Pharmacoeconomics of ColciGel® for the Treatment of Acute Gout Flares

By Gary E. Myerson, MD | Arthritis & Rheumatology of Georgia, P.C.

Dr. Myerson is a Founding Fellow of the American College of Rheumatology and is an active participant of the Arthritis Foundation.

SUMMARY

Oral Colchicine was effective in only 38% of patients treated for acute flares.[1] It is associated with poor tolerability due to a high-rate of gastrointestinal effects; typically nausea, vomiting, abdominal cramps and diarrhea. Less common but more significant is a strong potential for drug-drug interactions with oral colchicine as it is metabolized and transported by cytochrome P450-3A4 and P-glycoprotein, two systems used by many other drugs.[2] Fatalities have occurred from these drug-drug interactions with colchicine.[3,4]

ColciGel® is a new option for treating acute flares of gout. It is a transdermal gel that contains colchicine (colchicinum 4X) and is designed to be applied directly on the sites of a flare. Clinical experience has demonstrated the effectiveness of ColciGel in reducing inflammation and pain associated with acute flares.[5] ColciGel patients report a 50% or greater decrease in pain and inflammation within a few hours and improved pain relief with additional applications. ColciGel application is well tolerated as only non-clinically relevant concentrations of colchicine enter systemic circulation.[6] ColciGel, with direct application on the site of the flare, bypasses the gastrointestinal (GI) tract and has limited absorption into the systemic circulation, two sites of significant tolerability and safety issues common with **oral** colchicine.

In this paper, the pharmacoeconomics associated with treating acute flares with ColciGel and **oral** colchicine are examined. The drug costs for the two treatments are very similar, however **oral** colchicine therapy has the potential for large hidden costs associated with poor tolerability, serious adverse events (AEs), drug-drug interactions (DDIs), and treatment-failures. ColciGel, without these hidden costs, should be a much more cost-effective treatment.

ColciGel®

A new agent, ColciGel®, has recently emerged for the treatment of acute flares of gout. ColciGel is a transdermal gel preparation of Colchicinum (colchicine in its homeopathic state) that is applied topically. ColciGel contains Colchicinum 4X in a proprietary Organogel that is applied directly to the site of acute flares. It is supplied as an airless 15ml container that delivers 0.25 ml of ColciGel per pump. When ColciGel is applied to the site of the acute gouty flare, it crosses the dermal layer and reduces the inflammation and pain associated with the flare. With the topical application of ColciGel, only minimal amounts of colchicine enter systemic circulation, reaching sub-clinical concentrations of <50 pg/mL.[6] The combination of avoiding the gastrointestinal (GI) system and sub-clinical systemic circulation allows ColciGel to avoid the tolerability and safety issues commonly seen with **oral** colchicine. ColciGel patients report a 50% or greater decrease in pain and inflammation within a few hours and improved pain relief with additional applications.[5] The typical GI side effects usually seen with **oral** colchicine have not been observed with transdermal ColciGel.

INTRODUCTION

The purpose of this analysis is to review the pharmacoeconomic impact of treating acute gout flares with ColciGel or with **oral** colchicine.

Gout, the Disease and Epidemiology

In 2008, Gout affected more than 8.3 million Americans.[7] This number has increased with the aging of the U.S. population as gout is more prevalent among the elderly. Gout affects males about 3 times as often as females. African Americans, followed by whites, have the highest prevalence of gout (Table I).[5]

Table 1. Prevalence of Gout in the US*

	Prevalence	No. Affected (Millions)
Overall	3.9%	8.3
Male	5.9%	6.2
Female	2.0%	2.2
Ethnicity		
White	4.0%	6.0
Afr. Am.	5.0%	1.2
Mex. Am.	1.5%	0.3
Other	3.4%	0.8
Age (years)		
20-29	0.4%	0.2
30-39	1.3%	0.5
40-49	3.3%	1.5
50-59	3.7%	1.5
60-69	8.0%	2.0
70-80	9.3%	1.5
80+	12.6%	1.2

