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Use of canakinumab in recurrent gout attacks in patients with comorbidity — two clinical case reports

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Abstract

Gout is a chronic autoinflammatory joint disease affecting an increasing proportion of the population. Older-generation anti-inflammatory drugs are used to treat arthritis flares: nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and glucocorticoids, and a second-line is a biologic, which is a selective interleukin-1 beta (IL-1β) antagonist – canakinumab This paper presents two clinical cases of patients treated with canakinumab due to lack of efficacy and contraindications to first-line drugs.

Key words: gout; canakinumab; IL-1β; comorbidity; gout attack

Introduction

Gout is the most common autoinflammatory joint disease classified as a crystallopathy [1, 2]. Its course is divided into four periods: asymptomatic hyperuricaemia, acute gout attacks, intercritical gout and chronic tophaceous gout [1, 3]. Once the peripheral blood serum uric acid crystallisation threshold of 6.8 mg/dL is exceeded, deposits of monosodium urate may precipitate in the joints, surrounding tissues and other organs [3, 4].

The presence of crystals in the tissues leads to the development of an inflammatory process, also observed in the clinically silent intercritical gout, with elevated levels of C-reactive protein (CRP), tumour necrosis factor alpha (TNF-α), interleukins (IL:) IL-1 or IL-6, and increased congestion of the synovial membrane on ultrasound (USG) [5, 6]. During an exacerbation of the condition, clinical symptoms include pain and swelling of the joint with redness of the surrounding skin [7].

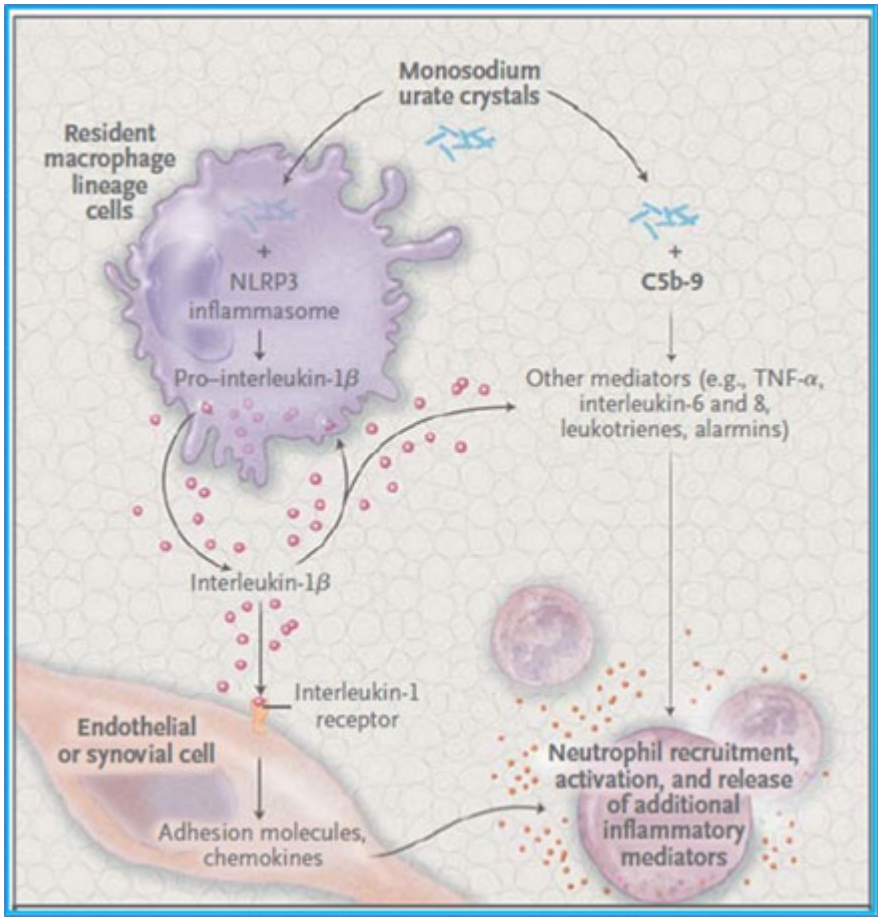

Figure 1. Diagram of an acute gout attack Neogi T. Clinical practice. Gout. N Engl J Med. 2011;364:443-452.

