58577	4		
Phar			
Bestelldatum	20.09.2010 17:16:00	20 AT	
Termin	**18.10.2010 18:00:00**	Email	
International Beteiligungs GmbH			
14 Arb. Fr. Schaupp			

4) Yang LP.
Oral colchicine (Colcrys): in the treatment and prophylaxis of gout.
Drugs. 2010 Aug 20;70(12):1603-13.

ADIS DRUG PROFILE

Drugs 2010; 70 (12): 1603-1613
0012-6667/10/0012-1603/$55.55/0

Oral Colchicine (Colcrys®)

In the Treatment and Prophylaxis of Gout

Lily P.H. Yang

Adis, a Wolters Kluwer Business, Auckland, New Zealand

Contents

Abstract 1603
1. Pharmacodynamic Profile 1605
2. Pharmacokinetic Profile 1605
3. Therapeutic Efficacy 1607
4. Tolerability 1610
5. Dosage and Administration 1611
6. Oral Colchicine (Colcrys®) in the Treatment and Prophylaxis of Gout: Current Status 1612

Abstract

Oral colchicine (Colcrys®) is approved in the US for the treatment of acute gout flares in adult patients and the prophylaxis of gout flares in patients aged >16 years.

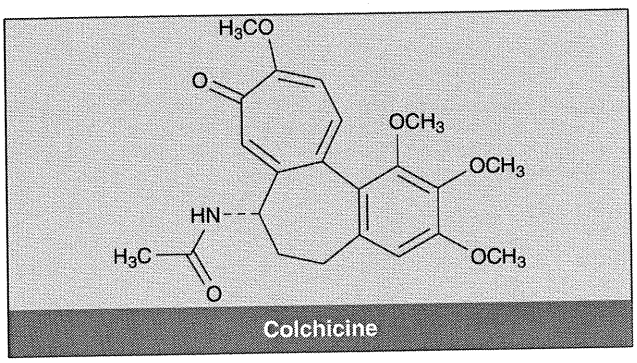
Colchicine is a tricyclic alkaloid that interrupts multiple inflammatory response pathways. Its principal mechanism of action in gout is thought to be inhibition of cytoskeletal microtubule polymerization, an important process in neutrophil functioning.

In a phase III, randomized, double-blind, placebo-controlled, multicentre trial, the recommended dosage of Colcrys® (1.2 mg at the first sign of the flare, followed by 0.6 mg in 1 hour) was significantly more effective than placebo in treating acute gout flare, as assessed by the proportion of patients experiencing a ≥50% reduction in pain within 24 hours of initiating treatment.

In a randomized, double-blind, placebo-controlled, single-centre trial, non-approved colchicine 0.6 mg once or twice daily (up to 6 months) was more effective than placebo in preventing gout flares in patients receiving allopurinol as urate-lowering therapy.

At the recommended dosage for the treatment of acute gout flares, Colcrys® was as well tolerated as placebo in patients with gout. The incidence of the most common adverse events was similar between recipients of the recommended dosage of Colcrys® and placebo.

Features and properties of oral colchicine (Colcrys®)		
Featured indications		
Treatment of acute gout flares in adult patients in the US		
Prophylaxis of gout flares in patients aged >16 y in the US		
Mechanism of action		
Thought to inhibit multiple inflammatory response pathways, primarily as a result of inhibition of β-tubulin polymerization in neutrophils		
Dosage and administration		
Recommended treatment dosage	1.2 mg at the first sign of the flare, followed by 0.6 mg in 1 h	
Maximum recommended treatment dosage	1.8 mg over a 1 h period, not to be repeated for at least 3 d	
Recommended prophylactic dosage	0.6 mg once or twice daily	
Maximum recommended prophylactic dosage	1.2 mg/d	
Route of administration	Oral	
Pharmacokinetic profile in healthy, fasting, adult volunteers who received oral Colcrys® 1.2 mg, followed by 0.6 mg in 1 h (total 1.8 mg; n = 13) or a single oral dose of Colcrys® 0.6 mg (n = 25)		
	1.8 mg	**0.6 mg**
Maximum plasma concentration (ng/mL)	6.2	2.5
Area under the plasma concentration-time curve from time zero to infinity (ng • h/mL)	52.1	14.1
Terminal half-life (h)	23.6	6.4
Most commonly reported adverse events		
Diarrhoea, nausea		



Gout is a disease with a descriptive history dating back to the time of Hippocrates.[1] It is a well known type of arthritis associated with impaired metabolism of purines, resulting in hyperuricaemia and an accumulation of the metabolic end product urate, in the form of monosodium urate crystals, in joints.[1] The build-up of these crystals induces an acute inflammatory response that involves leukocyte recruitment, in particular that of neutrophils.[2,3]

Hyperuricaemia is the most important risk factor in the development of gout, and is caused more commonly by decreased renal capacity to clear urate (in ≈90% of patients) than by over production of urate (≈10%).[1] Hyperuricaemia is physiochemically defined as urate levels >6.8 mg/dL (408 μmol/L) in men and women, as urate saturation leading to crystal formation occurs at 6.8 mg/dL at 37°C.[1,4] Although the risk of acute gout increases with serum urate concentration, not all patients with hyperuricaemia will develop gout.[1]

Other common risk factors for gout include excessive intake of certain purine-rich foods (e.g. meat and seafood), alcohol and fructose, obesity and the use of medications that affect urate levels (such as diuretics, furosemide and ciclosporin).[1,5] In addition, some common chronic disorders, such as diabetes mellitus, the metabolic syndrome, renal disease, hypertension, cardiovascular disease and hyperlipidaemia, are associated with gout.[5] Furthermore, hyperuricaemia may increase the risk of hypertension and chronic renal disease.[6]