* NHANES Data7

Gout is the most common cause of inflammatory arthritis among men. It is characterized by the deposition of crystals of monosodium urate in the joints and bursa.[8] These crystals result from elevated uric acid levels which in turn result from overproduction of uric acid and/or a decreased capacity to excrete uric acid.[9] Gout is a progressive disease that occurs in stages. The first stage is asymptomatic hyperuricemia, followed by acute gout flares (Stage II) interspersed with periods of intercritical gout (Stage III-asymptomatic periods between acute attacks), and can eventually develop into chronic gout (Stage IV).[10] With chronic gout, persistent arthritis ensues with progressive joint damage superimposed with acute attacks. Tophi (deposits of urate crystals under the skin) become visible with chronic gout.[10] Many individuals with asymptomatic hyperuricemia never develop gout. For those that do, the asymptomatic hyperuricemia often lasts for 20 years before the first acute attack, which often occurs between the ages of 40 and 60 in men and after 65 in women.[10] The average time between the initial acute

attack and development of chronic gout is about 12 years.[11] Acute gout presents as an attack of synovitis (inflammatory gout flares) that can be very painful. The first attacks often involve lower extremities, especially the first metatarsophalangeal joint (a joint of the big toe).[10]

TREATMENT OF GOUT

There are two major elements in the treatment of gout, Urate Lowering Therapy (ULT) and treatment of acute flares. The goals of treatment are:[10]

1. To stop acute attacks (gout flares)
2. To prevent recurrent attacks
3. To prevent or reverse complications resulting from chronic hyperuricemia and urate deposition.

ULT is aimed at the second two goals: preventing recurrent attacks and preventing or reversing the complications of gout.

Treatment of Acute Flares

The objectives of the treatment of acute flares of gout are pain relief and decreasing inflammation.[9] Treatment with pharmacologic therapy should be initiated within 24 hours of onset of an acute gout attack.[8] There are 3 pharmacologic treatments recommended for acute attack: colchicine, nonsteroidal anti-inflammatory agents (NSAIDs) and systemic or locally injected corticosteroids.[8]

Long-Term Urate Lowering Therapy

The goals of this therapy are to lower uric acid levels which can lower the incidence of future flares and to lower the risk of developing complications of gout (i.e. arthritis). ULT most commonly has two elements: a diet that restricts the intake of purines (the precursors for uric acid); and a pharmacologic agent, either allopurinol or febuxostat, which are xanthine oxidase inhibitors that reduce the synthesis of uric acid and lower its levels.[10] ULT is sometimes started after the first gout attack, but since a few individuals never have a second attack, many physicians start ULT after the second attack.[10]

COST OF GOUT

In 2001-2004, employees with gout incurred almost double the direct annual health care costs per year compared to employees without gout ($6,870 vs. $3,705). With over 8 million people with gout in the US, the extra health care costs for people with gout are likely to be over $20 billion per year.[12] Moreover, these costs are growing and are expected to be significantly higher in 2015.

Cost of Gout

Population	Gout	Non-Gout
Employed	$ 4,733	$ 2,562
Elderly	$16,925	$10,590
Treatment Refractory	$18,362	$ 7,188

The yearly costs for medical care for three specific populations of individuals with gout are significantly higher compared to patients without gout.[13 14]

All cause direct costs related to gout have been estimated to be between $11,080 and $13,170 per year per individual. Indirect costs related to gout are estimated to be as high as $4,341 per individual. A key contributing factor to the indirect costs is that employed individuals with gout miss more work days than individuals without gout.[15]

In 2008, there were 174,623 ER visits in the US where the primary cause for the visit was gout, with the cost of these visits reaching $182 million.[16] Medical comorbidities, hyperuricemia, and failed ULT are associated with repeated unplanned hospitalizations for gout. These data suggest that intense ULT that includes prophylaxis with colchicine while initiating ULT can help to make ULT successful, and therefore help to lower gout related costs. Elderly men and women have a high disease burden with gout.[17 18] An estimated 7 million ambulatory visits occurred annually in the US associated with gout between 2002 and 2008, with total ambulatory costs associated with gout estimated at $933 million.[19]

