclosporine is a prime example of a drug that can inhibit or modulate the ABCB1 transporter [75]. Potentiation of colchicine neuromyopathy can occur within weeks of commencement of cyclosporine therapy. This complication is often associated with cyclosporine nephropathy and a decline in the glomerular filtration rate [75, 76]. Notably, cyclosporine was found to delay colchicine-induced diarrhea in an animal model system, likely due to modulation of intestinal ABCB1. Hence, it is suspected that cyclosporine could mask the gastrointestinal side effects of colchicine in humans that might otherwise be a clue to the development of systemic colchicine toxicity.

CYP3A4 is the most abundant of the human P450 enzymes and metabolizes multiple structural classes of drugs (e.g. cyclosporine, quinidine, testosterone, nifedipine, etc) [77, 78]. CYP3A4 is a focal point of many drug– drug interactions and dietary and herbal interactions. CYP3A4 may be stimulated by its substrates ("normotropic cooperativity") or its effectors ("heterotropic cooperativity"), which renders prediction of drug–drug interactions difficult [79, 80]. These substances may be divided into three groups. The first group contains drugs, such as cimetidine, which have an inhibitory effect on the entire cytochrome system. Indeed, in animal studies, it was shown that concomitant administration of cimetidine and colchicine resulted in a significant rise in serum colchicine concentration. The second group contains substances that have a specific inhibitory effect on the isoform CYP3A4 which metabolizes colchicine. These include erythromycin, ketoconazole and other medications. The third group includes drugs that are also metabolized by CYP3A4, such as cyclosporine and nifedipine, and may compete with colchicine for binding to the enzyme. The interaction in these cases is dictated by the affinity of each medication for the enzyme. Thus, co-administration of medications and substances metabolized by the same cytochrome system may lead, in principle, to an increase of one or more of the drugs, exposing the patient to a higher risk of toxicity.

Certain drugs increase the potential for colchicine toxicity via dual modulation of ABCB1 and CYP3A4 (Table 40.3). These include the macrolide antibiotics erythromycin and clarithromycin, and the statins, e.g. lovastatin, simvastatin and atorvastatin [81]. Clarithromycin is a particularly striking case in point and has been associated with at least 2 fatalities with concomitant colchicine use [82]. However, azithromycin (a weak CYP3A4 inhibitor) had minimal effects on colchicine concentration and terminal elimination half-life, and decreased total apparent oral clearance by only 30%. Azithromycin should be recommended as a safer alternative to clarithromycin in patients taking colchicine [81]. Mutual potentiation by colchicine and statins of myopathy (sometimes including rhabdomyolysis) is a notable concern [83, 84]. Significantly, case studies have reported acute myopathy after concurrent use of colchicine with a statin that was either not metabolized or minimally metabolized by the CYP3A4 isoenzyme [78, 85]. In this context, fluvastatin can disrupt the integrity of the cytoskeleton and is linked with vacuolization and other

**Table 40.3** A list of drugs which may inhibit the cytochrome P (CYP)3A4 and P-glycoprotein affecting colchicine metabolism (reproduced from Slobodnick et al. [69] with permission)

| **Metabolism** | | **Excretion** | |
| --- | --- | --- | --- |
| Liver | | Kidney | Enterocyte |
| CYP3A4, P-glycoprotein | | P-glycoprotein | |

| CYP3A4 inhibitors | Strong inhibitors | P-glycoprotein inhibitors |
| --- | --- | --- |
| Clarithromycin | | Cyclosporine |
| Telithromycin | | Ketoconazole |
| Nefazodone | | Tacrolimus |
| Indinavir | | Clarithromycin |
| Saquinavir | | Verapamil |
| Ritonavir | | Diltiazem |
| Atazanavir | | Ranolazine |
| Ketaconazole | | Itraconazole |
| Itraconazole | | Grapefruit juice |
| Grapefruit juice | | Saquinavir |
| Erythromycin | | Telapravir |
| Fluconazole | | Lovastatin |
| Verapamil | | Simvastatin |
| Diltiazem | | Budesonide |
| Fluoxetine | | Dexamethasone |
| Paroxetine | | Hydrocortisone |
| Cimetidine | Weak inhibitors | Erythromycin |
| | | Atorvastatin |

pathology in muscle, which is pertinent given the capacity of colchicine to promote vacuolization in muscle by disruption of the microtubule network.