The prevalence of gout is difficult to quantify,[7] but is estimated to be ≈1% in adults in Western countries.[1,8] The incidence of gout increases with age,[9] and is particularly high among elderly men (aged >65 years).[1,7] In recent years, increases in the prevalence and incidence of gout have been reported, which are attributed in part to the aging population, who have a higher likelihood than younger individuals of co-morbidities and concurrent medication requirements that contribute to an increase in risk factors or gout-associated disorders.[1,8]

Although the symptoms of an acute gout flare are self limiting, they usually include extreme pain and can take ≥1 week to resolve.[10] Aside from pain, patients are most concerned with the loss of mobility, as well as emotional stress, interrupted sleep, work and social limitations, and joint swelling and deformities.[11] Therefore, treatment of acute gout flares is recommended to alleviate disease symptoms.[10] EU treatment guidelines recommend oral NSAIDs and colchicine as first-line treatment options for gout, with intra-articular corticosteroid injections as a second-line option;[10] no US treatment guidelines are currently available.[12] However, NSAIDs have been preferentially recommended over colchicine,[13,14] as colchicine has a narrow therapeutic margin[15] (section 4). In general, there are few randomized trial data for the use of colchicine and NSAIDs in patients with gout.[14,16,17]

In patients with recurrent acute gout flares or severe established gout, long-term management of hyperuricaemia is recommended, with a target urate level of ≤6 mg/dL (360 μmol/L),[10] to prohibit new crystals from forming and encourage existing crystals to dissolve.[17] The rapid decrease in serum urate levels at the start of urate-lowering therapy (with agents such as allopurinol, probenecid and febuxostat[10,18]) can cause acute 'mobilization flares';[17] therefore, concurrent gout flare prophylaxis, with agents such as colchicine or NSAIDs, is recommended during the first few months of urate-lowering therapy.[10]

Colchicine has been used since antiquity,[19,20] with an extensive history of clinical experience in the treatment of many inflammatory diseases.[21] Unlike newer medicines, colchicine did not go through the extensive testing required by regulatory bodies until recently.[22] In 2009, the US FDA approved the Colcrys® formulation of oral

colchicine for the treatment of acute gout flares and the prophylaxis of gout flares.[23] Colcrys® is currently the only single-agent colchicine with FDA approval;[24] all other FDA-approved colchicine formulations also contain probenecid. Although some NSAIDs (indometacin [indomethacin], naproxen, sulindac) are approved by the FDA for the treatment of acute gout flares, no NSAID is currently approved by the FDA for gout prophylaxis.[25]

A detailed discussion of the differences, including cost, between Colcrys® and non-approved colchicine[26-28] is beyond the scope of this article. Although Colcrys® is also approved in the US for the treatment of familial Mediterranean fever,[23] this article focuses on its use in gout, and provides an overview of the pharmacological properties, therapeutic efficacy and tolerability of Colcrys® and colchicine for the treatment and prophylaxis of gout. Where possible, the article focuses on the Colcrys® formulation of colchicine. The use of the otherwise unspecified term 'colchicine' refers to non-approved colchicine.

Medical literature on the use of colchicine in gout was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference list of published articles. Searches were last updated 2 July 2010.

1. Pharmacodynamic Profile

The pharmacodynamic properties of colchicine have been extensively reviewed;[3,19] therefore, only a brief summary is provided in this section, based on reviews,[3,15,19,21] studies[29,30] and the US prescribing information.[23]

- Colchicine is a tricyclic alkaloid extracted from the flowering plants *Colchicum autumnale* (meadow saffron or autumn crocus) and *Gloriosa superba* (glory lily).[3,15]
- The principal mechanism of action of colchicine in gout is thought to be inhibition of cytoskeletal microtubule polymerization.[3,19] Colchicine binds to β-tubulin in such a way that prohibits the formation of microtubules.[29] The resulting colchicine-tubulin complex has a high dissociation constant (10^{-6} to 10^{-7} mol/L).[21]
- Downstream consequences of the inhibition of microtubule polymerization by colchicine include inhibition of neutrophil activation, degranulation and migration, which are though to mediate some of the inflammatory symptoms of gout.[23] Analysis of the synovial fluid from asymptomatic knees that contained monosodium urate crystals (n = 18) from 12 patients with gout showed that treatment with oral colchicine 1 mg/day for 1 month significantly ($p < 0.005$) reduced the white cell count (274 vs 612 cells/mm^3) and the proportion of polymorphonuclear leukocytes (4.5% vs 13.0%) from baseline.[30] The clinical efficacy of Colcrys® and colchicine in patients with gout are presented in section 3.
- The slow accumulation of colchicine in leukocytes (reaching maximum concentration at 48 hours; section 2) and the long half-life of the colchicine-tubulin complex (20–30 hours) are thought to be correlated with the onset (24–48 hours after drug administration) and dissipation (24–48 hours after drug discontinuation) of the drug's inhibitory effects on leukocyte functioning.[21]
- As the separate use of colchicine (section 4) or certain lipid-lowering drugs has been associated with myopathy, concomitant administration of Colcrys® with atorvastatin, simvastatin, pravastatin, fluvastatin, gemifibrozil, fenofibrate, fenofibric acid or benzafibrate may further increase the risk of developing myopathy and rhabdomyolysis.[23] Rhabdomyolysis has been reported with the concomitant use of Colcrys® with digoxin, a P-glycoprotein substrate.[23]

2. Pharmacokinetic Profile

The pharmacokinetic properties of colchicine and Colcrys® were obtained from the US prescribing information,[23] reviews[3,21] and studies in healthy volunteers.[31,32] The discussion in this section focuses on the recommended Colcrys® dosages of 1.2 mg followed by 0.6 mg in 1 hour (for acute gout flare treatment) and 0.6 mg once or twice daily (for gout flare prophylaxis) [section 5].

