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Chapter

Prophylaxis of Acute Arthritis at Initiation of Urate-Lowering Therapy in Gout Patients

Maxim Eliseev, Maria Chikina and Evgeny Nasonov

Abstract

During the first months after the initiation of urate-lowering therapy in gout patients, the risk of exacerbation of arthritis considerably rises, which often results in discontinuation of the prescribed therapy by patients. The main way to avoid this risk is preventive prescription of colchicine, NSAIDs or glucocorticoids. Such prophylaxis of acute arthritis has been specified in a large number of the latest editions of various national and international guidelines; however, this tactics is rarely used in practice. The chapter includes the most significant studies on this problem.

Keywords: gout, prophylaxis, urate-lowering therapy, NSAID, colchicine, GC, canakinumab, acute attack

1. Introduction

It is known that the frequency of gout attacks increases at initiation of any medications (allopurinol, febuxostat, PEG-uricase, and benzbromarone) that lower serum uric acid level, irrespectively of their mechanism of action [1, 2]. The most promising method to reduce the risk of acute arthritis in gout patients is to initiate preventive anti-inflammatory drug therapy (NSAIDs, colchicine, or glucocorticoids).

The need for preventive therapy of gout flares is also stated in the current guidelines [3, 4]. Thus, according to the guidelines by the European League against Rheumatism (EULAR), the need for prophylaxis of future gout flares should be explained to every patient and discussed with them. As the first-line therapy drug, it is recommended to use 0.5–1.0 mg colchicine daily and the dose should be lowered if the patient was diagnosed with renal insufficiency. Besides, the authors of the guidelines emphasize the need for observing the patients with renal insufficiency who receive HMG-CoA reductase inhibitors (statins) at the initiation of colchicine, considering the potential risks of neuro- and/or muscle toxicity. According to the guidelines, simultaneous prescription of colchicine and strong P-glycoprotein inhibitors and/or CYP3A4 should be avoided. In cases of intolerance to colchicine or contraindications for thereof, it is advised to consider prophylaxis with NSAID (also in the minimum effective anti-inflammatory dose, with the use of gastroprotective therapy if needed) [3]. The guidelines by the American College of Rheumatology (ACR) are similar to those by EULAR, however, according to the

Source (study)	Type of study/trial	Drug	Period of observation	Number of patients	Results
Paulus et al., 1974 [9]	Double-blind placebo-controlled	Colchicine 0.5 mg 3 times daily	6 months	38	• The patients who received probenecid with colchicine had on average 0.19 gout flares per month, whereas in the patients who received probenecid and placebo, the frequency of attacks was on average 0.48 per month.
Borstad et al., 2004 [1]	Double-blind placebo-controlled	Colchicine 0.6 mg twice per day	6 months	43	• The patients who had colchicine therapy reported of acute arthritis much less often (0.52 vs. 2.91, p = 0.008), and in the case of development of acute arthritis, the intensity of pain at VAS was lower (3.64 vs. 5.08, p = 0.018).
Karimzadeh et al., 2006 [10]	Randomized without placebo control	Colchicine 1 mg daily	1 year	229	• Basing on the received data, the researchers came to the conclusion that the optimal length of colchicine therapy for prophylaxis of acute arthritis is 7–9 months from the start of urate-lowering therapy.
Wortmann et al., 2010 [38]	Randomized placebo-controlled	Colchicine 0.6 mg daily or naproxen 250 mg twice a day	6 months	4101	• In the groups where patients received colchicine or NSAIDs, they reported of reduction of the frequency of acute arthritis during the entire period of therapy, irrespectively of the selected medication. • Immediately after discontinuation of the 8-week prophylactic therapy, the frequency of acute arthritis increased by three times, irrespectively of the drug used for prophylaxis.
Jinquan et al., 2018 [45]	Comparative retrospective placebo-controlled	Colchicine 0.53 ± 0.15 mg daily or prednisolone 7.55 ± 1.3 mg daily	6 months	273	• Gout flares were noted more often in the patients who received therapy with prednisolone. • However, the intensity of pain during the acute arthritis was higher in the patients who received colchicine.
Schlesinger et al., 2011 [47]	Double-blind randomized active-controlled	Canakinumab 10, 25, 50, 90, 150 mg, one-time or triamcinolone acetonide (TA) 40 mg, one-time	8 weeks	200	• The reduction in pain on the canakinumab therapy was more marked than on TA in 25, 48 and 72 hours. • The period between gout flares on canakinumab was longer than on TA.
Schlesinger et al., 2012 [48]	Double-blind randomized multicenter controlled	Canakinumab 150 mg, one-time or triamcinolone acetonide (TA) 40 mg, one-time	24 weeks	465	• Reduction of the risk of gouty arthritis attacks by 66% in 12 weeks. • Reduction of the average number of new gouty arthritis attacks by 63% in 12 weeks.
Solomon et al., 2018 [49]	Randomized placebo-controlled	Canakinumab 50 mg, 150 or 300 mg once in 3 months	3.7 years	10,061	• Quarterly reception of canakinumab allowed to significantly reduce the risk of acute arthritis, irrespectively of the serum uric acid level.