A new set of evidence-based guidelines provides an algorithm for reducing colchicine doses to prevent toxicity in patients who are concomitantly taking other drugs [23]. The researchers conducted a series of studies designed to show the effects of a single-dose of colchicine given with known inhibitors of CYP3A4 or PGY1. Among the drugs tested were: cyclosporine, ketoconazole, ritonavir, clarithromycin, azithromycin, verapamil extended release (ER), and diltiazem ER. It was shown that the mean maxi-

mum concentration of colchicine was 100% higher when colchicine was co-administered with ketoconazole compared with colchicine alone. The mean maximum concentration of colchicine was 185% higher and the mean total colchicine exposure was 290% higher when colchicine was combined with ritonavir as compared with colchicine alone [86].

Colchicine treatment can alter absorption of other compounds or medications from the intestines. It may induce malabsorption of vitamin B12 by reducing the number of B12 intrinsic factor receptors as shown in the intestinal mucosa of guinea pigs [87]. Colchicine-induced lactose intolerance occurs in a significantly higher per-

centage of patients with FMF treated with oral colchicine compared with non-treated patients [88]. Reduction in iron absorption was also observed among patients with FMF taking colchicine.

## 40.9 Long-Term Effects of Colchicine Treatment

- **Colchicine rarely causes oligo/azoospermia**
- **Colchicine does not affect sperm motility**
- **It is safe to take colchicine during pregnancy and nursing provided the liver and kidney functions are normal**
- **Colchicine is relatively safe in treating children and toddlers and does not affect their growth**

### 40.9.1 Colchicine and Male Fertility

Colchicine is a drug which may affect the function of microtubules in various cells. In high concentrations, it may inhibit mitosis within the process of cell division. Therefore, concern was raised as to the effect of colchicine on sperm proliferation and motility in patients taking colchicine.

A case report by Merlin described a patient with gout who developed azoospermia following treatment with colchicine [89]. Re-challenge again induced azoospermia. Because patients with FMF receiving colchicine are often in their child-bearing years, the concern about fertility is pertinent. Indeed, rabbits treated with a relatively high dose of colchicine showed various degenerative changes of the testes, including loss of differentiation from spermatogonia to spermatozoa [90]. However, Cohen et al. performed cytogenetic evaluation in patients with FMF receiving long-term colchicine. Mitotic rates, percentage of tetraploidy, and chromosomal breakage rates were determined in lymphocytes [91]. No significant differences were found between the patients and controls.

In a study by Levy et al., 6 patients receiving long term colchicine therapy were evaluated. No effect on fertility was noted and levels of spermatocytes, testosterone stimulating hormone, luteinizing hormone and prolactin were all within normal limits [92]. Another study showed that four out of 16 males with FMF receiving colchicine suffered from infertility [93]. One had azoospermia and the others had a normal spermatogram, but the sperms could not penetrate the ova normally.

Since sperm motility and hence ovum penetration depends upon microtubule function, we hypothesized that colchicine may affect the movement of sperm. Accordingly, we studied the effect of colchicine on sperm motility in an in-vitro system employing the "swim up" technique for sperm selection [94]. Sperm motility was inhibited significantly only after an incubation period of at least 18 h, with a minimal colchicine concentration of 10 μg/mL. Because plasma colchicine concentration under therapeutic dose is about 3–9 ŋg/mL, the amount of colchicine needed for affecting sperm motility in vitro is 3000-fold higher. Thus, it seems unlikely that standard colchicine treatment would inhibit sperm motility unless the drug has a very high and special affinity to the testes.