During a gout attack, monosodium urate crystals are phagocytised by monocytes and macrophages, activating the NLRP3 inflammasome and further activating procaspase 1 (Fig. 1). The resulting caspase 1 converts proIL-1β to IL-1β, a key inflammation inducer in gout [3, 7]. IL-1β secretion results in the release of chemokines that increase the influx of leukocytes, especially neutrophils, into inflamed tissues [3, 8]. IL-1 increases the expression of receptor activator for nuclear factor κ B ligand (RANKL), which accelerates osteoclast differentiation. IL-1α and IL-1β subunits may also exert direct effects on osteoclasts, accelerating cartilage damage and bone erosion. IL-1 and IL-6 stimulate hepatic cells to produce CRP [9].

Additionally, sodium urate crystals increase TNFα production by monocytes and synoviocytes, which increases inflammatory activity, affects endothelial damage, increases endothelin-1 production and decreases nitric oxide release [10].

This paper presents the use of an IL-1β inhibitor in gout attack treatment in two patients hospitalised in the Department of Rheumatology and Internal Medicine at the Marciniak Lower Silesia Specialist Hospital in Wrocław, with concomitant diseases and contraindications to classic anti-inflammatory drugs.

Case one

A 59-year-old man, diagnosed with gout as per the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria, stage 4 chronic kidney disease as per Kidney Disease: Improving Global Outcomes (KDIGO) in the course of IgA nephropathy and secondary normocytic anaemia, was admitted to this department in October 2022 due to recurrent gout attacks with a frequency of one attack per month. The patient developed outpatient hyperuricaemia despite allopurinol therapy at a dose of 100 mg per day [maximum dose adjusted for glomerular filtration rate (GFR)] and adherence to a low-purine diet.

On admission, physical examination abnormalities included swelling and tenderness of the right knee and metatarsophalangeal joint (MTP I) of the left toe. Laboratory results showed elevated renal parameters and inflammatory markers, as well as hyperuricaemia (8.7 mg/dL with N < 7.0). X-rays of the knee joints showed erosions typical of gout. Foot joint ultrasound showed active inflammation with hypertrophy and congestion of the synovial membrane. Treatment included oral methylprednisolone at a dose of 24 mg per day with a subsequent dose reduction to 4 mg per day, maintained to prevent the attacks. Allopurinol was replaced with febuxostat at a daily dose of 80 mg.

Despite the treatment, another acute episode of the disease occurred one month later in the left knee joint. An ultrasound revealed active synovitis and sonographic signs of gout (double contour cartilage line – Fig. 2). After obtaining the patient's consent, a joint puncture with betamethasone injection was performed.