Table 1.
Efficacy of prophylactic anti-inflammatory therapy at initiation of urate-lowering drugs in gout patients.

latter, in cases of contraindications for NSAID and colchicine, it is possible to initiate low-dose glucocorticoids [4].

Such prophylaxis is recommended to be given for 6 months from the start of urate-lowering therapy. This exact tactic allows to not only minimize the risk of acute arthritis, but also to reduce probability of self-discontinuation of the urate-lowering therapy by the patient.

However, the evidence basis for these recommendations is not ample and there have been no randomized controlled comparative trials of certain medications.

The most considerable studies on preventive anti-inflammatory therapy at the start of urate-lowering drug therapy are presented in **Table 1**.

2. Colchicine

Colchicine, an alkaloid received from *Colchicum autumnale*, is the most well-studied medication used for prophylaxis of acute arthritis at the initiation of urate-lowering therapy [5].

The mechanisms by which colchicine has its anti-inflammatory action are manifold. Probably the most valuable of these mechanisms is the effect on tubulin molecule, which conditions its cytotoxic and anti-inflammatory action due to the inhibition of migration, chemotaxis, neutrophil adhesion, as well as the suppression of superoxide anion synthesis [5].

The modern data suggest the possibility of the direct anti-inflammatory action of colchicine associated with IL-1-stimulated neutrophil adhesion inhibition. It has been recently shown that colchicine reducing pro-caspase-1 mRNA and secreted caspase-1 protein, an enzymatic component of NLR of the NOD-like receptor Pirin-3 (NLRP3) which regulates conversion of pro-interleukin-1β (IL-1β) into active IL-1β [6].

In 1961, Yu and Gutman first performed a study to estimate the possibility to use low-dose colchicine for exacerbation prophylaxis, which resulted in reduction of the frequency of acute arthritis both in the patients who received colchicine monotherapy and in those who received colchicine with concurrent probenecid. The duration of the therapy was 2–10 years, the patients received 0.5–2.0 mg colchicine daily, which was less than the colchicine dose typically used for rapid relief from acute arthritis at that time. As a result, the frequency and severity of acute arthritis considerably reduced in 74% patients; there were no differences in the frequency in the groups of patients who received probenecid and of those who did not, and the discontinuation of colchicine caused arthritis exacerbation within several weeks or months in 20 out of 25 patients who had not had acute arthritis for several years [7].

In 1965, Gutman published the findings of a retrospective analysis of 734 gout patients in which it was stated that reception of colchicine significantly reduced frequency of acute arthritis, irrespectively of the chosen urate-lowering therapy [8].