- The absolute bioavailability of colchicine is ≈45%.[23]
- In 13 fasting, healthy volunteers, a mean maximum colchicine plasma concentration (C_{max}) of

2.5 ng/mL was reached a mean time (t_{max}) of 1.5 hours after oral administration of a single 0.6 mg dose of Colcrys®.[23] In 13 healthy volunteers who received Colcrys® 0.6 mg twice daily for 10 days, mean t_{max} was 1.3 hours and mean C_{max} was 3.6 ng/mL.[23]

- In healthy volunteers who received a single 0.6 mg dose of Colcrys® (n = 25) or Colcrys® 1.2 mg followed by 0.6 mg in 1 hour (n = 13), mean C_{max} was 2.5 and 6.2 ng/mL, and the mean area under the plasma concentration-time curve (AUC) from time zero to infinity was 14.1 and 52.1 ng • h/mL.[31]
- A secondary peak in colchicine plasma concentration is observed in some patients, which occurred 3–36 hours after drug administration and is 39–155% of the initial C_{max}.[23] The secondary increase in colchicine concentration is thought to be a result of intestinal secretion and reabsorption, and/or biliary recirculation of the drug.[23]
- Administration of Colcrys® with food was not associated with any clinically significant effects on the absorption of the drug.[23]
- In healthy volunteers, the mean apparent volume of distribution of colchicine is ≈5–8 L/kg,[23] indicating widespread tissue uptake of the drug.[21] Regardless of colchicine concentration, serum protein binding is 39%, primarily to albumin.[23] Colchicine also distributes to leukocytes and slowly accumulates in mononuclear cells and granulocytes, reaching maximum concentration at 48 hours after a single oral dose of 1 mg in healthy volunteers.[32]
- Colchicine crosses the placenta, and fetal plasma concentrations are ≈15% of that seen in the mother.[23] Colchicine distributes to breast milk at concentrations similar to those in the maternal serum; the infant receives <10% of the maternal weight-adjusted dose. However, because colchicine may affect gastrointestinal cell renewal and permeability, caution is recommended in breastfeeding patients who receive Colcrys®; the infant should be observed for adverse effects.[23]
- Colchicine is metabolized by cytochrome P450 (CYP) 3A4 *in vitro* into two primary metabolites; the plasma concentration of these metabolites is <5% of that of the parent drug.[23] Colchicine does not inhibit or induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 *in vitro*. Colchicine is a P-glycoprotein substrate.[23]
- Colchicine is excreted in the urine, and 40–65% of an orally administered dose of colchicine 1 mg was recovered unchanged in the urine.[23] Colchicine is also excreted via the biliary route, after metabolism in the liver,[3] and enterohepatic recirculation may have a role in the elimination of colchicine.[23] Haemodialysis does not remove colchicine.[23]
- The mean elimination half-life of colchicine in 13 healthy volunteers who received Colcrys® 0.6 mg twice daily for 10 days was 26.6 hours.[23] The mean terminal half-life was 6.4 and 23.6 hours in healthy volunteers who received a single 0.6 mg dose of Colcrys® (n = 25) and Colcrys® 1.2 mg followed by 0.6 mg in 1 hour (n = 13).[31]

Special Patient Populations

- Colchicine clearance is decreased in patients with renal impairment; in patients with end-stage renal disease who required dialysis, total body clearance of colchicine was reduced by 75%.[23] Reductions in the dosage and/or administration frequency of Colcrys® is recommended in patients with severe renal impairment (creatinine clearance [CL_{CR}] <30 mL/min [<1.8 L/h]) or patients requiring dialysis. Pharmacokinetic properties of colchicine have not been established in patients with mild (CL_{CR} 50–80 mL/min [3.0–4.8 L/h]) or moderate (CL_{CR} 30–50 mL/min [1.8–3.0 L/h]) renal impairment; although no Colcrys® dosage adjustments are recommended, close patient monitoring is advised in these patients.[23]
- No pharmacokinetic data are available for oral colchicine in patients with severe hepatic impairment (Child-Pugh class C).[23] Data from patients with alcoholic or primary biliary cirrhosis, severe chronic liver disease or no renal impairment who received intravenous colchicine indicate a high degree of inter-patient variability in the pharmacokinetic properties of the drug. Although no adjustments in Colcrys® dosages are required in patients with mild or moderate hepatic impairment, close patient monitoring is recommended; a reduction in dosage or the frequency of administration of Colcrys® should

be considered in patients with severe hepatic impairment.[23]

- Pharmacokinetic properties of colchicine have not been established in elderly patients with gout; a cautious approach in dosage selection is advised in this patient population, with consideration of the higher likelihood of renal impairment, co-morbidity and concomitant medication use compared with younger patients.[23] Pharmacokinetic properties, safety and efficacy of colchicine in paediatric patients with gout have not been established as gout rarely occurs in this patient population.[23]

Potential Drug Interactions

- Because colchicine is a CYP3A4 and a P-glycoprotein substrate, concomitant administration with moderate or strong CYP3A4 inhibitors or P-glycoprotein inhibitors is associated with significant increases in systemic exposure to colchicine (in terms of plasma concentrations and AUC).[23] Therefore, coadministration of Colcrys® with moderate (e.g. amprenavir, aprepitant, dilitiazem) or strong (e.g. atazanavir, clarithromycin, indinavir) CYP3A4 inhibitors or P-glycoprotein inhibitors (e.g. ciclosporin, ranolazine) should be avoided. Where avoidance is not possible, the dosage and/or administration frequency of Colcrys® should be reduced.[23]
- In patients with renal or hepatic impairment, coadministration of Colcrys® with strong CYP3A4 inhibitors or P-glycoprotein inhibitors is contraindicated (section 5), because of the increased risk in these patients of the development of life-threatening and fatal colchicine toxicity at therapeutic colchicine dosages.[23]
- In healthy volunteers, coadministration of Colcrys® with oral contraceptives containing ethinyl estradiol and norethindrome or with theophylline did not affect the concentrations of the coadministered drug.[23]