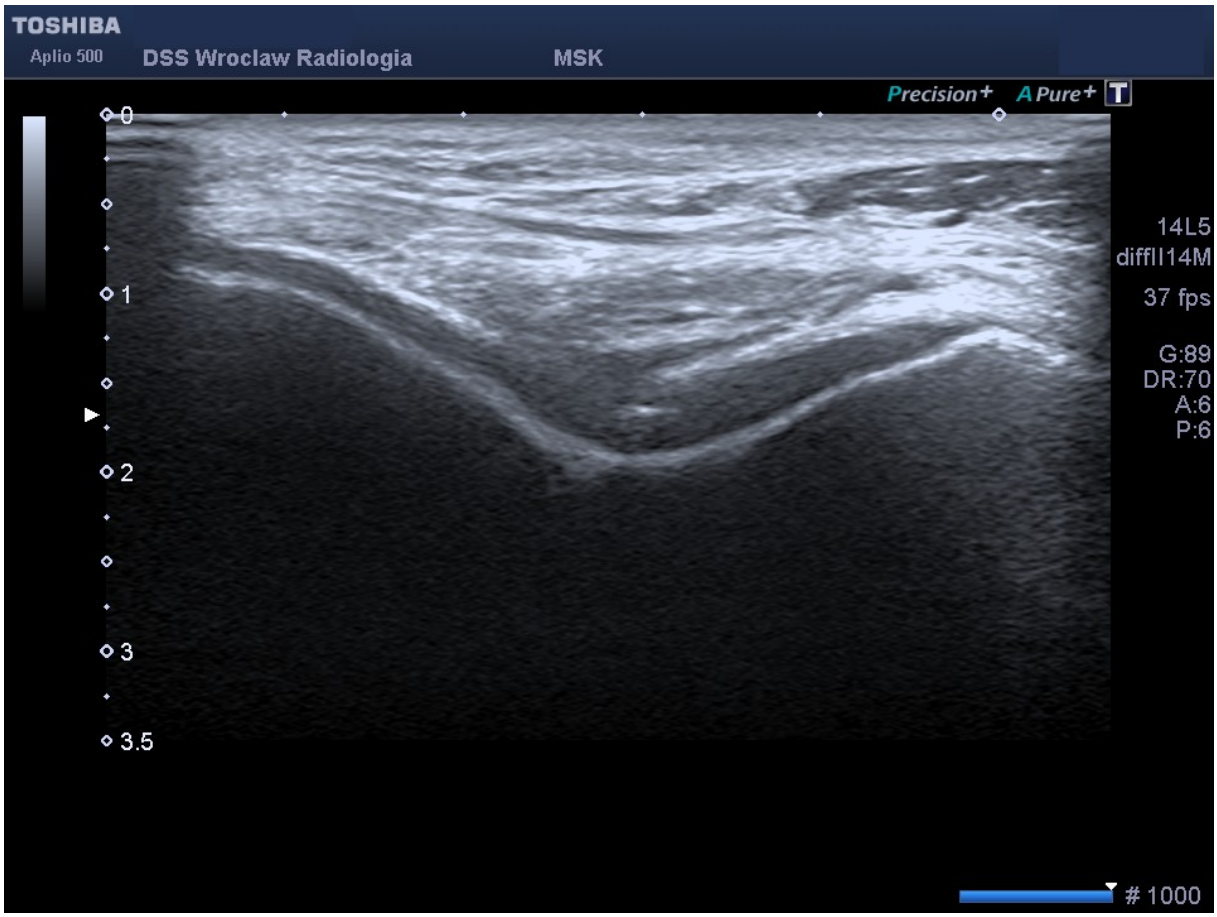

Figure 2. Patient 1 — image of the double contour cartilage line of the knee joint in the transverse plane

Due to the frequent gout flares (> 3 per year) and the existing contraindications (chronic kidney disease) to the use of NSAIDs and colchicine, in view of the ineffectiveness of previous glucocorticoid therapy, an Emergency Access To Drug Technologies (RDTL) procedure was initiated to initiate canakinumab therapy. Before starting it, the patient was checked for infections with hepatotropic viruses B and C, human immunodeficiency virus (HIV), and concomitant bacterial infections, and the Quantiferon test was negative.

Following therapy approval, 150 mg of canakinumab was administered subcutaneously to the patient in late 2022 and early 2023, achieving resolution of clinical symptoms and decreased inflammatory markers on the first day of treatment (Fig. 3). The patient is followed up – the disease remains in remission at 11 months after drug administration.

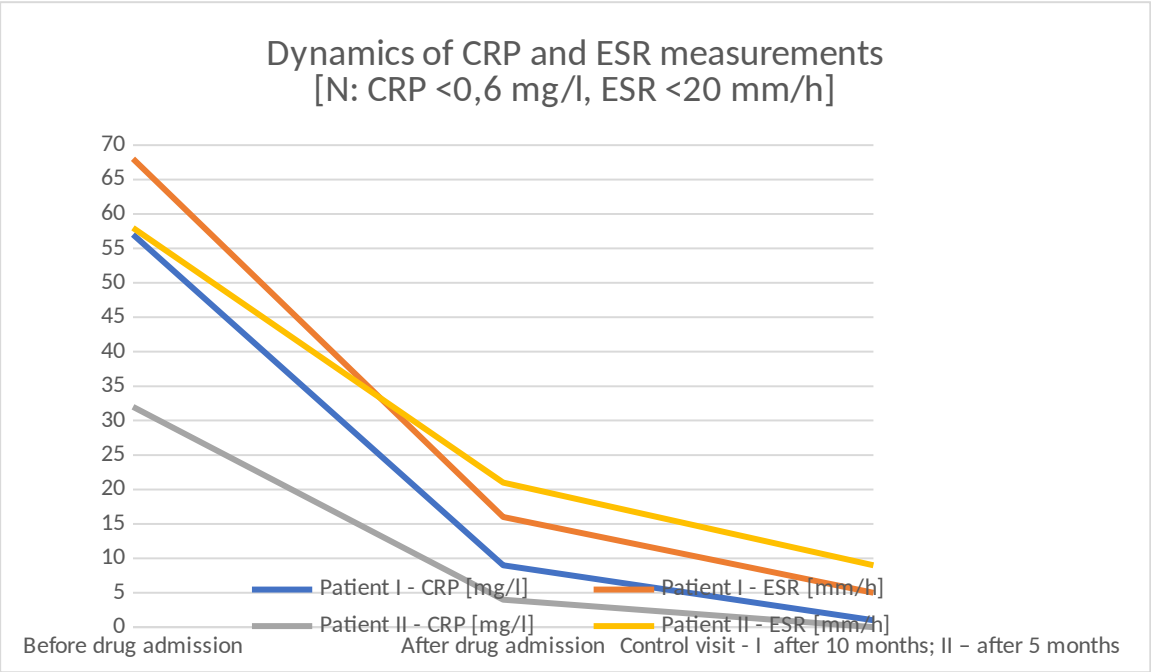

Figure 3. Change in the concentration of inflammatory markers: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). [Normal range: CRP < 0.6 mg/L, ESR < 20 mm/h]