The frequency of oligo or azoospermia with colchicine depends on the underlying disease. Bremner and Paulson failed to show any effect on spermatogenesis in six healthy volunteers who received commonly used doses of colchicine for 4–6 months [95]. Conversely, in a study of 62 Turkish men treated with colchicine for Behçet disease, oligospermia was evident in 23 (37%) patients and azoospermia in two patients [96]. If corroborated, these findings suggest that infertility and disturbed spermatogenesis result not only from colchicine use but also may depend on other factors such as genetic background or underlying disease. The vasculitis associated with Behçet disease may further contribute to this complication by adding local ischemia to the potential toxicity of colchicine.

Based upon the above observations, it is tempting to ascribe the development of azoospermia in patients with FMF to colchicine. However, in three cases of azoospermia we performed a testicular biopsy which demonstrated amyloido-

sis of the testes [97]. Thus, amyloidosis of the testes should also be considered in patients with FMF presenting with azoospermia (see Chaps. 15 and 16).

Another concern related to male fertility is the question on the outcome of pregnancies induced by male patients with FMF. In a study by Zemer et al. of 1000 patients with FMF, 24 females conceived while their male partners were treated with colchicine [98]. There was no mention concerning fertility or delivery problems. Due to limited data on this issue, some physicians in the past used to advise to discontinue colchicine 3 months before attempting to conceive. In a prospective study, we followed the outcome of pregnancies and deliveries of 60 female partners of males with FMF, 53 were on colchicine when their partners conceived [99]. As a control group, we followed the outcome of pregnancies and deliveries in 230 healthy women married to healthy men. Our findings revealed no difference regarding the rate of early or late abortions, or of congenital malformations. Therefore, it seems that there is no need for males with FMF to discontinue colchicine prior to planning conception.

## 40.9.2   Colchicine and Female Fertility

The potential effects of colchicine on microtubules, cell division and growth raise a serious concern as to the female reproduction system.

### 40.9.2.1   Menstruation
FMF attacks may be triggered in some patients by their menstrual period [100]. The association of FMF attacks and menstruation raises the possibility of hormonal influences (see Chap. 16). Indeed, it was shown that estrogen significantly decreases intercellular adhesion molecules [101]. Furthermore, it was demonstrated that estrogens inhibit tubulin assembly by interacting directly with tubulin 6S sites analogous to colchicine sites [102]. Moreover, estrogen is metabolized by the 3A4 liver CYP-450 complex and competes in binding it with colchicine. Thus, it

is tempting to speculate that estrogens mimic the effect of colchicine on tubules and adhesion molecules, thereby enhancing the effect of colchicine. During menstruation, there is a sharp decrease in estrogens, thus their accumulative suppressive effect on inflammation is suddenly diminished. In addition, the reduction in estrogen, allows for a more effective metabolism of colchicine by the 3A4 cytochrome (less inhibitory competition by estrogen) so that the effective level of colchicine may be further reduced. This situation may lead to menstruation associated FMF attack. To control these attacks, it is recommended to increase the dose of colchicine (by 0.5 mg) for 2 days prior to the onset of the menstrual period and for two more days after its onset (see Chap. 16).

### 40.9.2.2   Pregnancy
Theoretically, colchicine may affect female fertility by affecting the ovaries via its potential effect on cell division. However, this has not been shown. Serious concern was raised regarding a teratogenic effect of colchicine. Therefore, in the 1970s physicians advised their patients to discontinue colchicine 3 months before planning conception and during pregnancy. Sporadic reports claimed that colchicine was safe during pregnancy. Furthermore, in a study which followed 36 pregnant women with FMF treated with colchicine, the outcome of the newborns was the same as in an untreated control group [103]. In another study, all 13 women with FMF, who had 16 pregnancies and were on colchicine, gave birth to normal children [104]. However, Rabinovitch et al. reported that 4 newborns out of 2000 (1:500) deliveries of FMF patients were born with trisomy 21, twice the expected rate of a comparable normal population [105]. It was not clear whether colchicine therapy itself plays a role with this increment outcome. Recently, Diav-Citrin et al. examined the safety of fetuses by following mothers exposed to colchicine during pregnancy. In a prospective observational comparative cohort study between 1994 and 2006 they found that colchicine did not appear to be a major human teratogen, and, probably, has no cytogenetic effect [106].