The first placebo-controlled study to show the efficacy of colchicine prophylaxis in acute gout arthritis was the study by Paulus et al. [9]. The study involved 51 gout patients with typical gout flares and serum uric acid level of >7.5 mg/dl. The patients were randomized and divided into two groups: probenecid 500 mg and colchicine 0.5 mg three times daily, or probenecid 500 mg and a placebo three times daily. The analysis included 38 patients who showed significant reduction in their average serum uric acid level. During the study, the patients reported about gout attacks which were classified as light, moderate and severe, and only those classified as moderate and severe were included in the analysis. As a result, during the study period, the patients from the probenecid/colchicine group had on average 0.19 gout attacks per month, while the patients from the probenecid/placebo group reported about on average 0.48 attacks per month.

In 2004, Borstad et al. [1] carried out the first study to evaluate the efficacy of low-dose colchicine at initiation of urate-lowering therapy (allopurinol). The study included 43 patients with established gout who began allopurinol therapy. As a gout flare prophylaxis, the patients took either colchicine 0.6 mg twice a day or a placebo, depending on their randomization. Both groups were analogous in their basic characteristics and in the doses of allopurinol necessary to reach the target uric acid level. The observation period was 6 months. The patients who took colchicine reported about gout flares much less often (0.52 vs. 2.91, $p = 0.008$), and in the cases of development of gout flares, the intensity of pain according to VAS was lower (3.64 vs. 5.08, $p = 0.018$). The tolerance of colchicine was good, however, the frequency of diarrhea was higher in the patients who took colchicine (38.0% in the colchicine patients vs. 4.5% in the placebo patients), and the reduction of the dose of colchicine to 0.6 mg once a day leveled those differences almost completely.

The study by Karimzadeh et al. [10] estimated the optimal length of colchicine therapy for prophylaxis of acute arthritis in gout patients. 229 patients using the allopurinol and colchicine 1 mg daily therapy were randomized into three groups: group 1 took colchicine for 3–6 months, group 2 for 7–9 months and group 3 for 10–12 months. After a one-year observation period, 54% of the patients in group 1, 27.5% of the patients in group 2, and 23% of the patients in group 3 had at least one gout flare. Basing on the received data, it was concluded that the optimal length of colchicine treatment for prophylaxis is 7–9 months. However, that study had a number of limitations as it was not placebo-controlled, the patients only informed about the time interval until the flare, not about the number of flares. Besides, the study did not provide any information on which criteria had been used to diagnose gout. Another important limitation of this study, just like of many others, was absence of a clear definition of gout flare for self-assessment by the patient. Recently the results of a multicenter work have been published which compared several simple ways of self-assessment which, as is expected, can reduce the possibility of making mistakes in investigation findings [11].

It is proved that bioavailability of colchicine is the same for elderly and young people. However, the distribution volume of colchicine can go down, which leads to its higher concentration in plasma and a significantly higher risk of toxicity. To counteract this effect, some experts recommend reducing the dose of colchicine by two times in the patients over 70 years old [12].

Critics of long reception of colchicine for gout flare prophylaxis at the start of urate-lowering therapy discuss how safe this tactics of therapy is. The doses of colchicine of 0.5–0.8 mg/kg are highly toxic and the doses over 0.8 mg/kg are usually fatal; in order to reduce the risk of irreversible overdose, the US Food and Drug Administration called off the permission to use colchicine intravenously [13]. Acute overdose of colchicine usually appears as gastrointestinal symptoms within 24 hours after taking, multiple organ failure (renal insufficiency, circulatory deficiency, bone marrow destruction, muscle weakness, rhabdomyolysis, and respiratory failure) within 7 days, and finally ends up with either resolution of symptoms or progression of dysfunction of organs and eventual death [14–17].

Chronic overdose of colchicine can arise when daily doses of colchicine are not adjusted for renal insufficiency or simultaneous reception of certain medications; colchicine neuromyopathy and cytopenia are classical characteristics of chronic overdose [14].

Colchicine predominantly binds three proteins: tubulin, Cytochrome P3A4 (CYP3A4) and P-glycoprotein (Pgp) [18].