The costs of gout increase with the number of flares individuals have per year.[20]

The high costs per year for the ULT treatment refractory population ($18,362) is indicative of the costs that can be associated with treatment failure in gout.[13 14]

2009 Average Adjusted Gout Related Costs

Number of Flares	Gout-Related Cost
0-1	$1,804
2	$3,014
3+	$4,363

PHARMACOECONOMICS OF ORAL COLCHICINE

Treatment of Flares with Oral Colchicine

Gout flares have been treated with **oral** colchicine for centuries.[21] Colchicine can relieve the pain of acute flares and reduce the inflammation associated with the flare. Historically **oral** colchicine has been used aggressively; dosed until relief occurred or until intolerable GI adverse effects occurred.[21] **Oral** colchicine has a narrow therapeutic index with the toxic effects becoming apparent just above the therapeutic dose range.[3 10] It has the potential for severe and fatal toxicity.[3 7] A clinical study in 2009 of high- and low-dose **oral** colchicine in treating gout flares demonstrated that the low-dose treatment was more effective and better tolerated by patients. The lower dose regimens for dosing **oral** colchicine became more common. With FDA approval of Colcrys in 2012, the low-dose became the only approved and indicated dose for treating acute flares of gout.

The clinical evidence supporting low-dose **oral** colchicine was reviewed by van Echteld and stated that: "Based upon only two published trials, there is low-quality evidence that low-dose (**oral**) colchicine is likely to be an effective treatment for acute gout."[22] The clinical trial of low-dose **oral** colchicine versus high-dose **oral** colchicine had 184 patients in 3 groups (placebo was the 3rd group) treated for 1 day. In the low-dose group, pain relief was achieved in only 38% of patients but was better than in the high-dose group (33%) and placebo (15%). **Oral** colchicine therapy was not effective in most of the cases with 62% of low-dose patients and 67% of high-dose patients not achieving significant pain relief.[1]

Oral colchicine can be associated with a very high rate of adverse events. About 80% of high-dose patients have GI side effects.[7] These typically are diarrhea, nausea, vomiting, and abdominal cramps. Morris et al. in discussing **oral** colchicine therapy stated: "The side effects of nausea, vomiting, or diarrhea are particularly difficult to endure in patients who are in pain, incapacitated, and immobile from acute gouty arthritis."[23] Side effects are fewer with the low-dose,[1 23] although low-dose **oral** colchicine also can be associated with diarrhea, abdominal cramps, nausea, and vomiting.[24] Borstad reported that 38% of patients treated with low-dose **oral** colchicine had diarrhea as a side effect compared with 4.5% of patients in the placebo group.[24] The GI side effects from **oral** colchicine can be serious. The diarrhea can be severe and lead to dehydration and hospitalization.[23] Hospitalizations of patients with gout are associated with the use of **oral** colchicine.[21]

Drug-Drug Interactions (DDI) for Oral Colchicine

One of the reasons that **oral** colchicine can have serious adverse effects is that there is a strong potential for DDIs with **oral** colchicine therapy. Colchicine is metabolized by the cytochrome P450-3A4 (CYP3A4) and

transported by P-glycoprotein (Pgp).[2] Co-administration with inhibitors of CYP3A4 or Pgp can lead to increases in colchicine concentrations in circulation.[4] Since the concentrations at which colchicine is effective are just slightly below that which cause toxicity, circulating concentrations of colchicine can be raised to toxic levels by DDIs. The list in the Colcrys PI of drugs that can cause DDIs includes 26 drugs plus grapefruit juice.[4 25] **Oral** colchicine can also cause rhabdomyolysis (myopathy) which can be exacerbated by concomitant use of cholesterol-lowering drugs that are associated with myopathy (statins and fibrates).[4] This concern adds 8 more drugs (many of them commonly used) to the list of drugs with a potential for significant DDIs with **oral** colchicine.[4] Colchicine toxicity is very serious and can have fatal consequences.[4] One hundred and seventeen deaths have been reported for colchicine with **oral**, IV or intramuscular administration. Over half of these deaths have been attributed to DDIs.[2]