3. Therapeutic Efficacy

This section focuses on data from prospective trials that investigated the therapeutic[31] and prophylactic[33-36] efficacy of Colcrys® and colchicine at FDA-approved dosages for Colcrys® (section 5) in patients with gout. Of the five included trials,[31,33-36] only one[31] utilized Colcrys® and the other four[33-36] utilized non-approved colchicine. Results from the only other placebo-controlled trial[37] that evaluated the therapeutic efficacy of colchicine in patients with gout are not discussed in this section as the dosage employed (mean total 6.7 mg over 48 hours) exceeds the approved dosage of Colcrys®, and was associated with a high incidence of adverse events (section 4).

Treatment of Acute Gout Flares

The clinical efficacy of Colcrys® in patients with gout was evaluated in the phase III, randomized, double-blind, placebo-controlled, multicentre AGREE (Acute Gout Flare Receiving Colchicine Evaluation) trial.[31] Additional data from this trial were obtained from the manufacturer's clinical study report[38] and an abstract presentation.[39]

Adult patients aged ≥18 years (female patients had to be postmenopausal) with a confirmed diagnosis of gout (according to the American College of Rheumatology [ACR] preliminary criteria) and at least two gout flares in the previous 12 months were enrolled.[31] The study was designed for patients to initiate study medication, after mandatory clearance from a centralized call centre, within 12 hours of the onset of gout flare. Of the 575 randomized patients who received pre-dispensed study medication, 185 patients had an eligible acute gout flare and self administered study medication. The following criteria were to be met prior to initiating study medication: onset of the flare was within the previous 12 hours; the presence of the four cardinal inflammatory signs (swelling, redness, marked tenderness and pain); joint pain score of ≥4 (on a scale ranging 0–10); no use of prohibited medication; and no change in medical history.[31,38]

Key exclusion criteria were: acute polyarticular gout (affecting more than four joints); a history of more than two acute gouty arthritic attacks per month or >12 attacks in the previous 6 months; routine use of colchicine; history of cardiovascular or cerebrovascular events in the previous 6 months; active myeloid leukaemia, obstructive

gastrointestinal cancer or metastatic cancer, or chronic renal or hepatic impairment; the use of adalimumab, infliximab or abatacept within the previous 90 days; the use of drugs including systemic corticosteroids, etanercept, anakinra, mycophenolate, ciclosporin, macrolide antibacterials, warfarin or heparin within the previous 30 days; and the use of drugs including azathioprine, NSAIDS, paracetamol (acetaminophen) or tramadol within the previous 3 days.[31,38]

Patients (mean age 51.5 years) were randomized to one of three treatment groups: low-dose Colcrys® 1.8 mg (an initial 1.2 mg dose, one 0.6 mg dose in 1 hour and five hourly doses of placebo [1.8 mg over 1 hour]; n = 118); high-dose Colcrys® 4.8 mg (an initial 1.2 mg dose and six hourly 0.6 mg doses [4.8 mg over 6 hours]; n = 141); or placebo (seven hourly doses; n = 131).[31] Of the 185 patients with an eligible gout flare, 74, 52 and 59, respectively, were in each treatment group; efficacy data were unavailable for one placebo recipient. The low-dose regimen (i.e. 1.8 mg over 1 hour), but not the high-dose regimen (i.e. 4.8 mg over 6 hours), is the FDA-approved dosage (section 5).

All study medications were taken orally, with the first dose at the onset of the gout flare and one subsequent dose every hour for the next 6 hours.[31] The use of rescue pain medication, individually prescribed for each patient, was permitted for intolerable pain after one or more doses of study medication. The most commonly used rescue medications were NSAIDs, in particular indometacin. Continuation of a stable regimen of urate-lowering therapy was permitted, and was not to be discontinued at the onset of the flare.[31]

The primary endpoint was the treatment response rate, defined as a ≥50% reduction in pain scores at 24 hours after taking the first dose of study medication and no use of rescue medication during this time.[31] The primary analysis was the comparison between the high-dose (4.8 mg over 6 hours) Colcrys® group and the placebo group. Comparison between the low-dose (1.8 mg over 1 hour) Colcrys® group and the placebo group, and alternative definitions of treatment response, were *a priori* secondary analyses. Alternative definitions of treatment response were a ≥50% reduction in pain scores at 32 hours, and a ≥2-point reduction in pain scores at 24 hours and at 32 hours.[31]

- High-dose (4.8 mg over 6 hours) Colcrys® was significantly more effective than placebo in reducing the pain associated with acute gout flare in adult patients. The proportion of patients with a ≥50% reduction in pain scores at 24 hours and no use of rescue medication was significantly higher with high-dose Colcrys® than with placebo (32.7% vs 15.5%; p = 0.034; odds ratio [OR] 2.64 [95% CI 1.06, 6.62]) [primary analysis]. However, this Colcrys® dosage is not recommended (section 5) because of the high incidence of adverse events (section 4).
- Low-dose (1.8 mg over 1 hour; the recommended dosage) Colcrys® was also significantly more effective than placebo in treating acute gout flare pain.[31] The proportion of low-dose Colcrys® recipients with a ≥50% reduction in pain scores at 24 hours and no use of rescue medication was significantly higher than that in the placebo group (37.8% vs 15.5% [figure 1]) [*a priori* secondary analysis].[31] Importantly, the proportion of patients achieving this efficacy outcome did not differ significantly between recipients of low- and high-dose Colcrys® (OR 0.80 [95% CI 0.38, 1.68]).[38]
- Analysis by *a priori* alternative definitions of treatment response also showed a statistically significant difference between the recommended dosage of Colcrys® and placebo (41.9% vs 17.2% [≥50% reduction in pain scores at 32 hours], 43.2% vs 17.2% [≥2-point reduction in pain scores at 24 hours], 45.9% vs 17.2% [≥2-point reduction in pain scores at 32 hours]; all p ≤ 0.002 and all 95% CIs of the ORs were >1).[31] No significant difference was reported between the two Colcrys® dosage groups as assessed by all alternative treatment response definitions.[38,39]
- Significantly fewer patients used rescue medication in the 24-hour study period in the low-dose Colcrys® group than the placebo group (31.1% vs 50.0%; p = 0.027; OR 0.45 [95% CI 0.22, 0.92]).[31]