CYP3A4 is contained in hepatocytes and enterocytes and metabolizes colchicine to 2.3 dimethyl colchicine. P-glycoprotein, which is contained in enterocytes, hepatocytes, renal and other cells, limits gastrointestinal absorption of colchicine.

Along with renal excretion, these systems determine general level of colchicine in blood serum. Individual content of CYP3A4 and P-glycoprotein conditions absence of adequate response to colchicine in some patients, which can be associated with excessive expression of one or both of these proteins [19]. CYP3A4 and P-glycoprotein are also responsible for interaction between colchicine and other medications. Because of its interaction with CYP3A4, colchicine can have harmful effect if simultaneously taken with clarithromycin, fluoxetine, paroxetine and other inhibitors of proteases, which are metabolized with the aid of this ferment [20].

Several descriptions of clinical cases and one retrospective review show that combination of colchicine and inhibitors of HMG-CoA reductase, which also interact with CYP3A4, can sometimes increase the risk of acute myopathy [21–23].

Kuritzky and Panchal debate about advisability and safety of prophylactic reception of anti-inflammatory medications at the start of urate-lowering therapy, referring to a large number of adverse drug reactions in such a therapy [24]. Under discussion is the possibility for the patient to choose between constant therapy during average 6 months or rapid relief of flares as required. Also, the authors came to the conclusion that long use of colchicine is safer than that of NSAIDs. It was noted that myopathy and rhabdomyolysis are registered more often in the cases of high doses and simultaneous use with not only HMG-CoA reductase inhibitors (statins) but also with fibrates, verapamil, diltiazem, cyclosporine and others, which presupposes the need for serious control in case of their simultaneous use.

Kuncl et al. [14] presented a description of 12 new cases of typical syndromes of myopathy and neuropathy amid use of colchicine by gout patients. Myopathy usually appears as proximal weakness and is always accompanied by higher serum level of creatine kinase; both appearances remain for at least 3 or 4 weeks after discontinuation of the medication. Accompanying axonal polyneuropathy is usually mild, but resolves slowly after discontinuation. Electromyography of proximal muscles usually reveals myopathy which is characterized by abnormal spontaneous activity. Due to these peculiarities, c-induced myopathy is often diagnosed incorrectly, either as probable polymyositis or uremic neuropathy. C-induced myopathy is characterized by accumulation of lysosomes and autophagosomes unrelated to necrosis or moderate denervation in distal muscles. Morphological changes in muscles indicate that pathogenesis relates to damage of microtubular cytoskeletal network which interacts with lysosomes. Correct diagnosis can save patients with such a disorder from a wrong therapy. Myotoxicity most often arises in people over 50–70 years old who take 1.2 mg colchicine daily. Thus, prescription of a long-term colchicine therapy for patients over 50 years old should be carried out with maximal caution.

Tolerance to colchicine is dose-dependent and the recommended dose for prophylaxis of arthritis (0.6 mg once or twice a day), as a rule, is better tolerable than higher doses used earlier to treat acute gout arthritis (1.2 mg at acute flare with subsequent increase by 0.6 mg hourly) [25]. The most common colchicine-induced adverse drug reactions occur with the gastrointestinal tract, namely nausea and diarrhea, which are reported by 5–10% of the patients, even in cases of low-dose colchicine [26]. Gastrotoxicity is highly likely to depend on the dose and can be reduced by decreasing the dose of colchicine.

Among other adverse drug reactions related to the toxicity of colchicine, we should note neuropathy [24], cytopenia (thrombo-, leuko-, pancytopenia, and aplastic anemia), disseminated intravascular coagulation and metabolic acidosis [27, 28].

Fortunately, probability of adverse drug reactions is low, nevertheless in cases of long-term treatment with colchicine it is necessary to perform regular analysis of clinical blood test, level of creatine phosphokinase, transaminases, which is particularly important in elderly patients, especially in cases of simultaneous reception of some of the abovementioned medications.