Cost of Treating Acute Flares with Oral Colchicine

Cost of Medication

The recommended treatment for Colcrys is 1.2 mg (two pills, 0.6 mg each) at first sign of flare and 0.6 mg (1 pill) 1 hour later, for a total of 3 pills total per treatment.[4] This can be repeated on the second day. The cost of drug is approximately $6.00/pill, so the range of costs (3-6 pills) for treatment of a flare is $18 to $36.

Hidden Costs of Severe Adverse Events with Oral Colchicine Treatment of Acute Flares

Adverse events (AEs) from **oral** colchicine will contribute to the cost of treating patients with acute flares. Some AEs will warrant other medications (those for diarrhea, for example) and some AEs will lead to office visits or other care. The percent of patients with side effects is quite high with the high-dose (80%) and is significant with the low-dose.[1 24] Some of the successfully treated individuals will have adverse events (particularly of diarrhea) and will also use anti-diarrheal medications (minimal cost).

Severe adverse events can occur with **oral** colchicine, particularly those that occur because of DDIs. The costs of adverse events that could arise from DDIs could be very high. Although a dose-reduction algorithm has been devised to reduce the risk of these DDIs,[2] there are a large number of potential drugs that can induce DDIs with **oral** colchicine.[4] Thus, there is a real potential that serious DDI cases will arise with the use or **oral** colchicine. Numerous deaths have occurred because of DDIs involving colchicine.[3 4]

A study at a veterans hospital is illustrative of the costs that could arise from adverse drug reactions including DDIs.[26] This study found that 12.6% of all ER visits were related to pharmaceuticals and 33% of those events (4.2% of total ER visits) were due to adverse drug reactions. The adverse drug reactions were either side effects of the drug, allergic reactions to the drug, or DDIs. Hospitalizations occurred in 35% of all drug related ER visits (4.4% of total ER visits) and these hospitalizations lasted an average of 9.3 days. The average cost in the US of a hospital room was $1,625 in 2010.[27] The 9.3 day hospitalization caused by adverse drug reactions would cost an average of $15,112 and that would not include other medical costs like physician fees, tests and treatments.

Hidden Costs of Treatment Failure with Oral Colchicine of Acute Flares

In the clinical trial, only 38% of treated patients had at least 50% relief of pain. This suggests that 62% of patients will not get adequate pain relief from acute flares and have treatment-failure.[1] Many of these treatment-failure patients will seek other medical help as the intense pain and suffering from the acute gout flare will continue. Some individuals will use other medications for pain and inflammation, e.g., NSAIDS. Others will see their physician for corticosteroid treatments. Added costs for these individuals would include the cost of the medication plus the office visit. Li et al. reported that there were 50.1 million gout-related ambulatory visits from 2002 to 2008 in the US, with a corresponding cost of $1 billion annually.[19] **Oral** colchicine treatment-failure patients will contribute to that cost. In some treatment-failure patients the patients will seek help at the ER because the pain will be so intense or physicians might not be available at the office. It is estimated that there were 174,823 ER visits in 2008 where the primary indication was gout. The average cost of any ER visit in the US in 2008 was $2,168. With the rise in health care costs since then, the figure will be substantially higher now in 2016. A few of the treatment-failure patients may even need to be hospitalized.