Case two

A man aged 69, diagnosed with seropositive rheumatoid arthritis meeting the 2010 ACR/EULAR classification criteria and with coexisting gout meeting the 2015 ACR/EULAR classification criteria, with a cardiac burden [with a history of chronic heart failure in the course of the ischaemic disease, having undergone radiofrequency (RF) ablation for ventricular arrhythmia and three cardiac RF ablations for sustained ventricular tachycardia, with third-degree atrioventricular block, having undergone implantation of a cardioverter-defibrillator, having undergone implantation of a pacemaker improving myocardial contractility, having undergone coronary artery bypass grafting), in addition to, among others, chronic kidney disease at stage G3a according to the KDIGO, after radioiodine treatment due to amiodarone-induced hyperthyroidism, was admitted to the Department of Rheumatology in March 2023. Five gout attacks were observed in the previous year. As part of treatment aimed at lowering uric acid, the patient was taking 300 mg of allopurinol daily — in line with GFR (febuxostat was contraindicated due to high cardiovascular risk).

Physical examination revealed swelling and pain in the small joints of the left hand and left olecranon bursitis. Increased values of inflammatory markers were observed in the results of laboratory tests. Infection with hepatotropic viruses B and C and HIV was excluded. The Quantiferon test was negative.

Due to contraindications to NSAIDs (heart and renal failure), colchicine (multiple cardiac burdens, older age, renal impairment) and chronic glucocorticoid therapy (multiple cardiac burdens), an emergency access to drug technologies procedure was initiated to implement canakinumab treatment.

After two weeks, a 150 mg canakinumab injection was administered, achieving resolution of pain and joint swelling (including left elbow bursitis – Fig. 4). Remission of symptoms has persisted for eight months.

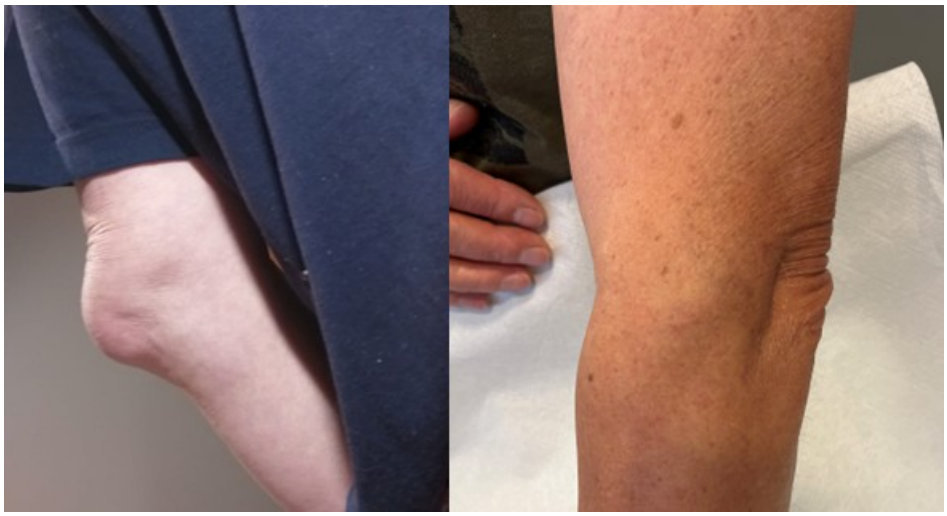

Figure 4. Patient II — left elbow bursa before (left) and after administration of canakinumab (right)

Discussion

Gout therapy covers non-pharmacological treatment, acute attack treatment, reduction of uric acid levels, and prevention of recurrence [3].

Non-pharmacological treatment includes lifestyle changes (weight reduction, regular physical activity), adequate hydration, limiting alcohol intake and changing to a low-purine diet (limiting red meat, fructose-sweetened beverages, legumes, and beer, among others) [1].