Prophylaxis of Gout Flares

The efficacy of colchicine for preventing gout flares in patients with gout was evaluated in

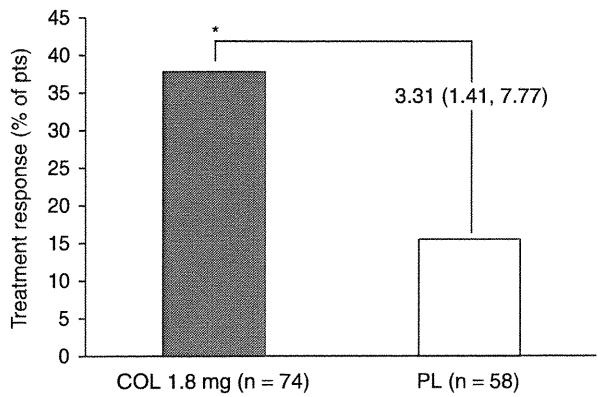


Fig. 1. Clinical efficacy of oral colchicine (Colcrys®) [COL] in adult patients (pts) with gout. Treatment response rate from a randomized, double-blind, placebo (PL)-controlled, multicentre trial,[31] defined as a ≥50% reduction in pain scores at 24 h after taking the first dose of study drug, without the use of rescue medication. Pts received COL 1.8 mg (the recommended dosage; COL 1.2 mg followed by COL 0.6 mg in 1 h and five PL doses every h), COL 4.8 mg (COL 1.2 mg followed by six doses of COL 0.6 mg every h) or PL, within 12 h of a confirmed episode of acute gout flare. Data from the COL 4.8 mg group are not presented. Odds ratio is presented with the corresponding 95% confidence intervals in parentheses. * p = 0.005 vs PL.

a randomized, double-blind, placebo-controlled, single-centre trial.[33] In addition, some[35,36] or all[34] patients received colchicine as prophylaxis for gout flares in three randomized, double-blind, multicentre trials. The main purpose of the latter trials was to evaluate the efficacy of allopurinol[35,36] or febuxostat[34-36] in patients with gout, and reported limited data on the prophylactic efficacy of colchicine.

Adult patients (mean age 51.8–63 years) enrolled in the trials had gout diagnosed in accordance with the ACR preliminary criteria[34-36] or confirmed by the presence of monosodium urate crystals.[33] Patients were included if serum urate levels were ≥8.0 mg/dL (480 μmol/L)[34-36] or elevated to an unspecified threshold,[33] and if at least three flares were reported per year.[33] Key exclusion criteria included severe renal impairment,[33-36] hepatic dysfunction[33-36] and a history of (or current) alcohol abuse.[34-36]

In the trial comparing colchicine prophylaxis with placebo, patients starting treatment with oral allopurinol 100 mg once daily were randomized to receive oral colchicine 0.6 mg twice daily (n = 21) or placebo (n = 22).[33] The allopurinol dosage was titrated to serum urate levels, with a mean dosage of 265 mg/day in colchicine recipients and 245 mg/day in placebo recipients, and the colchicine dosage was reduced to 0.6 mg once daily in patients with chronic renal insufficiency or in those who experienced gastrointestinal adverse events with twice-daily administration of colchicine. Colchicine was continued for 3 months after a serum urate level of <6.5 mg/dL was reached, for up to 6 months. Acute gout flares were managed as deemed appropriate by individual physicians; short-term NSAID therapy, but not oral colchicine, was permitted to manage acute flares.[33]

In terms of the other three trials,[34-36] following a 2-week washout period, patients (n = 153) in one trial were randomized to receive oral febuxostat 40, 80 or 120 mg or placebo once daily for 28 days.[34] Oral colchicine 0.6 mg twice daily was administered during the washout period and for the first 2 weeks of the double-blind treatment period.[34] In the other two trials, following 2-week[35] or 30-day[36] washout periods, patients (n = 762[35] or 2269[36]) were randomized to receive oral febuxostat or oral allopurinol for 52 weeks[35] or 6 months.[36] Dosages were febuxostat 80 or 120 mg/day and allopurinol 300 mg/day in one trial,[35] and febuxostat 40 or 80 mg/day and allopurinol 300 mg/day (or 200 mg/day in patients with moderate renal impairment) in the other trial.[36] In these two trials, prophylaxis comprising colchicine 0.6 mg once daily or naproxen 250 mg twice daily was administered during the washout period[35,36] and the first 8 weeks of the double-blind treatment period[35] or the entire 6-month double-blind treatment period.[36] Naproxen recipients in one trial also received lansoprazole 15 mg/day;[36] gout flares were managed as deemed appropriate by individual physicians.[35]

The primary efficacy endpoint was the proportion of patients achieving serum urate levels <6.0 mg/dL at study end (4 weeks[34] or 6 months[36]) or at each of the last three (of 12) monthly assessments;[35] the remaining trial[33] did not specify a primary endpoint. All trials assessed the incidence of gout flares.

