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Q / Which prophylactic therapies best prevent gout attacks?

EVIDENCE-BASED ANSWER

A / ALLOPURINOL AND FEBUXOSTAT reduce the frequency of gout attacks equally after 8 weeks of treatment (strength of recommendation [SOR]: **B**, multiple randomized control trials [RCTs] with limitations).

Intravenous pegloticase decreases

serum uric acid and gout attacks and improves quality of life (QOL) (SOR: **A**, 2 RCTs).

Colchicine reduces gout attacks when combined with probenecid or allopurinol at the start of urate-lowering therapy (SOR: **B**, 1 high-quality and 1 low-quality RCT).

Evidence summary

A 28-week RCT compared the effects of placebo, allopurinol (300 mg/d), and febuxostat (80 mg, 120 mg, and 240 mg) on serum uric acid levels (sUA) and gout attacks in 1067 patients with gout and hyperuricemia (94% male, 78% white, 18 to 85 years of age with mean age ranging from 51 to 54 years \pm 12 years in each group).¹ Patients also received prophylaxis with either colchicine or naproxen during the first 8 weeks of the study.

During Weeks 1 through 8, investigators found no statistically significant differences in the percentage of patients requiring treatment for gout attacks between the febuxostat 80 mg, allopurinol, and placebo groups (28%, 23%, and 20%, respectively). During Weeks 8 through 28, no statistically significant differences in gout attack rates occurred between the allopurinol and febuxostat groups, although the study didn't report specific attack rates for this period.

Both allopurinol and all doses of febuxostat reduced sUA to <6 mg/dL more effectively than placebo; more patients treated with febuxostat than allopurinol achieved a uric acid level of less than <6 mg/dL.

Another RCT of 762 mostly white, male patients (mean age 52 years) with gout and sUA >8 mg/dL—35% of whom had renal impairment, defined as creatinine clearance

<80 mL/min/1.73m²—also concluded that febuxostat and allopurinol are equally effective in reducing gout attacks (incidence of gout flares during Weeks 9 to 52 was 64% with both febuxostat 80 mg and allopurinol 300 mg).² The percentage of patients with sUA <6 mg/dL at the last 3 monthly visits was 53% in the febuxostat 80 mg group compared with 21% in the allopurinol 300 mg group ($P<.001$; number needed to treat [NNT]=4).

One significant limitation of both RCTs was the fixed dose of allopurinol (300 mg/d). US Food and Drug Administration-approved dosing for allopurinol allows for titration to a maximum of 800 mg/d to achieve serum uric acid <6 mg/dL.

IV pegloticase decreases gout attacks after 3 months, improves quality of life

Pegloticase is an intravenously administered, recombinant form of uricase, the natural enzyme that converts uric acid to more soluble allantoin. Two RCTs compared pegloticase with placebo in a total of 212 patients with gout (mean age 54 to 59 years; 70% to 90% male) intolerant or refractory to allopurinol (defined as baseline sUA of ≥ 8 mg/dL and at least one of the following: ≥ 3 self-reported gout flares during the previous 18 months, ≥ 1 tophi, or gouty arthropathy).

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These trials found that treatment with 8 mg of pegloticase every 2 weeks for 6 months initially increased gout flares during Months 1 to 3 (75% with pegloticase, 53% with placebo; $P=.02$; number needed to harm [NNH]=5) but then decreased the incidence of acute gout attacks during Months 4 to 6 (41% with pegloticase, 67% with placebo; $P=.007$; NNT=4).³ In addition, pegloticase resulted in statistically significant improvements in QOL measured at the final visit using the Health Assessment Questionnaire (HAQ) pain scale, the HAQ-Disability Index, and the 36-item Short Form Health Survey.

Colchicine plus probenecid or allopurinol reduces gout attacks

One small, low-quality RCT (N=38) found that colchicine 0.5 mg administered 3 times daily effectively prevented gout attacks when administered concomitantly with probenecid initiated to lower urate (gout attacks per month in colchicine and placebo-treated patients, respectively, were 0.19 ± 0.05 and 0.48 ± 0.12 ; $P<.05$).⁴

Another RCT that compared allopurinol with and without colchicine showed that coadministration of colchicine 0.6 mg twice daily reduced gout attacks: 33% of patients

treated with colchicine experienced a gout flare compared with 77% of placebo-treated patients ($P=.008$; NNT=3 over 6 months).⁵

We identified no RCTs that evaluated the uricosuric agent probenecid and no studies that assessed the use of nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent recurrent gout attacks.

Recommendations

The American College of Rheumatology (ACR) guidelines on managing gout recommend allopurinol or febuxostat as first-line pharmacologic urate-lowering therapy, with a goal of reducing sUA to <6 mg/dL. They recommend probenecid as an alternative if contraindications exist or the patient is intolerant to allopurinol and febuxostat.⁶ The guidelines note that allopurinol doses may exceed 300 mg/d, even in patients with chronic kidney disease.

The ACR recommends anti-inflammatory prophylaxis with colchicine or NSAIDs upon initiation of urate-lowering therapy. Anti-inflammatory prophylaxis should be continued as long as clinical evidence of continuing gout disease exists and until the sUA target has been achieved.⁷

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Eight weeks of treatment with either allopurinol or febuxostat reduces the frequency of gout attacks equally.

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