We followed the outcome of pregnancy in a group of patients with FMF who took colchicine during pregnancy and compared them with a group of patients with FMF who were not treated with colchicine and with a group of healthy pregnant individuals [107]. We showed that colchicine was not associated with a higher rate of miscarriage or stillbirth. There was no reduction of the duration of pregnancy or the birth weight of the babies. Based upon these results, we do not recommend amniocentesis for patients with FMF solely because of treatment with colchicine during pregnancy.

### 40.9.3  Colchicine and Nursing

Leaflets of pharmaceutical companies and textbooks of pharmacology warn women not to nurse their babies while treated with colchicine. Milunsky and Milunsky found that colchicine was present in the breast milk of patients taking the drug [108]. We also measured the levels of colchicine in sera and milk of 4 women with FMF at various time points after drug ingestion [109]. Colchicine was detected in all samples of sera and milk, with similar concentrations. However, the estimated daily amount of colchicine ingestion by the nursing babies was less than one tenth the therapeutic dose (per kilogram) given to adult patients with FMF. This rough estimation was concordant with our favorable clinical experience in following more than 50 children of mothers who continued to breastfeed while taking colchicine. Therefore, we suggest that breast feeding is safe while taking colchicine.

### 40.9.4  The Effect of Colchicine on Child Growth and Development

Since growth depends upon cell division, the potential effect of colchicine on child growth and development may raise concerns. The diagnosis of FMF can be made as early as several months of age. Initially, we were reluctant to start treatment with colchicine before the age of 4 years.

During this period, children continued to suffer from recurrent attacks of FMF and were also at risk of developing amyloidosis. Furthermore, they exhibited growth delay when compared with healthy children of the same age. Following the start of colchicine treatment and control of FMF attacks, their appetites improved and a marked growth spurt was evident. We followed seven children since the age of 5–6 years and measured their height and weight every 6 months for a period of 10 years [110]. Their growth while treated with colchicine was within the normal expected percentile range. Similar results were observed in larger and more recent studies [111]. Savgan-Gurol et al. evaluated the growth process and insulin like growth factor-1 (IGF-1) levels in children with FMF [112]. They found that IGF-1 levels of children with FMF did not differ from their healthy peers. However, there was a positive correlation between the rate of growth and the cumulative colchicine dose. Therefore, they suggested that colchicine enhances the growth of children with FMF by suppressing disease activity and inflammation.

## 40.10  Treatment Indications

- **Colchicine is the first line therapy for the treatment of acute gouty arthritis and FMF**
- **Due to the anti-inflammatory and anti-fibrotic effects of colchicine on multiple pathways, the therapeutic use of colchicine has extended beyond these diseases**
- **Recent studies have showed that colchicine may have a beneficial effect in preventing secondary cardiovascular events, and cardiac dysrhythmias**

### 40.10.1  Familial Mediterranean Fever (FMF) (Chap. 16)

#### 40.10.1.1  How to Use Colchicine in Daily Practice

The literature suggests that the minimal daily dose for preventing the development of amyloidosis in adult FMF patients is 1 mg/day, even if

attacks can be suppressed with a lower dose [113]. Nevertheless, several series from Japan, reported that their adult patients with FMF were controlled by low-dose colchicine (0.5 mg daily). It is hypothesized that the reason for that is their carriage of mutations (in exon 2 and 3) which are known to cause a milder disease [114].

The dose of colchicine should not exceed the maximal tolerated dose and should not be more than 3 mg per day in adults without comorbidity and 2 mg per day in prepubertal children [115].

It is of paramount importance to avoid toxicity due to concomitant administration of CYP 3A4 or PGY1 inhibitors (Table 40.3). Drug-drug interactions need to be considered and the dose of colchicine should be appropriately adjusted. It is necessary to closely monitor the kidney and liver function of these patients (see Sect. 40.7 for details). We recommend taking the entire colchicine dose at once in order to improve compliance. If the patient develops diarrhea due to ingestion of a relatively high single dose of colchicine the dose should be divided to twice per day without affecting its effectiveness [116].