In the treatment of acute gout attacks, NSAIDs, colchicine and glucocorticoids administered orally or intravenously are used as first-line drugs [4, 11]. However, these cannot be used in some patients due to contraindications, intolerance, or lack of efficacy [2, 4]. In addition,

these drugs may worsen the course of comorbidities such as ischaemic heart disease, hypertension, diabetes mellitus, chronic heart or renal failure, which in turn leads to more frequent gout attacks, the development of uric acid nephrolithiasis, gouty nephropathy and the formation of tophi [4, 10, 12, 13].

The main contraindications to the use of anti-inflammatory drugs are the following:

— cardiovascular, renal and gastrointestinal diseases in the case of NSAIDs;

— diabetes mellitus, cardiovascular and gastrointestinal diseases, hyperlipidaemia, osteoporosis in the case of glucocorticoids;

— chronic kidney disease, chronic hepatitis, use of P-glycoprotein inhibitors and potent cytochrome P4503A inhibitors in the case of colchicine [2, 3].

The second-line drug for acute gout attacks is the IL-1 antagonist canakinumab, which is also used to treat hereditary recurrent fever syndromes [14] or Still's disease (with onset in adolescence or adulthood) [15, 16]. There are currently three IL-1 blockers with different mechanisms of action: anakinra, a recombinant human IL-1Ra protein; canakinumab, a human monoclonal antibody that selectively inhibits IL-1β [the only drug registered by the *European Medicines Agency* (EMA) for use in acute gout]; and rilonacept, a fusion protein that binds IL-1α and IL-1β non-selectively. These drugs differ in their biological half-life, with anakinra having a half-life of 4–6 hours, rilonacept 6 days and canakinumab 26 days [18], which is a clear advantage as it requires the lowest injection frequency. Canakinumab additionally shows the lowest incidence of skin lesions at the injection site, which occur in only 10% of patients, compared with 60% for rilonacept and 50–70% for anakinra [18, 19, 20]. The advantage of anakinra, however, is the lowest incidence of infection during treatment. The favourable safety profile of canakinumab allows it to be used in patients with multimorbidity.

The following adverse reactions were observed for canakinumab (in order of decreasing frequency): increased incidence of infections, injection site reactions, neutropenia, dizziness, arthralgia and myalgia, gastrointestinal disorders, transient thrombocytopenia, mild increase in transaminases and increase in triglycerides [15]. The main contraindications to its use are infections due to the risk of a septic course, which must be ruled out before treatment is initiated [15]. The drug can be used in chronic kidney disease [15, 21].

Serum uric acid-lowering drugs should be continued after canakinumab, as this treatment dissolves tophi and sodium urate deposits in the synovial tissues and reduces the frequency of subsequent exacerbations [12].

Uric acid-lowering treatment may include drugs that inhibit uric acid formation (allopurinol and febuxostat), increase uric acid excretion (lesinurad, probenecid, benzbromarone, sulfinpyrazone, fenofibrate, losartan) or cause uric acid breakdown – pegloticase [1]. There is an increased risk of a gout attack while the above-mentioned therapies are administered, so concomitant use of anti-inflammatory drugs is recommended [7]. Low-dose NSAIDs and colchicine are used as a preventive treatment, followed by glucocorticoids in a dose equivalent to 30–35 mg of prednisone for 3–5 days [3, 11]. According to the available reports, canakinumab can reduce the risk of subsequent gout attacks during allopurinol treatment with an efficacy 50–70% higher than colchicine [4, 7, 22], but it has not yet been registered for use for this indication. After canakinumab administration, a reduction in inflammatory markers, including CRP and serum amyloid A (SAA), is observed for up to 6 months [4, 23]. According to data from a meta-analysis by Zeng et al., canakinumab showed the highest efficacy in reducing pain and more effectively lowered the frequency of gout attacks compared to NSAIDs and glucocorticoids administered intravenously or intramuscularly [24]. A literature review by Schlesinger et al. indicates greater efficacy, faster duration of action and longer attack-free time after canakinumab and rilonacept compared to glucocorticoids and colchicine [25].

Conclusions

This study presented examples of the use of canakinumab in patients with contraindications to first-line drugs. In the cases described, rapid improvement in clinical status and laboratory results was observed, as well as the persistence of remission for several months, which was previously impossible.

This drug may be a favourable therapeutic option for patients with contraindications to, and intolerance of, NSAIDs and colchicine or in the absence of their efficacy, especially in patients in whom repeated doses of glucocorticoids are not recommended. Due to the high price of the drug and the need to exclude latent infection (practically possible in the hospital setting), the availability of canakinumab therapy is currently limited to a small group of carefully selected patients.

Author contributions

A.P. – 80%; M.S. – 10%; K.G. – 10%.

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Conflict of interest

The authors declare no conflict of interest.

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