CASE REPORT

A Beacon in the Dark: Canakinumab. A New Therapeutic Perspective in Chronic Tophaceous Gout

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ABSTRACT

Gout is the most common form of arthritis in adults. It is often associated with other comorbidities, which contraindicate the use of conventional therapies. The discovery of the role of interleukin-1 β (IL-1 β) in orchestrating the monosodium urate crystal-induced inflammatory response offered new therapeutic prospects to refractory patients, or to those in whom standard therapies are contraindicated. This paper describes a clinical case of a 65-year-old man with chronic tophaceous gouty arthropathy and subintraflares, who had comorbidities contraindicating the use of conventional gout therapies—to which he did not respond—who was treated with canakinumab, a monoclonal selective inhibitor of IL-1 β . The patient

reported a gradual, rapid, and significant reduction in pain, with a response observed within 12 h of the administration of the drug. Consistent with previous clinical studies, canakinumab appeared to be a viable, safe, and effective alternative to conventional therapies in this patient with gout who had limited therapeutic options.

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Keywords: Canakinumab; Chronic tophaceous gout; Interleukin-1 β ; Refractory gouty arthropathy; Treatment options

INTRODUCTION

Known since ancient times, gout is the most common form of arthritis among the adult population, with a prevalence of 4% in the USA and 0.46% in Italy; it affects approximately 8.3 million people in America alone [1, 2]. The economic burden of gout is significant, not only because epidemiological data show an increase in its prevalence and incidence worldwide but also because it has a high level of disability and mortality [3].

Gout is caused by the deposit of monosodium urate crystals inside the joints and tissues. The drugs conventionally used for the treatment of acute gout are non-steroidal anti-

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inflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2 inhibitors, colchicine, and corticosteroids [4]. However, an increasing number of patients with gout are intolerant or refractory, or have contraindications, to the use of conventional drugs.

Recently, studies have highlighted the key role of interleukin-1 β (IL-1 β) in the inflammatory process related to the tissue and articular deposit of monosodium urate crystals in patients with gout [5–9]. According to this theory, at the start of a bout of acute gout, monosodium urate crystals activate inflammasome NLRP3, leading to the release of IL-1 β and consequently an inflammatory response, with vasodilation and recruitment of immune cells, preferentially neutrophils, in the site of the crystal deposit. Based on the identification of the role of IL-1 β in gout, development of drugs that inhibit IL-1 signal transduction was initiated, expanding the small number of therapeutic options available for the management of the acute attack in the patient with gouty arthritis.

Among currently available IL-1 inhibitors are anakinra, an IL-1 receptor human antagonist, rilonacept, an inhibitor of both IL-1 β and IL-1 α , and canakinumab, a fully human monoclonal antibody selectively inhibiting IL-1 β . Several publications have demonstrated the efficacy of these drugs in patients with gout for whom conventional therapies are contraindicated or ineffective [10–15].

Reported here is the case of a patient with chronic tophaceous gout refractory to conventional therapies, to the use of which he also presented contraindications, who responded to treatment with canakinumab.

CASE REPORT

In October 2016, a 65-year-old male patient, who had been hospitalized for acute heart failure, was referred to our operative unit (OU) for a consultation by the medicine OU of the same hospital for a severe acute attack of gout. He had a history of type 2 diabetes mellitus, arterial hypertension,

ischemic dilated cardiomyopathy, and chronic atrial fibrillation. He had also experienced a previous myocardial infarction, had chronic grade III renal insufficiency for the last 3 years, was obese, and was diagnosed with gouty arthropathy in 2011. Since his diagnosis of gout the patient had experienced over 15 acute attacks, and was treated with colchicine, high-dose steroids, NSAIDs, and allopurinol (replaced in 2016 with febuxostat). His family history was negative for gout, and there was a personal history of high dietary purine intake and previous smoking and alcohol abuse.