Besides the possibility of prophylaxis of acute gout flares at the initiation of urate-lowering medications and titration of their dose, there have been discussions about the favorable effect of colchicine on the cardiovascular system [29]. Retrospective cohort studies in patients with gout report a lower incidence of combined cardiovascular outcomes in those treated with colchicine [30].

Thus, in the retrospective crossover study Crittenden et al. [31] investigated whether use of colchicine relates to reduction of risk of myocardial infarction (MI) in gout patients. The primary outcome was diagnostication of MI, the secondary outcomes included all-cause mortality and C-reactive protein (CRP) level. Altogether 1288 patients were diagnosed with gout. The groups of patients who received colchicine (n = 576) and of those who did not (n = 712) were comparable in demographic criteria and their serum uric acid level. Prevalence of MI was 1.2% in the group who received colchicine, as against 2.6% in the group who did not ($p = 0.03$).

In the next study it was proved that reception of 0.5 mg of colchicine daily in addition to the therapy with statins and other medications used for secondary prevention of cardiovascular catastrophes, led to reduction of cases of development of acute coronary syndrome, out-of-hospital cardiac arrest and ischemic stroke [hazard ratio (HR) 0.33; 95% confidence interval (CI) 0.18–0.59; $p < 0.001$] [32].

Meta-analysis of trials of colchicine in multiple cardiovascular diseases revealed a decrease in myocardial infarction with varying levels of evidence [30].

Currently the randomized controlled CONVINCE trial is enrolling stroke patients to evaluate the effect of a daily low-dose of colchicine in reducing the rate of recurrent stroke and major vascular events [33].

3. NSAIDs

Along with colchicine, NSAIDs are used as the first line drug therapy for acute arthritis prophylaxis in gout patients. Just like with colchicine, the history of using NSAIDs for gout is centuries old. Thus, among the ancestors of the modern anti-inflammatory drugs there were vegetable foods containing salicylic acid, such as willow bark, meadowsweet, dried raspberries and others [34–36].

At present, there are no works which could determine the optimal dose or duration of NSAIDs treatment for prophylaxis of acute gout arthritis [37].

Within the frameworks of phase 3 trial on comparison of efficacy of inhibitors of xanthine oxidase of allopurinol and febuxostat, the effect of low-dose colchicine therapy on the frequency of acute arthritis during the first weeks of urate-lowering therapy was assessed. Selection of a certain drug for prophylaxis of acute arthritis was performed directly by the doctor. In 79.6% cases they chose colchicine in the dose of 0.6 mg daily, in 15.2% cases—NSAIDs (naproxen 250 mg twice a day), and the remaining 5.1% patients did not receive prophylactic treatment. In the groups where the patients took colchicine or NSAIDs, the frequency of gout attacks during the entire period of treatment reduced, irrespectively of the medication. It is interesting that immediately after the discontinuation of the 8-week prophylactic therapy, the frequency of gout attacked increased by three times irrespectively of which medication was used for prophylaxis and remained higher than the original during several months of treatment with both xanthine oxidase inhibitors. The frequency of unfavorable effects of colchicine treatment (55.1%) was higher than that of naproxen (44.3%) ($p < 0.001$), however, colchicine was used more often (selection of the medication was carried out by the researcher, without randomization), and in the case of decrease of creatinine clearance <50 ml/min naproxen was not prescribed [38].

These facts explains limitation of long-term use of NSAIDs. Firstly, it relates to the increase in the frequency of NSAIDs-related adverse drug reactions from the gastrointestinal tract [39]. Secondly, to the need of a considerable part of gout patients for acetylsalicylic acid medications.

Besides, NSAIDs should be used with caution in gout patients with lower glomerular filtration rate (long use of NSAIDs by such patients is contraindicated) because they can lead to acute and chronic renal insufficiency, nephrotic syndrome with interstitial nephritis, papillary necrosis, lower clearance of potassium and sodium [40].