Summary of Costs of Treating Acute Flares Oral Colchicine

1. Drug costs are minimal - $18-$36 per flare
2. Treatment-failure: Most patients (~62%) will not experience pain relief and will seek other treatments. This will result in the use of other medications, office visits and ER visits (average cost >$2,612/per ER visit) and some hospitalizations will ensue ($1,625/-day plus physician and other costs)
3. Adverse effects: Many patients will have adverse drug-related effects. There is a substantial risk of DDIs. Drug-related effects can lead to hospitalizations with costs in the tens of thousands of dollars
4. The major cost to the health care system for treating acute flares with **oral** colchicine will not be from the cost of drug, but will come from further care for treatment-failure patients and for care of adverse drug events including DDIs

PHARMACOECONOMICS OF COLCIGEL®

Treatment of Acute Flares with ColciGel

Costs of Medication

The cost of treatment of an acute flare with ColciGel is very similar to those for **oral** colchicine. Treatment typically consists of 1 or 2 pumps of ColciGel applied directly to the site of the flare when it is first noticed, this is repeated after one hour. The cost per pump is approximately $6. This can be repeated on the second day if needed. This comes to 2-4 pumps/-day for the typical treatment, with a range of 2-8 pumps for treatment over 2 days. The typical costs would run between $12 and $48 per flare. If there are flares occurring simultaneously at more than one site, the typical costs could be higher.

Costs from Adverse Events

ColciGel is well tolerated. Mild skin irritation at the site of application is possible but has not been reported. The concentration of colchicine that enters systemic circulation with ColciGel is less than 50 pg/mL.[5] This is 100-fold less than the peak concentrations of colchicine (about 6 ng/ml or 6000 pg/ml) reported for **oral** colchicine.[1] These low levels are unlikely to cause SAEs and DDIs. This is a major difference with **oral** colchicine.

Costs from Treatment-Failures

Case studies demonstrate that ColciGel is effective, and will be effective in many patients within a few hours following administration. Careful statistics on what percentage of patients will achieve 50% or greater reduction of pain have not been compiled. Thus the costs arising from treatment-failures with ColciGel cannot be estimated.

Costs and Comparisons of Treating Acute Flares with ColciGel and Oral Colchicine[1,28]

	Oral Colchicine	ColciGel
Drug Costs	$18-$36/day	$12-$24/day
>50% pain relief	38% of patients	Not yet known
Treatment failure	62%	Not yet known
AEs (% of patients)	37% - 80%	Very low
Reported AEs	Diarrhea, nausea, vomiting, abdominal cramps	Mild skin irritation at site of application
Severe intensity AEs	Potential for severe GI AEs and DDIs	Very low risk
Secondary treatments for acute attack	Anti-diarrhea and anti nausea medications	Probably none needed
Costs for secondary treatments	Low	Very low if any
Costs with treatment-failures	Most patients will have treatment failure: These patients will switch to other medications, visit their doctor, and in severe cases go to the ER or be hospitalized	Based on Transdermal delivery fewer patients may experience treatment-failure due to tolerability

CONCLUSIONS

Acute Flares

- The costs for treating an acute flare is very similar for ColciGel and Colcrys
- **Oral** colchicine is a drug that is not very effective (62% of patients fail treatment) and has the potential for serious adverse events including life-threatening drug-drug interactions
- **Oral** colchicine has a two potential significant hidden costs
- Treatment-failure occurs in a large percentage of patients. This could result in extra costs for further treatment of flares including other medications, office calls, ER visits and hospitalizations
- Serious adverse events associated with DDIs and GI side effects could also result in other medications, office calls, ER visits and hospitalizations that would result in large extra costs
- The major costs to the health care system for treating acute flares with **oral** colchicine would not come from the cost of the drug, but would come from extra care for treatment-failure patients and for treatments of SAEs including severe diarrhea and from drug-drug interactions
- ColciGel costs largely come from the cost of the drug, as indirect costs from adverse events should be minimal
- ColciGel is well tolerated and administration of topically applied ColciGel does not result in clinically significant systemic circulation of colchicine (at least 100 fold less than **oral** colchicine) greatly diminishing the risks of drug-drug interactions and GI related adverse events
- Case studies demonstrate that ColciGel is effective, and will be effective in many patients within a few hours following administration
- ColciGel is the cost-effective treatment option for acute flares of gout when both the direct and hidden costs of therapy are considered
- A prescription for ColciGel needs to be filled beforehand so that treatment can begin immediately at the first sign of an acute gout flare

References

1 Terkeltaub, R.A., et al., High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum, 2010. 62(4): p. 1060-8.

2 Terkeltaub, R.A., et al., Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. Arthritis Rheum, 2011. 63(8): p. 2226-37.

