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# LEFLUNOMIDE USE IN THE PROPHYLACTIC TREATMENT OF GOUT

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## Abstract

Gout is one of the most common inflammatory arthritides and is under-treated despite effective treatment options. Colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (CSs) are usually used for prophylactic treatment. Drugs used in prophylactic treatment may have some limitations. Colchicine, the most commonly used agent in prophylactic treatment, has a low level of evidence, while NSAIDs and CSs, which are recommended when colchicine cannot be used, have a very low level of evidence. There are unmet needs in the prophylactic treatment of gout. Our patient, a 69-year-old man, had his first episode of arthritis 19 years ago in the first metatarsophalangeal joint. The patient presented with classic gout attacks and no additional rheumatic disease findings. However, he could not use allopurinol and febuxostat, which are urate-lowering treatments; or colchicine, CSs, and NSAIDs used in prophylactic treatment, for various reasons. In the 12<sup>th</sup> year of the disease, he had an arthritis attack in his wrist. No gout attacks were detected for a long time after starting leflunomide (LEF). LEF appears effective for the treatment of some patients.

**Keywords:** Gout, leflunomide, prophylaxis, treatment

## INTRODUCTION

Gout is one of the most prevalent inflammatory arthritic conditions, yet it remains undertreated despite the availability of effective therapeutic options. The most important reason for this is the under-initiation of urate-lowering therapy (ULT). However, the increased frequency of attacks after ULT is one of the major challenges in treating patients, and effective anti-inflammatory treatments should be developed (1). Guidelines for gout strongly recommend prophylactic treatment when starting ULT. Colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (CS) are usually used for prophylactic treatment (2). Comorbidities such as chronic renal failure, diabetes mellitus (DM), hypertension, ischemic heart disease, heart failure, often accompany gout patients. Therefore, drugs used in prophylactic treatment may have some limitations, especially in patients

with comorbidities (3). Here we report a patient who underwent prophylactic gout treatment with leflunomide (LEF).

## CASE PRESENTATION

A 69 years old male patient experienced his first episode of arthritis 19 years ago, affecting the first metatarsophalangeal (MTF) joint. His arthritis was typical of gout (podagra) with acute, red, monoarthritis attacks lasting 7-10 days. Serum uric acid (sUA) levels were between 8.3 to 9.7 mg/dL (normal sUA 3.5 to 7.2) measured at different times. Allopurinol, which was started as ULT for the patient who was using colchicine (1.2 mg/day bid) regularly and NSAIDs during an acute episode, was discontinued after 1 week of use because it caused skin rash. The patient had four to five gout attacks per year, but after the seventh year, he developed monoarthritis attacks in his ankles and knees.

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In the 12<sup>th</sup> year of the disease, he had an arthritis attack in his wrist. No tophi were detected on clinical examination or imaging. The patient had a family history of gout, as his father and brother had a history of the disease, but no additional rheumatic disease (including psoriatic arthritis) history or findings. Rheumatoid factor, anti-cyclic citrulline peptide, and HLA B27 were negative; a hand X-ray showed no findings suggestive of rheumatoid arthritis, and sacroiliac radiography was normal. Ultrasonography of the foot MTF showed a double contour appearance. Febuxostat (FEB), which was approved as the second ULT agent in Türkiye, was titrated and started in a patient experiencing 3-5 arthritis attacks per year on average, despite regular colchicine use. The sUA level decreased to 4.2 mg/dL within 2 months, but the frequency of attacks increased. For this reason, the patient was provided with regular NSAIDs; prednisolone was given as prophylactic treatment because the attacks continued. The patient whose attacks recurred under a CS dose of 10 mg/day was started on LEF for prophylactic treatment. CS was discontinued in the first month of treatment. The patient was followed up on FEB and LEF for 6 months and experienced no complaints. However, in the 12<sup>th</sup> month of FEB treatment, the patient underwent angioplasty and left anterior descending coronary artery stenting after angina. Meanwhile, the patient discontinued FEB and LEF medications and presented with ankle arthritis 6 months later. After the treatment of the attack, the patient refused the use of FEB. The sUA was 8.3 mg/dL. LEF and CS were initiated as prophylactic treatment, but CS was stopped in the first month of treatment due to elevated blood glucose levels and a diagnosis of DM. Colchicine was not used by the patient because it did not change the frequency of attacks. The patient who used clopidogrel for cardiac disease did not use diuretics, acetylsalicylic acid, fenofibrate, which may affect uric acid levels. Glomerular filtration rate was >90 mL/min/1.73 m<sup>2</sup> and sUA was between 7.4-8.2 mg/dL with no significant change in lifestyle and weight. The patient has been followed with LEF monotherapy for 33 months without an attack.

## DISCUSSION

We present a patient whose gout attacks were successfully suppressed with LEF prophylaxis. ULT is the mainstay of management of gout. However, the factors that most affect the quality of life in gout patients are the number of attacks, the severity of attacks, and the pain between attacks (4). Therefore, prophylactic treatment for gout should be administered effectively to improve quality of life and treatment compliance. However, the evidence supporting the efficacy of drugs used for prophylactic treatment remains limited. Colchicine, the most

commonly used agent in prophylactic treatment, has a low level of evidence, while NSAIDs and CSs, which are recommended when colchicine cannot be used, have a very low level of evidence (5). The frequency of acute gout exacerbation was found to be 33.6% with treatment involving colchicine, which is the first recommended drug for prophylactic treatment (6). This suggests that other treatment options are needed for gout prophylaxis.

While colchicine is the first recommended drug in many guidelines for prophylactic treatment, there is no consensus on the drug to be preferred afterwards. The British Society guideline recommends colchicine first and then CS (7). In addition, anti-interleukin 1 therapies such as canakinumab and rilonacept are not the most recommended agents (8). On the other hand, colchicine is not always effective; NSAIDs have disadvantages such as renal dysfunction, and CS has disadvantages such as hyperglycemia. Canakinumab is a very expensive drug.

Gout consists of different clinical stages, and the course of arthritis may differ depending on the stage of the disease and the treatments administered. Moreover, it is known that there are differences in the pathogenesis of acute and chronic gout (9). To our knowledge, no comparative studies have evaluated the efficacy of prophylactic treatments administered during the early versus chronic stages of gout. Colchicine, NSAIDs, and CSs currently used in prophylactic treatment have the advantages of being short-acting and having a rapid onset of action. LEF, which we used in the chronic phase of gout in our patient, is a long-acting agent whose anti-inflammatory effect starts later but lasts longer. In addition, its use in renal failure and DM is an important advantage (10). Determining at which stage LEF therapy is effective and whether it is effective in the prophylactic treatment of gout may fulfill an important need in the management of gout.

However, concomitant calcium pyrophosphate dihydrate arthritis could not be excluded in the patient. Although there is no evidence of chondrocalcinosis on X-ray, this is because polarized light microscopy and dual energy computed tomography are not available to definitively distinguish crystals.

## CONCLUSION

In summary, there are unmet needs in the prophylactic treatment of gout. LEF appears to be a potential therapeutic option for selected patients with contraindications to conventional prophylactic treatments. Gout is a disease with a high prevalence; the importance of planning studies on LEF in its prophylactic treatment is emphasized.

## Ethics

**Informed Consent:** Informed consent form was obtained.

## Footnotes

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