In 2010, a study was carried out to assess efficacy of urate-lowering therapy with allopurinol and febuxostat. During the period from February 2010 to December 2010, 516 out of 679 respondents were randomly (1:1:1) prescribed febuxostat 40, 80 mg or allopurinol 300 mg. As prophylactic anti-inflammatory therapy, the patients, during the first 8 weeks, received 0.5 mg of colchicine daily or 7.5 mg of meloxicam daily. As a result, the number of patients who needed treatment of acute gout attacks from the 9th to the 28th week was extremely low: 4.07% (7/172) in the group on 80 mg febuxostat, 5.23% (9/172) in the group on 40 mg febuxostat and 9.3% (16/172) in the group on allopurinol. Besides the considerable reduction of the number of acute attacks during the urate-lowering therapy in all groups, the study revealed high adherence of patients and low percentage of patients who discontinued urate-lowering therapy (on average 5%), which often related to development of unfavorable reactions [41].

Use of NSAIDs also related to increased risk of cardiovascular pathology, which makes it even harder to choose a certain medication because every other gout patient has a high risk of cardiovascular complications [42].

4. Glucocorticoids

In case of impossibility to prescribe NSAIDs or colchicine and/or their inefficacy for prophylaxis of acute arthritis in gout patients, it is proposed to prescribe low-dose glucocorticoids, however, there is little data on their long-term therapy in gout patients [43].

It is thought that prescription of low-dose prednisolone can be efficient and safer than NSAIDs for treatment of acute arthritis in gout patients. However, there have been no randomized controlled trials aimed at investigating comparative efficacy of glucocorticoids and NSAIDs [44].

So far, the first and only comparative study of efficacy of colchicine and glucocorticoids at the initiation of urate-lowering therapy, namely febuxostat therapy, is the study by Yu et al. [45]. The study included 273 patients, where 152 patients received colchicine as acute arthritis prophylactic therapy, 49 received prednisolone, and the remaining 72 patients did not receive any anti-inflammatory medications. The mean daily dosage of febuxostat in the groups of patients receiving colchicine, glucocorticoids and in the control group was 41.97 ± 10.74, 40.82 ± 9.09, and 41.67 ± 9.93 mg daily respectively. The mean daily dosage of colchicine was 0.53 ± 0.15 mg daily, the duration of therapy 6.13 ± 1.14 months. The mean daily dosage of prednisolone was 7.55 ± 1.30 mg daily, the duration of therapy was 6.20 ± 1.36 months. The target serum uric acid level of <360 μmol/l was achieved in each group. No severe ADRs were noted. The analysis of the data showed that acute arthritis attacks were reported 271 times altogether, where 46 attacks (21.7%) in the colchicine group, 47 (44.9%) in the glucocorticoids group and 178 (91.7%) in the control group. However, at high frequency of recurrent gouty arthritis, the intensity of pain during acute arthritis was lower in the patients who received glucocorticoids therapy.

5. Canakinumab

A considerable part of gout patients have contraindications for NSAID, colchicine and glucocorticoids, and often such therapy can be ineffective, especially in patients with severe tophaseous gout, which implies the need for using other methods of therapy. For such patients, it is advisable to consider the use of IL-1 inhibitors, at least the use of long half-life medications (in particular IL-1β: canakinumab).

Among possible methods of prophylaxis, use of IL-1 inhibitors can be discussed, at least use of medications with long half-life (in particular IL-1β: canakinumab). Use of the medication in gout patients is limited to solely rapid relief of arthritis resistant to any other anti-inflammatory therapy or in case of its impossibility. However, the steady anti-inflammatory effect of the medication, which surpasses that of both colchicine and glucocorticoids, allows to initiate therapy with urate-lowering drugs and perform titration of the dose of allopurinol with minimal risk of development of acute arthritis [46, 47].

