

Is colchicine prophylaxis required with start-low go-slow allopurinol dose escalation in gout?

A non- inferiority randomized double- blind placebo-controlled trial

Trial Summary¹

SUMMARY

When comparing placebo to colchicine during the initial titration of allopurinol to a target serum urate level of 360 mcmol/L, placebo was determined to be not non inferior to colchicine in the context of reducing the mean number of monthly gout flares for the first 6 months of therapy. Non inferiority margin was 0.12 flares per month over 6 months and mean difference of number of gout flares between colchicine and placebo group was 0.25 (95% CI 0.07-0.44). The mean number of monthly gout flares was 0.61 in the first 6 month whereas the mean number of monthly gout flares was 0.35 in the colchicine group. This results in a NNT of 4 patients to prevent 1 gout flare over 6 months. However, after 6 months, colchicine was stopped and between month 6 to 12, the mean number of monthly gout flares in the colchicine vs placebo group was 0.46 vs 0.32. The mean number of monthly gout flare between 0 to 12 months was found to be 0.44 in the colchicine group and 0.48 in the placebo group. There is no difference in the mean number of gout flares per month between the randomized groups from baseline to 12 months. Adverse events were similar between groups however serious AEs were numerically more common in the colchicine vs placebo group (11 vs 3 events) in the first 6 months.

Bottom Line: While initiating allopurinol at a “start low go slow” approach (50-100 mg/day), colchicine prophylaxis reduces the number of gout flares a patient may experience in the first 6 months, while on prophylaxis. However, flares may reoccur after stopping flare prophylaxis, mitigating the initial benefit. These results, being mixed, suggest that some patients may require more than 6 months flare prophylaxis. A simple “start low go slow” approach, without flare prophylaxis may also be reasonable, and preferred by some.

BACKGROUND

- Allopurinol ‘start-low go-slow’ dose escalation strategy is a newer initial treatment option for gout flare prevention where it may theoretically reduce the number of flares a person experiences after starting urate lowering therapy. Colchicine is widely used and is specifically recommended as the first line agent for prophylaxis. However, there is a lack of evidence to see if colchicine prophylaxis is required for “start-low go slow” approach where it is a standard of care when starting at higher doses of allopurinol.

TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN:

- Randomized, blinded (patient, clinician, research staff), placebo-control, non-inferiority, allocation concealed, 2 centers in New Zealand, 6 months on colchicine vs placebo, primary analysis using per protocol and sensitivity analysis using intention to treat; colchicine and placebo stopped after 6 months and then followed for another 6 months (total study duration = 12 months), starting dose of 50 mg of allopurinol if eGFR 60 < ml/min/1.73 m² and 100 mg of allopurinol if eGFR 60 > ml/min/1.73 m² and doses increased by 50 mg and 100 mg monthly respectively until SU was < 360 mcmol/L (6 mg/dL or 0.36 mmol/L)
- Non inferiority margin of 0.12 flares per month over 6 months (equivalent to 0.7 flares over the 6-month period)
- Funded by Health Research Council of New Zealand

POPULATION: n=200

- Inclusion criteria:** ≥18 years of age, gout defined by the 2015 American College of Rheumatology, one self-reported gout flare in the preceding 6 month, met ACR recommendation for starting ULT, SU greater than or equal than 360 mcmol/L at screening
- Exclusion criteria:** Intolerance or contraindication to allopurinol or colchicine (receiving azathioprine, cyclosporin, or other immunosuppression), stage 4 or 5 CKD (eGFR 60 < ml/min/1.73 m²), unstable comorbid health conditions (e.g. NYHA stage 4 HF, recent MI, advance cancer) dementia
- Population at baseline:** avg age 56, male 93%, New Zealand of European decent 69%, avg serum urate 500 mcmol/L, duration of gout 11.2 years, avg BMI 32.3 kg/m², presence of subcutaneous tophi 24.5%, obesity 54.5 % (BMI over 30 kg/m² more), HTN 44.5%, T2DM 6.5%, hyperlipidemia 33.5%, cardiovascular disease 20% (IHD HF or PVD), eGFR < 60 ml/min/1.73 m² 14.5%, concurrent diuretic use 13%, concurrent Aspirin use 16%
- When comparing both colchicine and placebo group at baseline, **groups are relatively similar**

INTERVENTION/COMPARISON:

- 2 study arms: **Colchicine 0.5 mg once daily vs. placebo**
- Is comparison fair? Likely reasonable
 - Looking into whether colchicine prophylaxis is needed for “start-low go slow” approach to prevent gout flares. Comparison to placebo is reasonable as standard of care (i.e., whether we need prophylaxis in the first place) is not established
- If gout flares occurred, patients were treated with NSAID or prednisone. Rescue medication and doses were agreed by the participant and investigator

OUTCOMES:

- Primary:** mean number of gout flares per month between 0 and 6 months; **Secondary:** mean number of gout flares per month at 0 to 12 months and 6 to 12 months (numerous other secondary outcomes included in study, refer original articles for additional secondary outcomes). *Values are per protocol unless stated otherwise.

RESULTS	n=100	n=100		
Primary outcome	Colchicine	Placebo	Mean difference	Comments
Mean number of gout flares per month between 0 to 6 months	0.35 0.22–0.49	0.61 0.47–0.74	0.25 0.07–0.44 P value 0.92 (noninferiority)	CI intervals of the mean number of gout flares per month between 0 to 6 months between colchicine and placebo overlap, therefore a lack statistical significance. However, <u>if difference turned out to be true</u> , 0.61 – 0.35 = 0.26 absolute risk reduction results in 1 gout flare prevented per ~4 patients after 6 month or an NNT≈4/6 months when taking colchicine (<u>assumes</u> flares distributed equally between patients) ** Similarly, in the ITT population, the mean (95% CI) number of gout flares per month between baseline and month 6 was 0.61 (0.48 to 0.75) in the placebo group compared with 0.39 (0.26 to 0.52) in the colchicine group; with the mean difference of 0.22 (0.04 to 0.41). Mean difference crosses over non inferiority margin as set out by authors. (For placebo to be consider non inferior, no more than 2.5 gout flares per 6 months, 0.12 flares per month over 6 months or 0.7 flares over the 6-month period). Predefined non inferiority margin was not met.