### 40.10.2   Gout (Chap. 34)

Although colchicine has been used to treat gout for centuries, relatively few controlled trials have assessed its efficacy. The most recent major trial, Acute Gout Flare Receiving Colchicine Evaluation (AGREE), randomized 184 patients with acute gout to receive a lower-dose colchicine regimen (1.2 mg dose followed by one 0.6 mg dose 1 h later), a traditional higher dose regimen (1.2 mg dose followed by 0.6 mg every hour for a maximum of 4.8 mg) or placebo within 12 h of the onset of attack [117]. The lower- and higher-dose regimens demonstrated similar efficacy (37.8% vs. 32.7% achieving ≥50% improvement within 24 h), but adverse events in the lower-dose regimen were similar to placebo. Accordingly, the lower-dose regimen was approved by the FDA. American College of Rheumatology guidelines recommend the lower-dose colchicine regimen as a first-line therapy option for acute gouty attacks [118].

In addition to its role in acute gout, colchicine is used prophylactically to reduce gout flare frequency, particularly when patients are initiating urate-lowering therapy. An analysis of three randomized controlled trials found that colchicine use for up to 6 months during initial urate lowering provided greater prophylaxis of flares than its use for only 8 weeks [119].

### 40.10.3   Pseudogout

There is only limited evidence for the use of colchicine in prophylaxis of pseudogout, although this is recommended practice [120]. The rationale is the shared NLRP3-inflammasome and IL-1 driven inflammatory pathogenesis of urate and calcium pyrophosphate crystal deposition. Recent European League Against Rheumatism (EULAR) guidelines recommend giving colchicine for acute attacks at a dose of 0.5 mg three times daily with or without a 1 mg loading dose and for prophylaxis 0.5 mg per day. These recommendations are based largely on expert opinion and a single uncontrolled trial [120, 121].

### 40.10.4   Behçet Disease (Chap. 35)

Colchicine is recommended in the management of Behçet disease, particularly for the mucocutaneous manifestations (oral and genital ulcers) and joint symptoms, based on controlled trials performed to date [122, 123].

### 40.10.5   Hepatic Disorders

Over the years colchicine has been studied for disorders of hepatic fibrosis. Primary biliary cirrhosis is a rational potential indication, given the intense concentration of colchicine in bile and the evolving understanding of the capacity of colchicine to modulate bile composition [124]. However, a meta-analysis combining the results of 15 randomized controlled trials encompassing 1714 subjects with alcoholic or non-alcoholic liver cirrhosis, demonstrated no significant

effects of colchicine on mortality, liver related mortality, complications and other outcomes [125]. In a recent double blind, randomized controlled trial in 74 subjects with chronic liver cirrhosis who could not be treated with interferon-α, Muntoni et al. demonstrated that colchicine at a dose of 1 mg per day significantly increased survival (94.6% vs. 78.4% p = 0.001), and decreased serum procollagen III (a biomarker of liver fibrosis) over a follow up period of 4.4 years [126].This suggests that there may be a beneficial effect of colchicine for selected subjects with liver cirrhosis. Additional research has assessed whether colchicine can delay the development of hepatic cell carcinoma (HCC) in patients diagnosed with hepatitis virus-related liver cirrhosis [127]. While the effect of colchicine on the progression of cirrhosis was disappointing, colchicine suppressed the development of HCC. Nine percent of patients treated with colchicine developed HCC versus 29% of untreated patients ($P$ −0.0001), and the time to development of HCC was longer in the colchicine-treated group.

### 40.10.6    Neutrophilic Dermatoses

Colchicine is beneficial in neutrophilic skin conditions. Sweet syndrome typically occurs in women aged 30–50 years and is characterized by fever, neutrophilia, arthralgia, tender erythematous skin lesions, and neutrophilic infiltrates in the upper dermis. Maillard et al. gave colchicine to 20 patients with Sweet syndrome (0.5 mg three times daily for 10–21 days). They reported that 18 patients experienced resolution of fever, skin lesions, arthralgia and neutrophilia within 14 days [128].