Within the framework of a 24-week phase 2 trial, the efficacy of different doses of canakinumab and colchicine was compared in 432 gout patients [46]. The plans of therapy determined by randomization included subcutaneous injections of 25, 50, 100, 200 or 300 mg of canakinumab on the first day or four injections with four-week intervals (50 mg on the first day and in the fourth week and 25 mg on the eighth and twelfth weeks) or daily reception of colchicine 0.5 mg per os daily during 16 weeks. It was established that the average number of gout attacks was lower with any dose of canakinumab, with maximal of 100–300 mg. In the cases of the use of canakinumab doses of ≥50 mg, the average number of attacks was lower by 62–72% than in the case of colchicine, and the risk of at least one attack was lower by 64–72%.

The two following 12-week double-blind multicenter controlled trials of phase 3 carried out with the same design and united for analysis (β-RELIEVED and β-RELIEVED II) compared the efficacy of 150 mg canakinumab and 40 mg triamcinolone acetonide (TA) as a means of prophylaxis of acute arthritis [48]. Canakinumab significantly increased the period between attacks and reduced the risk of recurrent gouty arthritis (by 63% in 12 weeks and by 56% in 24 weeks). Moreover, the median time period between attacks for canakinumab was 168 days, which exceeded the duration of the trial (24 weeks).

In their study Solomon et al. [49] compared the frequency of gout attacks at the initiation of urate-lowering therapy in patients with different original serum uric acid levels (≤404.5, 404.6–535.3, and ≥ 535.4 μmol/l). As prophylaxis of gout flares they used canakinumab in different doses (50, 150, and 300 mg), which was injected subcutaneously every 3 months. The observation period was almost 4 years and after analyzing the received data it was found that quarterly injection of canakinumab was associated with a significantly lower risk of acute arthritis, irrespectively of the serum uric acid level.

Canakinumab therapy is generally well-tolerated, although all the studies associated the use of canakinumab with the increase in infectious adverse drug reactions (ADR), including severe ones. The probability of ADR was comparable for any of the used doses of canakinumab (51.9–58.5%) and colchicine (53.7%) [46]. Most of the ADR were light or moderate, and severe ADR were registered in 14 (4.3%) patients receiving canakinumab and six (5.6%) patients receiving colchicine. All six cases of severe ADR in four patients were registered in the canakinumab group. In another phase 2 trial, the total frequency of ADR was also comparable (41.3% in the canakinumab group and 42.1% in the TA group) with the frequency of severe ADR (2.8 and 1.8% respectively) [50]. The only case of infectious bronchitis was registered in the canakinumab group, but, from the researchers' point of view, it was unlikely to be associated with the reception of the drug. Finally, in the phase 3 trials

united for the analysis, where the dose of canakinumab was one-time 150 mg, the differences in the frequency of ADR (66.2% in the canakinumab group and 52.8% in the TA group) were conditioned by infectious ADR, mainly non-severe infections of upper airways (20.4% in the canakinumab group and 12.2% in the TA group) [48].

None of the studies registered fatal cases associated with infectious diseases. Although the use of canakinumab was accompanied by moderate reduction of the levels of thrombocytes, leucocytes and neutrophils in the blood, it did not have clinical relevance.

Canakinumab therapy should be carried out by a rheumatologist experienced in gout treatment and genetically biological disease modifying antirheumatic drugs (bDMARDs). Before the start of the therapy, it is important to exclude active and latent tuberculosis infections. The recommended dose of canakinumab is 150 mg (subcutaneously). If there is need for a repeated injection, the interval between the two should be over 12 weeks. In case of no effect after the first injection, it is inadvisable to give repeated injections.