Secondary outcomes				
Mean number of gout flares per month at 6 to 12 months	0.46 ±0.07	0.32 ±0.07	0.14 P value 0.15	Between 6 to 12 months, mean number of gout flares increased in colchicine group after stopping colchicine. This trend of increased gout flares was not seen in placebo group.
Mean number of gout flares per month at 0 to 12 months	0.44 ±0.06	0.48 ±0.06	0.03 P value 0.68	Between 0 to 12 months, there was no difference in the mean number of gout flares per month between randomized groups between baseline and 12 months. Other secondary outcomes include patient rated severity scales such as visual analog scales, HAQ, EQD3L and patient global. All patient rating scales were found to be not statically significant when comparing between placebo and colchicine group.
Mean number of gout flares per month at 0 to 3 months	0.45 ±0.09	0.74 ±0.09	0.25 P value 0.02	
Mean number of gout flares per month between 4 to 6 months	0.29 ±0.09	0.43 ±0.07	0.15 P value 0.10	
Median (IQR) time to first gout flare (in months)	3 (1 – 6)	1 (1 – 3)	P value 0.004	
Serious adverse outcomes from baseline to month 6	11	3		None of the serious AEs in either colchicine group or placebo were thought to be related to be colchicine or placebo. Serious adverse effects occurred in 7 patients vs 2 patients in colchicine and placebo group respectively.
Serious adverse outcomes from month 6 to 12	12	4		1 serious AE was thought to be possibly related to placebo. Serious AE was diarrhoea. 2 patients died during the study in the colchicine group both due to cardiac issues (cardiac arrest and ischaemic heart disease).

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Study addresses a gap in care as it is unknown whether prophylaxis is needed when using a “start low go slow” approach for allopurinol titration
- Primary outcomes (gout flares) are relevant to patients, numerous secondary outcomes which are relevant to patients are included in study such as mean number of gout flares from 6 to 12 months as well as patient rated pain scales (VAS, HAQ).
- 6 months of prophylaxis and 6 months of follow up thereafter reasonable considering current practices of gout prophylaxis.
- Per protocol and intention to treat analysis was done which increases certainty of results at least for primary outcome.

LIMITATIONS

- Small RCT limiting power to assess outcomes and harms. Study stated it needed 200 patients which accounts for a 10% drop and 80% power which is achieved however, by end of study, 182 patients included in per protocol analysis.
- Study population has various unknown factors such as smoking history, diet, and ACEi/ARB use. These risk factors may make it more likely that a patient suffers from a gout flare.
- The degree of the severity of certain conditions was not stated such as average BP for HTN and LDL for dyslipidemia. Differences in severity of comorbid conditions may lead to differences in the rates of gout flares.
- Patient population is predominantly male and of European decent, results may not be generalizable to other populations around the world.
- As with all non-inferiority trials, what is considered for the non-inferior margin is essentially arbitrary.
- Non inferiority margin was not met, however, this does not prove placebo is worse than colchicine but rather that it only **MAY** be worse than colchicine at least for first 6 months of colchicine use.

UNCERTAINTIES

- If colchicine was continued for greater than 6 months, would prophylaxis continue to be helpful for reducing gout flares (what is the optimal duration for gout prophylaxis)?
- Do other prophylaxis options such as NSAIDs or steroid share the same trend as colchicine when stopped after 6 months of prophylaxis?
- Does targeting a lower serum urate level lead to a reduction in the number of gout flares a patient may experience? A systematic review and meta-analysis (10 RCTs, 3 open label extension studies and 11 observational cohort studies) looking at the serum urate as surrogate endpoint for flares in people with gout found that clinical trial data could not find an association between serum urate and gout flares. However, based on observational ecological study design data, including longer duration extension studies, serum levels less than 6 mg/dL or roughly 330 mcmol/L was associated with reduced gout flare.²

Other notes of interest:

Costs: 30-day supply of colchicine cost around 7 dollars. Relatively inexpensive for patient and health care system

Other related RxFiles materials: [Gout Treatment Chart](#)

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Abbreviations and Definitions: IHD: Ischemic heart disease, HTN: Hypertension, TD2M: Type 2 diabetes, HF: Heart failure, PVD: Peripheral vascular disease, eGFR: Estimated glomerular filtration rate, BMI: Body mass index, IQR: Interquartile range, CKD: Chronic kidney disease, SU: Serum urate, RCT: Randomized control trial, NSAID: non-steroidal anti-inflammatory drug, LDL: Low density lipoprotein, ACEi: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin II receptor blockers, VAS: Visual analogue scale, HAQ: Health Assessment Questionnaire, AE: Adverse effect, ULT: Urate lowering treatment, NYHA: New York Heart association, MI: Myocardial Infarction

¹ Stamp L, Horne A, Mihov B, et al. Is colchicine prophylaxis required with start-low go-slow allopurinol dose escalation in gout? A non-inferiority randomized double-blind placebo-controlled trial. *Ann Rheum Dis.* 2023;82(12)

² Stamp L, Morillon MB, Taylor WJ, et al. Serum urate as surrogate endpoint for flares in people with gout: A systematic review and meta-regression analysis. *Semin Arthritis Rheum.* 2018;48(2):293-301.