- In patients with gout who were receiving allopurinol to lower serum urate levels, colchicine 0.6 mg once or twice daily was significantly more effective than placebo as gout flare prophylaxis, given until 3 months after serum urate levels

reached <6.5 mg/dL, for up to 6 months.[33] The mean number of flares was significantly ($p < 0.05$) fewer in colchicine than placebo recipients (0.52 vs 2.91 [0–6 months]; 0.57 vs 1.91 [0–3 months]; 0 vs 1.05 [3–6 months]). The total number of flares reported was 12 with colchicine and 62 with placebo (no p-value reported).[33]

- In this trial,[33] the proportion of patients reporting acute flares (33% vs 77%) or recurrent flares (14% vs 63%) was significantly ($p < 0.01$) lower with colchicine than with placebo. In addition, the mean flare severity score was significantly ($p < 0.05$) lower with colchicine than with placebo (3.64 vs 5.08 [assessed by patients on a visual analogue scale, with higher scores corresponding to worsening severity; the range of possible scores was not reported]).[33]
- Colchicine 0.6 mg once or twice daily provided effective prophylaxis for gout flares in three trials in patients with gout who were receiving febuxostat or placebo[34] or febuxostat or allopurinol[35,36] as serum urate-lowering therapy. In one trial (n = 153),[34] the incidence of gout flares was 8–13% during the 4-week period in which patients received colchicine 0.6 mg twice daily, and was 30–42% in the subsequent 2-week period without colchicine (no statistical analyses reported).[34] In another trial (n = 762),[35] the incidence of gout flares was 21–36% in the first 8 weeks of the double-blind treatment period, during which patients were receiving prophylaxis with colchicine 0.6 mg once daily or naproxen 250 mg twice daily, compared with 64–70% from week 9 to 52 without prophylaxis (no statistical analyses reported). In the third trial (n = 2269),[36] the incidence of gout flares was ≤15% throughout the study period (28 weeks) in which all patients received either colchicine 0.6 mg once daily or naproxen 250 mg twice daily as gout flare prophylaxis.

4. Tolerability

The tolerability data pertaining to Colcrys® that are discussed in this section were obtained primarily from the AGREE trial,[31] supplemented by data from a placebo-controlled trial[37] and two prophylaxis trials[33,35] that employed non-approved colchicine, a systematic review[15] and the US prescribing information.[23] Trial design details are presented in section 3.

- Colchicine has a narrow therapeutic margin.[15] At therapeutic dosages, myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia and aplastic anaemia have been reported in colchicine recipients.[23] Long-term use of colchicine at therapeutic dosages has been associated with colchicine-induced neuromuscular toxicity and rhabdomyolysis, with an increased risk in patients with renal impairment and elderly patients (including elderly patients without renal or hepatic impairment) and those receiving lipid-lowering drugs[23] (section 1). The use of colchicine has been associated with accidental and intentional fatal overdoses.[23]
- In the AGREE trial,[31] the recommended dosage of Colcrys® (1.2 mg followed by 0.6 mg in 1 hour) was as well tolerated as placebo. The incidence of all adverse events did not differ significantly between low-dose Colcrys® (n = 74) and placebo (n = 59) recipients (36.5% vs 27.1%; OR 1.5 [95% CI 0.7, 3.2]). However, the incidence of all adverse events was significantly higher in the high-dose Colcrys® group (76.9%; n = 52) than in either the low-dose Colcrys® group (OR 9.0 [95% CI 3.8, 21.2]) or the placebo group (OR 5.8 [95% CI 2.6, 12.9]).[31]
- The most commonly reported adverse events in the AGREE trial[31] were gastrointestinal in nature (diarrhoea, nausea and vomiting) [figure 2]. Importantly, although the incidence of these adverse events did not differ significantly between the low-dose Colcrys® group and the placebo group, a significantly higher incidence was seen with high-dose Colcrys® than with either low-dose Colcrys® or placebo (figure 2).
- In general, colchicine has a dose-dependent tolerability profile.[15,31] A high incidence of gastrointestinal adverse events with the use of colchicine at dosages exceeding those recommended for Colcrys® was reported in a placebo-controlled trial.[37] Fatalities have been reported with dosages of 7–26 mg.[15]
- Severe diarrhoea, melaena or nausea was not reported in patients receiving low-dose Colcrys®, but was reported in 19.2%, 1.9% and 1.9%, respectively, of high-dose Colcrys® recipients.[31] No serious adverse events (including death) or study

withdrawal because of adverse events were reported in the AGREE trial.[31]

- In patients receiving colchicine as prophylaxis for gout flares in clinical trials, the most commonly reported adverse event was diarrhoea.[23] In a trial in which patients who also received allopurinol,[33] diarrhoea was reported in significantly more colchicine than placebo recipients (38% [of 21] vs 4.5% [of 22]; p = 0.009). However, no patient withdrew from the study because of diarrhoea, and all patients with this adverse event responded to a reduction in study drug administration frequency. Overall, study drug administration frequency was reduced from twice daily to once daily in 62% of colchicine and 36% of placebo recipients (the difference was not statistically significant).[33]
- In another trial in which patients received prophylaxis with colchicine or naproxen in addition to treatment with febuxostat or allopurinol,[35] 9 of 760 patients (1.2%) withdrew from the study because of rashes. Most of these cases were localized and comprised transient maculopapular rashes, which occurred during prophylaxis with colchicine or naproxen and resolved after topical treatment.