6. Conclusion

To summarize, it should be noted that neglect of recommendations on prophylaxis of acute arthritis during the first months of urate-lowering therapy, despite the

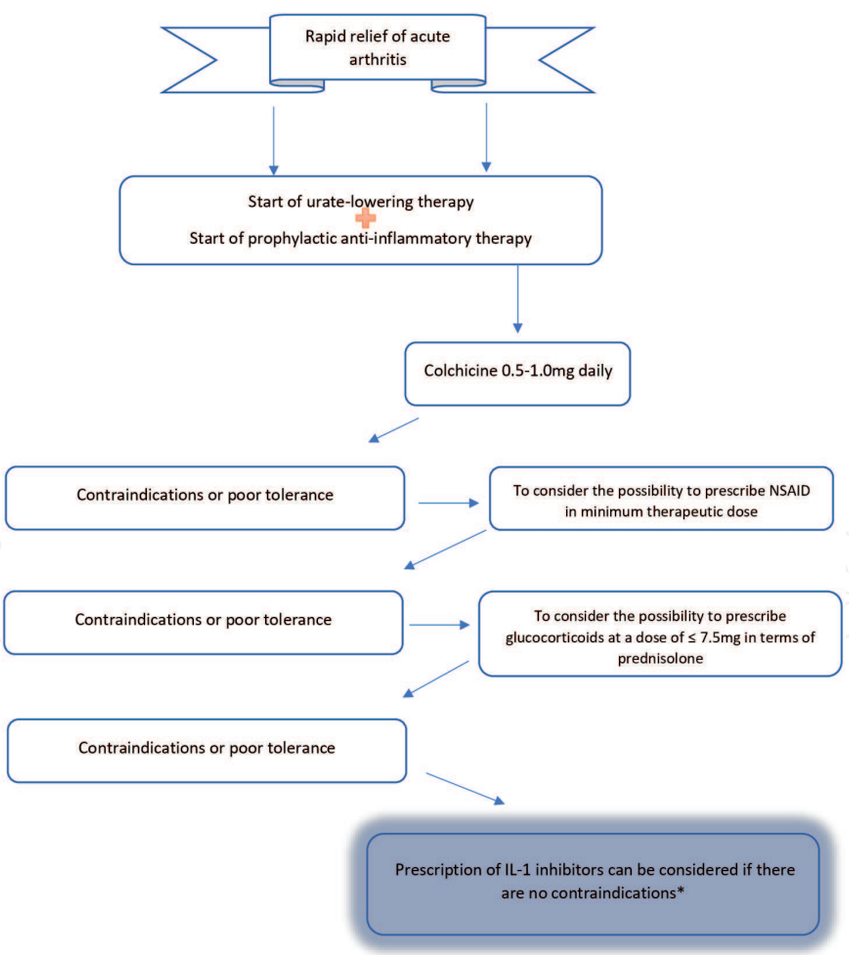

Figure 1.
*Acute arthritis prophylaxis algorithm at initiation of urate-lowering therapy in gout patients. *There are no recommendations for use of canakinumab for prophylaxis of acute arthritis, however, it can be effective at initiation of urate-lowering therapy in patients with severe tophaceous gout and frequent gout flares [48, 49].*

firm guidelines of its necessity, is one of the most common mistakes in treatment of gout [51]. For example, according to the analysis of the database of 643 gout patients who were first prescribed allopurinol, only 26% were also prescribed prophylactic anti-inflammatory therapy (16% received NSAIDs and 10%—colchicine) [52]. At that, besides the burden of pain and poorer working ability which result from acute arthritis, this exact mistake can be the main cause of patient's discontinuation of urate-lowering medications and patient's low adherence to treatment. As a result—development of chronic arthritis, formation of tophi, as well as gouty arthropathy and bone tissue destruction. One of the ways to avoid the above said is to adhere to the recommendations on gout treatment whose integral part is prophylaxis of acute arthritis at the initiation of urate-lowering medications. The suggested algorithm of the drug prophylaxis of acute arthritis during the first months of urate-lowering therapy presupposes sequential selection of the anti-inflammatory medication (see **Figure 1**). As the first-line medication, it is advised to use colchicine, in cases of contraindications for or poor tolerance to thereof—NSAID, and if NSAID therapy is not possible either—glucocorticoids. Finally, for the patients with chronic arthritis and the need for regular use of anti-inflammatory drugs, it is possible to consider IL-1 inhibitors (canakinumab).

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