3 Mullins, M., et al., Unrecognized fatalities related to colchicine in hospitalized patients. Clin Toxicol (Phila), 2011. 49(7): p. 648-52.

4 Colcrys Prescribing Information, I. Takeda Pharmaceuticals America, Editor. 2012: Deerfield, IL.

5 Data on file at Gensco Laboratories, LLC.

6 ColciGel® Package Insert

7 Zhu, Y., B.J. Pandya, and H.K. Choi, Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum, 2011. 63(10): p. 3136-41.

8 Khanna, D., et al., 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken), 2012. 64(10): p. 1447-61.

9 Wertheimer, A.I., M.W. Davis, and T.J. Lauterio, A new perspective on the pharmacoeconomics of colchicine. Curr Med Res Opin, 2011. 27(5): p. 931-7.

10 Burns, C. and R. Wortmann, Latest evidence in gout management: what the clinician needs to know. Therapeutic Advances in Chronic Disease, 2012. 3(6): p. 271-286.

11 Hench, P., Diagnosis and treatment of gout and gouty arthritis. JAMA, 1941. 116(6): p. 453-459.

12 Wertheimer, A., R. Morlock, and M.A. Becker, A revised estimate of the burden of illness of gout. Curr Ther Res Clin Exp, 2013. 75: p. 1-4.

13 Wu, E.Q., et al., Comorbidy burden, healthcare resource utilization, and costs in chronic gout patients refractory to conventional urate-lowering therapy. American Journal of Therapeutics, 2012. 19: p. e157-e166.

14 Rai, S.K., et al., The economic burden of gout: A systematic review. Semin Arthritis Rheum, 2015. 45(1): p. 75-80.

15 Kleinman, N.L., et al., The impact of gout on work absence and productivity. Value Health, 2007. 10(4): p. 231-7.

16 Garg, R., et al., Gout-related health care utilization in US emergency departments, 2006-2008. Arthritis Care and Research, 2013. 65(4): p. 571-577.

17 Hanly, J.G., et al., Gout in the elderly--a population health study. J Rheumatol, 2009. 36(4): p. 822-30.

18 Wu, E.Q., et al., Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? J Rheumatol, 2009. 36(5): p. 1032-40.

19 Li, C., et al., Ambulatory resource utilization and cost for gout in United States. The American Journal of Pharmacy Benefits, 2013. 5(2): p. e46-e54.

20 Jackson, R., et al., Flare frequency, healthcare resource utilisation and costs among patients with gout in a managed care setting: a retrospective medical claims-based analysis. BMJ Open, 2015. 5(6): p. e007214.

21 Todd, B., et al., Assessment of the association between colchicine therapy and serious adverse events. Pharmacotherapy, 2012. 32(11): p. 974-980.

22 van Echteld, I., et al., Colchicine for acute gout (Review). Cochrane Collaboration, 2014(8): p. 1-41.

23 Morris, I., G. Varughese, and P. Mattingly, Colchicine in Gout. British Medical Journal, 2003. 327: p. 1275-1276.

24 Borstad, G., et al., Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. Journal of Rheumatology, 2004. 31: p. 2429-2432.

25 Peterson, D.M., Nonsteroidal anti-inflammatory drugs and colchicine to prevent gout flare during early urate-lowering therapy: perspectives on alternative therapies and costs. J Pain Palliat Care Pharmacother, 2010. 24(4): p. 402-4.

26 Yee JL, Hasson NK, Schreiber DII. Drug-related emergency department visits in an elderly veteran population. Ann Pharmacother. 2005; 39(12):1990-5.

27 Cost Helper Health. Emergency Room Visit Cost. Available at: http://health.costhelper.com/emergency-room.html Accessed Dec. 2, 2015.

28 Hutton, I., et al., Factors associated with recurrent hospital admissions for gout: a case-control study. J Clin Rheumatol, 2009. 15(6): p. 271-4.