5. Dosage and Administration

Colcrys® is approved in the US for the treatment of acute gout flares in adult patients and for the prophylaxis of gout flares in patients aged >16 years.[23] Concomitant use of Colcrys® and strong CYP3A4 or P-glycoprotein inhibitors in patients with renal or hepatic impairment is contraindicated.[23]

The recommended Colcrys® dosages are 1.2 mg followed by 0.6 mg in 1 hour for the treatment of acute gout flare, and 0.6 mg once or twice daily for the prophylaxis of gout flares.[23] In patients already receiving Colcrys® for gout prophylaxis, treatment of acute gout flares with Colcrys® is permitted, although the dosage should not exceed 1.2 mg at the first sign of a flare, followed by 0.6 mg in 1 hour; prophylaxis can be resumed after 12 hours.[23] In patients receiving Colcrys®

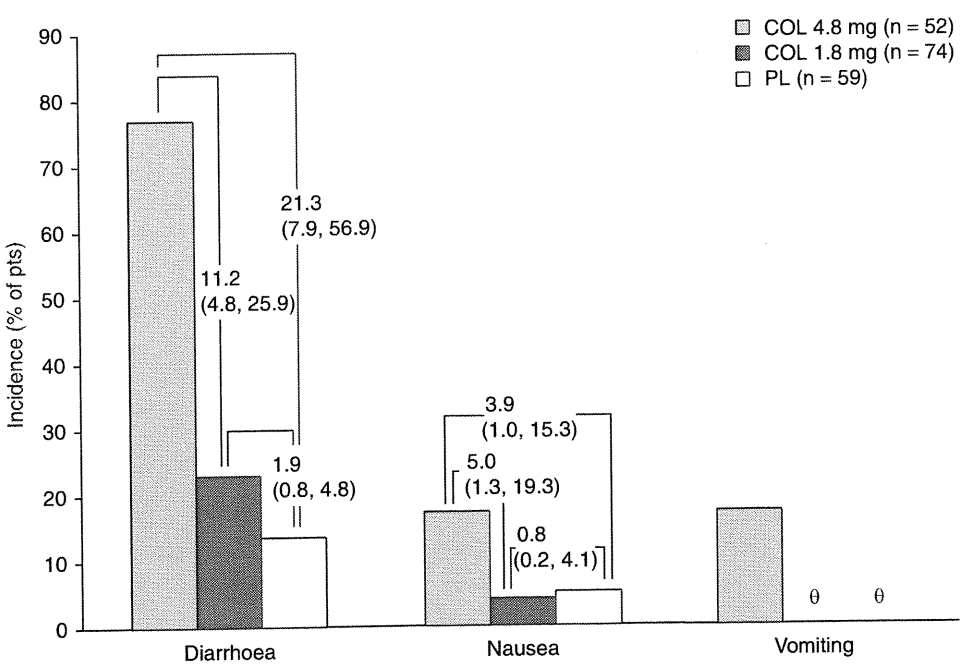


Fig. 2. Tolerability of oral colchicine (Colcrys®) [COL] in adult patients (pts) with gout. The most commonly reported adverse events (incidence >5% in any treatment group) from a randomized, double-blind, placebo (PL)-controlled, multicentre trial.[31] Pts received COL 1.8 mg (the recommended dosage; COL 1.2 mg followed by COL 0.6 mg in 1 h and five PL doses every h), COL 4.8 mg (COL 1.2 mg followed by six doses of COL 0.6 mg every h) or PL, within 12 h of a confirmed episode of acute gout flare. Odds ratios are presented with the corresponding 95% confidence intervals in parentheses. θ = incidence of 0%.

as gout flare prophylaxis and CYP3A4 inhibitors, treatment of acute gout flares with Colcrys® is not recommended.[23]

The local manufacturer's prescribing information should be consulted for detailed information regarding contraindications, warnings and precautions, drug interactions, dosage adjustment and patient monitoring recommendations and use in special patient populations.

6. Oral Colchicine (Colcrys®) in the Treatment and Prophylaxis of Gout: Current Status

Colcrys® is currently approved in the US for the treatment of acute gout flares in adult patients and for the prophylaxis of gout flares in patients aged >16 years. In a randomized, double-blind, placebo-controlled, multicentre trial, the recommended dosage of Colcrys® was more effective than placebo in reducing the pain associated with acute gout flare. In this trial, the tolerability profile of Colcrys® in patients who received the recommended dosage was similar to the tolerability profile seen in placebo recipients. In another controlled trial, colchicine (at recommended dosages for Colcrys®) was more effective than placebo as a short-term (up to 6 months) in preventing gout flares in patients who also received allopurinol, and was generally well tolerated.