Interestingly, in pyrin associated autoinflammatory disease with neutrophilic dermatosis (PAAND) colchicine is not effective and anti-IL 1 agents are required for disease control [129].

### 40.10.7    Colchicine and Cardiovascular Disease

The accumulating understanding of the role of inflammation in cardiovascular diseases has been accompanied by recognition of the potential anti-inflammatory benefit of colchicine in these settings.

#### 40.10.7.1    Pericarditis (Chap. 36)
Practice guidelines from the European Society of Cardiology advocate that colchicine appears to be effective when added to a nonsteroidal anti-inflammatory drug regimen or as monotherapy to treat an initial attack or to prevent recurrence of pericarditis [130]. These recommendations have subsequently been supported by randomized trials [131, 132]. Colchicine was as effective at reducing multiple recurrences of pericarditis as it was for first recurrences. [133, 134] Similar benefits were observed for treatment of an initial attack of acute pericarditis [135, 136].

#### 40.10.7.2    Coronary Artery Disease (Chap. 39)
C-reactive protein (CRP) is a biomarker of inflammation and infection. Elevated high-sensitivity (hs) CRP is both a predictor and a pathogenic factor in vascular events such as coronary artery disease [137]. A recent pilot study evaluated whether low-dose colchicine as an anti-inflammatory treatment could lower hs-CRP levels in patients with stable coronary artery disease whose CRP remained elevated despite aspirin and high-dose atorvastatin therapy [138]. Low-dose oral colchicine (0.5 mg twice daily) was associated with decreased hs-CRP levels by 60%. However, in a separate, randomized study of 80 patients with acute coronary syndrome or stroke, Raju et al. found no significant association between colchicine use (1 mg daily) and CRP reduction, suggesting either that the dose studied was insufficient in the acute setting, or that colchicine may be more effective when administered as a prophylactic rather than as a treatment agent [139]. More recently, Nidorf et al. evaluated the effect of colchicine (0.5 mg daily) on secondary cardiovascular events in 532 patients with stable coronary artery disease already on aspirin and/or clopidogrel and statin therapy [140]. Patients were followed for a median of 3 years. The primary outcome,-the composite incidence of acute syndromes, out-of-hospital cardiac arrest, and non-cardio-embolic ischemic stroke-occurred in 5.3% of patients

treated with colchicine versus 16% of patients receiving placebo. These results warrant further study of the potential benefit of colchicine in the prevention of acute coronary syndrome.

There is growing evidence that inflammation plays a role in the re-stenosis process. Therefore, one study randomized 196 patients with diabetes mellitus and coronary artery disease who underwent percutaneous coronary intervention with bare-metal stent placement to receive either colchicine 0.5 mg or placebo twice daily for 6 months [141]. Subsequent angiography indicated that the rate of angiographic in-stent re-stenosis was 16% in the colchicine group versus 33% in the placebo group (p = 0.007).

### 40.10.7.3  Secondary Atrial Fibrillation

Post-operative atrial fibrillation is a common occurrence after cardiac surgery and is presumed to be driven by surgery-related inflammation. The COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) atrial fibrillation substudy demonstrated that post-operative administration of colchicine was associated with a 45% reduction in the incidence of post-operative atrial fibrillation [142]. However, a second multi-center, randomized, double-blind, placebo-controlled trial (COPPS-2) found no reduction in post-operative atrial fibrillation among patients receiving colchicine [143].

Colchicine may also reduce the risk of recurrence of atrial fibrillation after ablation therapy. In a randomized, double-blind, placebo-controlled study by Deftereos et al., 3 months of colchicine monotherapy was associated with a 16% reduction in the incidence of atrial fibrillation after pulmonary vein isolation with radiofrequency ablation [144]. The colchicine group also experienced a significant decrease in IL-6 and CRP levels.

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