At the time of referral, the patient had swelling of multiple joints, including his right knee, wrists, and the metacarpophalangeal (MCP) and interphalangeal (IP) joints of his hands, feet, and ankles. In the days prior to hospitalization, he had progressive clinical worsening of his gout, which he treated with NSAIDs, colchicine (up to 3 mg/day), and high-dose steroids without any benefit. He presented at the emergency room of our hospital where, over several days additional boluses of steroids were administered without clinical response, but with a worsening of dyspnea, fatigue, poor control of blood pressure, and onset of swelling. At admission, he was receiving the following therapies: bisoprolol 7.5 mg/day (5 + 2.5 mg), colchicine 1 mg twice daily, rivaroxaban 15 mg/day, prednisone 25 mg/day, tramadol as needed, pantoprazole 40 mg/day, febuxostat 80 mg/day, and olmesartan 20 mg/day.

Upon physical examination, the patient was in severe pain, numerous tophaceous nodules were observed bilaterally on the hands, feet, elbows, and knees (Figs. 1a, 2), and symmetric arthritis of the feet, right knee, and right hand was present, with the overlying skin warm and erythematous. Walking was impossible.

Blood tests revealed elevated uric acid, blood urea nitrogen, blood count, serum creatinine, erythrocyte sedimentation rate, and C-reactive protein (Table 1), while culture tests (blood culture, urinoculture, stool test, synovial fluid culture), tests for antinuclear antibodies, anti-double stranded DNA, anti-citrullinated protein antibody, extractable nuclear antigen

Fig. 1 Joint swelling and tophi in the right and left hands **a** at the start of treatment, **b** at day 14, and **c** at day 30

antibodies, rheumatoid factor, prostate-specific antigen, hepatitis B and hepatitis C markers, and his thyroid profile were all negative. The examination of the right knee synovial fluid showed the presence of monosodium urate crystals, with marked leukocytosis.

An X-ray of the hands revealed multiple asymmetrical thickening of periarticular soft tissue, with increased nubecula-type density, erosions of the interphalangeal joints, cystic lesions and initial reduction of the corresponding articular rimae, while a chest X-ray

was normal. Echocardiography showed widely dilated left ventricular hypokinetic LV and an ejection fraction of 20% while electrocardiography (ECG) revealed full atrial fibrillation arrhythmia, an average heart rate of 95 bpm, and left bundle branch block.

Considering the failure to respond to conventional gout therapies, to which the patient by now had proved to be refractory, as well as the contraindications to their use due to his comorbidities, canakinumab was administered subcutaneously, in a single dose of 150 mg.

Fig. 2 Change in joint swelling **a** from baseline to day 30 in the right foot, **b** from day 14 to day 30 in the right elbow

The patient reported a gradual, rapid, and significant reduction in pain (calculated using a 0–100 VAS scale), which was apparent 12 h after the administration of the drug (Fig. 3a). After 24 h, the patient was able to walk independently, without any help or support. Over the next few days there was a progressive improvement in the patient's daily activities, as assessed by the Barthel Index of Activities of Daily Living and the Lawton–Brody Instrumental Activities of Daily Living Scale, which improved from 30 to 100 and from 2/5 to 5/5 at 4 weeks after treatment. In parallel with the reduction of pain, the dose of his steroid (prednisone) was gradually scaled down, until its complete suspension, after 22 days (Fig. 3b). Blood tests carried out 10 days after the administration showed improvement of all parameters previously elevated (Table 2).

Fourteen days after receiving canakinumab, the patient was discharged from hospital. At this time, the patient had a marked improvement in his cardiac and renal function. Echocardiography revealed post-ischemic dilated hypokinetic cardiomyopathy, severe dilation of the left ventricle, moderate reduction in global kinetics, moderate–severe diastolic dysfunction, biatrial enlargement (severe in left atrium), mild pulmonary hypertension, mild mitral insufficiency, ectasia of the aortic root and ascending aorta, and an injection fraction of 40%.

The patient was discharged with instructions to take tramadol three times per day as needed, which he did not (as reported at the follow-up visits made on days 30, 45, 60, and 90); the patient also reported no new acute attacks or adverse events.

Table 1 Characteristics and demographics of patient at hospital admission

Parameter	Value
Age, years	65
Height, cm	170
Weight, kg	107
BMI, kg/m ²	37
Ejection fraction, %	20
Heart rate, bpm	95
Blood test results	
Uric acid, mg/dL	10
ESR, mm/h	96
CRP, mg/dL	28.99
WBC, /mm ³	14,600
Neutrophils, %	87.9
Lymphocytes, %	4.3
Creatinine, µmol/L	176
Creatinine clearance ^a , mL/min	56.47
Calcium, mg/dL	7.9
Azotemia, mg/dL	78
Glucose, mg/dL	142
Albumin, g/dL	2.4
AST, U/L	9
ALT, U/L	7
GGT, U/L	44

^a Assessed using the Cockcroft–Gault equation

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *GGT* gamma-glutamyl transferase

Four weeks after the administration of canakinumab, he presented for a follow-up, where the number and size of tophi observed at hospitalization were reduced (Figs. 1c and 2).

Informed consent was obtained from the patient for his information to be used in this case report.

DISCUSSION

To date, canakinumab is the only drug to have obtained approval from the Italian Medicines Agency (AIFA) for the symptomatic treatment of adult patients with gouty arthritis. Canakinumab is approved by the European Medicines Agency for the treatment of adult patients with frequent attacks of gouty arthritis refractory to NSAIDs, colchicine, and repeated courses of corticosteroids [16, 17]. The efficacy of canakinumab was investigated in two phase 2 variable-dose studies [11, 12] and in two phase 3, randomized, multicenter, double-blind studies (β-RELIEVED and β-RELIEVED-II) [10], which showed that a single dose of canakinumab (150 mg) can control new exacerbations and causes a rapid reduction of the pain and inflammatory state in patients with gout who have contraindications, intolerance, or non-responsiveness to colchicine and/or to NSAIDs. Long-term follow-up studies with canakinumab have also reported similar efficacy [18]. Post hoc analysis of the phase 3 studies to determine the safety and efficacy of canakinumab in a subgroup of patients refractory to NSAIDs and colchicine reported similar results to the main studies [19]. Canakinumab is also reported to improve health-related quality of life in patients with difficult-to-treat gouty arthritis [20]. The safety profile of canakinumab from the phase 3 studies showed that the treatment is well tolerated and the main adverse events reported with treatment include infections, hypertension, headache, and back pain [10]. However, canakinumab is not approved by the US Food and Drug Administration for the treatment of gouty arthritis because of concerns regarding its safety, particularly related to the incidence of infections and hypertension with its use [21].

Despite the presence of multiple comorbidities (diabetes, hypertension, heart failure) contraindicating the use of conventional therapies, the baseline characteristics of the patient in the present case report were globally similar to the patients enrolled in the phase 3 studies with canakinumab [10]. Our case, which appears to be the first in Italy in which a patient with gouty arthropathy refractory to conventional

Fig. 3 Change in **a** visual analogue scale (VAS) pain score and **b** dose of steroid (prednisone) over time after administration of canakinumab

therapies was treated with canakinumab, supports the findings of the clinical trials by demonstrating how a single dose of canakinumab 150 mg results in a rapid and significant improvement of the pain, the inflammatory

state, and thus the patient's quality of life. A single dose of canakinumab (150 mg) also seemed to reduce the number and size of tophi in the patient, and further studies are required to confirm this effect.

Table 2 Blood test results at 10 days

Blood test	N = 1
Uric acid, mg/dL	8.4
ESR, mm/h	22
CRP, mg/dL	1.09
White blood cells, $\times 10^9/L$	6.90
Neutrophils, %	57.4
Lymphocytes, %	28.7
Creatinine	1.8

CRP C-reactive protein, ESR erythrocyte sedimentation rate

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Compliance with Ethics Guidelines. Informed consent was obtained from the patient for his information to be used in this case report.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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