Acknowledgements and Disclosures

The manuscript was reviewed by: ***F. Perez-Ruiz***, Servicio de Reumatología, Hospital de Cruces, Vizcaya, Spain; ***N. Schlesinger***, Division of Rheumatology, Department of Medicine, University of Medicine and Dentistry of New Jersey/ Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA; ***M. Underwood***, Warwick Medical School, University of Warwick, Coventry, Warwickshire, England.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. Richette P, Bardin T. Gout. Lancet 2010 Jan 23; 375 (9711): 318-28
2. Dalbeth N, Haskard DO. Mechanisms of inflammation in gout. Rheumatol 2005 Sep; 44 (9): 1090-6
3. Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. Curr Rheumatol Rep 2008 Jul; 10 (3): 218-27
4. Schumacher Jr HR, Edwards LN, Perez-Ruiz F, et al. Outcome measures for acute and chronic gout. OMERACT 7 Special Interest Group. J Rheumatol 2005 Dec; 32 (12): 2452-5
5. Teng GG, Nair R, Saag KG. Pathophysiology, clinical presentation and treatment of gout. Drugs 2006; 66 (12): 1547-63
6. Terkeltaub R, Zelman D, Scavulli J, et al. Gout Study Group: update on hyperuricemia and gout. Joint Bone Spine 2009 Jul; 76 (4): 444-6
7. Doherty M. New insights into the epidemiology of gout. Rheumatology (Oxford) 2009 May; 48 Suppl. 2: ii2-8
8. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther 2006; 8 Suppl. 1: S2
9. Bhole V, de Vera M, Rahman MM, et al. Epidemiology of gout in women: fifty-two-year followup of a prospective cohort. Arthritis Rheum 2010 Apr; 62 (4): 1069-76
10. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006 Oct; 65 (10): 1312-24
11. Schumacker HR, Taylor W, Edwards L, et al. Outcome domains for studies of acute and chronic gout. J Rheumatol 2009 Oct; 36 (10): 2342-5
12. Schlesinger N. Overview of the management of acute gout and the role of adrenocorticotropic hormone. Drugs 2008; 68 (4): 407-15
13. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). Rheumatology (Oxford) 2007 Aug; 46 (8): 1372-4
14. Schlesinger N, Schumacher R, Catton M, et al. Colchicine for acute gout. Cochrane Database Syst Rev 2006 Oct 18; (4): CD006190
15. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila) 2010 Jun; 48 (5): 407-14
16. Sutaria S, Katbamna R, Underwood M. Effectiveness of interventions for the treatment of acute and prevention of recurrent gout: a systematic review. Rheumatology (Oxford) 2006 Nov; 45 (11): 1422-31
17. Perez-Ruiz F. Treating to target: a strategy to cure gout. Rhuematology (Oxford) 2009 May; 48 Suppl. 2: ii9-14
18. Terkeltaub R. Update on gout: new therapeutic strategies and options. Nat Rev Rheumatol 2010 Jan; 6 (1): 30-8
19. Terkeltaub RA. Colchicine update: 2008. Semin Arthritis Rheum 2009 Jun; 38 (6): 411-9
20. Bhat A, Naguwa SM, Cheema GS, et al. Colchicine revisited. Ann N Y Acad Sci 2009 Sep; 1173: 766-73

21. Niel E, Scherrmann J-M. Colchicine today. Joint Bone Spine 2006 Dec; 73 (6): 672-8
22. Sundy JS. Progress in the pharmacotherapy of gout. Curr Opin Rheumatol 2010 Mar; 22 (2): 188-93
23. Mutual Pharmaceutical Company, Inc. Colcrys® (colchicine) oral tablets: US prescribing information [online]. Available from URL: http://www.colcrys.com/assets/pdf/COLCRYS_Full_Prescribing_Information.pdf [Accessed 2010 Jul 2]
24. URL Pharma, Inc. FDA approves Colcrys™ (colchicine, USP) for prevention of gout flares [online]. Available from URL: http://colcrys.com/assets/pdf/Gout%20Prophylaxis%20Press%20Release.pdf [Accessed 2010 Jul 2]
25. US FDA. Rheumatology information: non-selective non-steroidal anti-inflammatory drugs [online]. Available from URL: http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm106979.htm [Accessed 2010 Jul 2]
26. Kesselheim AS, Solomon DH. Incentives for drug development: the curious case of colchicine. N Engl J Med 2010 Jun 3; 362 (22): 2045-7
27. Woodcock J. Letter from the US FDA to the American College of Rheumatology [online]. Available from URL: http://www.rheumatology.org/advocacy/colcrys_letter_from_woodcock.pdf [Accessed 2010 Jul 2]
28. Roberts RH. Letter from URL Pharma Inc. to the American College of Rheumatology [online]. Available from URL: http://www.colcrys.com/assets/pdf/Dr%20Roberts%20letter%20to%20Dr%20Cohen.pdf [Accessed 2010 Jul 2]
29. Ravelli RBG, Gigant B, Curmi PA, et al. Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. Nature 2004 Mar 11; 428 (6979): 198-202
30. Pascual E, Castellano JA. Treatment with colchicine decreases white cell counts in synovial fluid of asymptomatic knees that contain monosodium urate crystals. J Rheumatol 1992 Apr; 19 (4): 600-3
31. Terkeltaub RA, Furst DE, Bennett K, et al. High vs low dosing of oral colchicine for early acute gout flare: twenty-four hour outcome results of the first randomized, placebo-controlled, dose comparison colchicine trial. Arthritis Rheum 2010 Apr; 62 (4): 1060-8
32. Chappey ON, Niel E, Wautier J-L, et al. Colchicine disposition in human leukocytes after single and multiple oral administration. Clin Pharmacol Ther 1993 Oct; 54 (4): 360-7
33. Borstad GC, Bryant LR, Abel MP, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004 Dec; 31 (12): 2429-32
34. Becker MA, Schumacher Jr HR, Wortmann RL, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. Arthritis Rheum 2005 Mar; 52 (3): 916-23
35. Becker MA, Schumacher Jr HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005 Dec 8; 353 (23): 2450-61
36. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther 2010 Apr 6; 12 (2): R63
37. Ahern MJ, Reid C, Gordon TP. Does colchicine work? The results of the first controlled study in acute gout. Aust N Z J Med 1987 Jun; 17 (3): 301-4
38. AR Scientific, Inc. A multicenter, randomized, double-blind, placebo-controlled, parallel group, 1-week, dose-comparison study to evaluate the efficacy, safety, and tolerability of colchicine in subjects with an acute gout flare. Philadelphia (PA): AR Scientific, Inc., 2008 Sep 23. Report no. MPC-004-06-001
39. Terkeltaub R, Furst DE, Bennett K, et al. Colchicine efficacy assessed by time to 50% reduction of pain is comparable in low dose and high dose regimens: secondary analyses of the AGREE trial [abstract no. 1103]. 73rd Annual Meeting of the American College of Rheumatology and the 44th Annual Meeting of the Association of Rheumatology Health Professionals; 2009 Oct 16-21; Philadelphia (PA)

Correspondence: *Lily P.H. Yang*, Adis, a Wolters Kluwer Business, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz