Review

IL-1 inhibition in familial Mediterranean fever: clinical outcomes and expectations

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ABSTRACT

Familial Mediterranean fever (FMF) is a hereditary auto-inflammatory disease, characterised by recurrent episodes of fever and serositis. Since 1972, colchicine has been the drug of choice for FMF. It is effective in preventing the attacks and withholding amyloidosis in most patients with FMF. Colchicine blood and tissue levels are regulated by a glycoprotein pump (GLP) and by Cytochrome P450 3A4 (CYP450 3A4). It is secreted through the bile system and the kidneys. Over the years, several problems have been raised following the use of colchicine in FMF. These include potential side effects (particularly gastrointestinal), non-compliance, inefficacy due to drug resistance, many drug-drug interactions and high risk for intoxication due to a narrow therapeutic range. In addition, colchicine does not prevent protracted febrile myalgia or exertional leg pain.

Based upon our current understanding of the pathogenesis of FMF, it seems that anti-interleukin-1 (anti-IL-1) agents can solve many of the aforementioned problems related to colchicine therapy. The gastrointestinal side effects of colchicine are extremely uncommon with anti-IL-1 biologics. Drug-drug interactions are also unlikely, and their therapeutic window is not narrow. The once daily injection of anakinra, the once weekly injection of rilonacept, and the once monthly injection of canakinumab result in a better compliance to therapy. Nevertheless, there are no controlled trials showing the efficacy of anti-IL-1 agents in preventing amyloidosis or their safety in pregnancy. Therefore, it is still needed to give IL-1 blockers with concomitant colchicine in its tolerable dose effective in preventing amyloidosis (1.5 mg daily in adult).

Introduction

Familial Mediterranean fever (FMF) is a hereditary auto-inflammatory disease, characterised by recurrent episodes of fever and serositis, such as peritonitis and pleuritis (1). Each attack lasts between 24-72 hours, with a frequency that varies from once a week to a few attacks per year. The disease is prevalent among populations in Middle Eastern countries and Armenia, but sporadic cases have been described all over the world (2). Clinical manifestations may vary among different populations (Middle Eastern patients versus European or Japanese) (3). The most devastating complication of FMF in untreated patients is AA amyloidosis (secondary amyloidosis), which may affect the kidneys leading to renal failure and end stage renal disease (ESRD) (4).

Since 1972, the drug of choice for FMF has been colchicine (5). Colchicine is an alkaloid, which has been used for centuries for the treatment of gout. In ancient times, it was extracted from the bulb of the plant Colchicum autumnale. It is effective in FMF in controlling the attacks and preventing the development of amyloidosis.(6) The drug enters the cells and can be effluxed by a glycoprotein pump encoded by the Multiple Drug Resistance (MDR1) gene. It is metabolised in the liver by Cytochrome P450 3A4 (CYP450 3A4), and is secreted predominantly through the bile system; renal elimination is responsible for 20% of drug disposition. (6, 7) The drug's therapeutic range is narrow, and the potential for intoxication is relatively high.(8) It is noteworthy that parenteral use by weekly intravenous injections had been tried, but found to be associated with a substantially increased risk of toxicity (9, 10). Colchicine is a cheap medication, ef-

fective in most patients with FMF and significantly improved their quality of life (11). Nevertheless, over the years we have faced several problems with using the drug in FMF. These obstacles demand attention, and in some cases alternative solutions.

Based on our current understanding of the pathogenesis of FMF, anti-interleukin-1 (anti-IL-1) agents can inhibit the pyrin cascade of inflammation, thus preventing acute attacks (12, 13). Therefore, it has been suggested that such agents may solve some of the problems related to colchicine therapy in FMF (12, 14).

At this point, there are three anti-IL-1 drugs that have been tested in FMF patients: anakinra, a recombinant IL-1 receptor antagonist; canakinumab a fully human monoclonal antibody targeting IL-1 β, and rilonacept, an IL-1 α and β cytokine trap molecule. So far, canakinumab and anakinra are the only approved agents for treating FMF.

In the current review, we would like to evaluate the efficacy of anti-IL-1 agents in several clinical situations where colchicine is contraindicated, ineffective or associated with side effects. In addition, we describe our treatment policy in these conditions, based upon the current available literature and our personal experience.

Anti-IL-1 agents in colchicine-resistant FMF

Colchicine is effective in 90-95% of FMF patients. Still, it is ineffective in 5-10%, who are deemed resistant to it (15). In a patient receiving the maximal tolerated dose of colchicine (up to 3 mg daily in adults), resistance to this medication is defined as ongoing disease activity (either recurrent clinical attacks [average one or more attacks per month over a 3-month period]), or persistently elevated C-reactive protein (CRP) or serum amyloid A (SAA) between attacks (16).

Several case reports, case series and other studies have described the efficacy of the three drugs (especially anakinra and canakinumab) in colchicine-resistant FMF patients (14, 16-55).

In a randomised controlled trial (RCT), 25 patients with colchicine-resistant FMF were assigned to receive anakinra or placebo. The mean number of attacks per patient per month, and the number of patients with <1 attack per month were significantly less in the anakinra arm. Beneficial effects were also noted in terms of the number of attacks in joints per month and the patients' quality of life. Adverse events were comparable between the two groups (38).

In an RCT evaluating the efficacy and safety of canakinumab in patients with auto-inflammatory recurrent fever syndromes, three cohorts of patients were defined: those with colchicine-resistant FMF, mevalonate kinase deficiency, and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) (27). In the FMF group, which included 63 patients, 61% (19/31) of the patients on canakinumab versus 6% (2/32) of those on placebo met the primary outcome of complete response (resolution of the baseline flare at day 15 and no new flare) at week 16. Inclusion of a subset of patients who received a blinded dose increase to 300 mg every 4 weeks led to a complete response in 71% (22/31). There were more serious adverse events in the canakinumab group, mostly infections (particularly respiratory), abdominal pain, headaches, and injection-site reactions.

In a long-term efficacy and safety evaluation of canakinumab in patients with colchicine-resistant FMF, results of a 72-week extension period were published (34). Fifty-eight percent of the patients had no flares and 38% had a single flare. Forty percent received the lower dose regimen of 150 mg q8w throughout the study and 44% received intermediate-dose regimens of 150 mg q4w or 300 mg q8w; up-titration to the highest dose regimen of 300 mg q4w was required in 16% of the patients (34).

In general, comparing the safety profile of anakinra and canakinumab, side effects like anaphylactic reactions and leukopenia are more common with the former. Headache and respiratory infections seem to be more frequent in canakinumab-treated patients (12).

There is little available data about the efficacy of rilonacept in FMF. Hashkes et al. performed a randomised, double-blind, placebo-controlled trial including 14 patients, 12 of which completed the trial. The rate of FMF attacks decreased from a median of 3.30 per month during the screening period to 0.77 per month during rilonacept therapy, as opposed to 2.00 while receiving placebo. Injection site reactions were more frequent with rilonacept. No significant differences were seen in other adverse events, including infections (36).

Take home message

- The available anti-IL-1 agents may solve the problem of colchicine resistance in most FMF cases and may be used quite safely.

Colchicine intolerance

About 5% of FMF patients are intolerant to colchicine. These patients experience abdominal discomfort or pain, diarrhoea and vomiting. In addition, colchicine may interfere with the absorption of iron and vitamin B12, resulting in anaemia.(56, 57) Unfortunately, there are no controlled studies evaluating the use of anti-IL-1 agents in this specific group of patients. However, based on the experience in colchicine-resistant cases, it seems reasonable to use anti-IL-1 agents in this clinical scenario.

Take home message

- Anti-IL-1 formulas may replace colchicine in the rare cases of severe colchicine intolerance.

Colchicine compliance

Compliance is very important for achieving the full effect of colchicine in FMF. If a patient misses even a single dose of colchicine, an acute attack may occur within a few days. In fact, several studies have shown that full compliance with treatment may not be particularly common. In a cohort of 38 FMF patients from Israel, only 13% filled all of the colchicine prescriptions they received from their physician (58). 34% filled less than 50% of their prescriptions and 8% did not fill any, suggesting that approximately 40% had poor compliance. Similar results were reported in a cohort of 96 Turkish FMF patients (59).

Since anti-IL-1 agents are given as injections, compliance appears to be better. This is especially relevant for

rilonacept and canakinumab, where the injections are given every 1 and 4 weeks, respectively.

Take home message

- Colchicine treatment requires close monitoring and surveillance, whereas anti IL-1 agents may not require firm follow-up, due to better compliance.

Treatment difficulties in new-borns and toddlers

For many years, there was no liquid formula of colchicine for oral treatment, thus new-borns and toddlers had to inconveniently swallow the bitter tablets, culminating in poor compliance. About ten years ago, we performed a study where toddlers were given a liquid formula of the drug, mixed with mashed apple purée (60). The treatment was effective and well-tolerated, but unfortunately did not make it to the market. Recently, a colchicine syrup was approved in the USA for the treatment of gout, but it is not widely available. Treatment with injections of anakinra or canakinumab may overcome the bitter taste of colchicine tablets or liquid preparations, thereby improving the compliance of children with FMF.

Take home message

- The use of anti-IL-1 agents may facilitate the treatment of young children with FMF, especially if canakinumab is used as a monthly injection.

Colchicine in FMF patients with disturbed liver and kidney functions

In light of colchicine's hepatic metabolism and renal and hepatobiliary excretion, we may face a problem when using it in FMF patients with liver or kidney disturbances. Owing to the narrow therapeutic window of the drug, the risk of intoxication is relatively high. The absence of an antidote and the lack of appropriate treatment for colchicine toxicity present additional problems.

No solid data is available regarding the use of anakinra, canakinumab, and rilonacept in patients with chronic liver disease. In fact, in a cross-sectional observational study that recorded the off-label use of anti-IL-1 drugs in France, anakinra caused hepatotoxicity in about 7% of the patients and canakinumab in 9%. Liver injury was more common in the paediatric age group and with prolonged use (61). Rarely, severe disturbances of liver function tests have been reported as side effects of anakinra therapy in adult-onset Still's disease (AOSD).(62-64) It is worth mentioning that a multicentre RCT has been recently designed to test the benefit of canakinumab in patients with alcoholic hepatitis (65).

In contrast, IL-1 is involved in the pathogenesis of renal disease, including nephrocalcinosis and diabetic nephropathy. Therefore, its blocking has both direct and indirect beneficial effects on kidney function, including deactivation of nuclear factor (NF-κB) pathway, suppression of pro-inflammatory cytokines, and improvement of vascular oxidative stress (66). Since anakinra is predominantly cleared renally in humans, a dose or schedule adjustment may be indicated for patients with severe renal impairment or end-stage renal disease (ESRD). Haemodialysis appears to have a minimal effect on the removal of the drug.(67) In patients with ESRD on haemodialysis, it may be given as a 100 mg dose three times per week (68, 69).

No dosage adjustments are present in the manufacturer's labelling of canakinumab and rilonacept in cases of liver or kidney impairment. In fact, canakinumab had been used at its usual dosing in patients with renal failure and secondary amyloidosis (70-72). In a small pharmacologic trial, ESRD and related haemodialysis were not found to prolong the elimination of rilonacept, suggesting that no dose adjustment is needed (73).

Take home message

- We are careful in using anakinra in FMF patients with liver impairment and recommend reducing its dosage in ESRD. Regarding canakinumab, we do not adjust the dose, but we follow closely the renal and liver functions.

Colchicine drug-drug interactions

Colchicine is metabolised by CYP450 3A4, and its cellular concentrations are regulated by P-glycoprotein pump. Therefore, any food or drug that interferes with these regulators may affect the levels of serum and tissue colchicine (8, 74, 75).

In a study by Terkeltaub *et al*., it was shown that clarithromycin, ritonavir and ketoconazole could increase the mean peak levels of blood colchicine by about 200-300% when administered concomitantly (76). This, of course, poses a serious risk of intoxication. For instance, an FMF patient who was found to carry gastric Helicobacter pylori was given clarithromycin concomitantly with colchicine. Within two weeks, he developed severe muscle weakness and was unable to walk. Mild weakness persisted even 6 months after halting the clarithromycin (unpublished data). While myopathy is a well-known complication of supra-therapeutic doses of colchicine (77), co-administration with statins may augment this risk (78).

Take home message

- Treatment with IL-1 blockers may overcome the limitations associated with the use of colchicine in FMF patients requiring additional medications concomitantly.

Protracted febrile myalgia and exertional leg pain

One of the serious clinical manifestations of FMF is protracted febrile myalgia (PFM), where patients suffer from fever and myalgia lasting several weeks. PFM is refractory to colchicine treatment, and oftentimes necessitates the administration of high dose corticosteroids for several weeks (74, 79, 80). In one study, 2 out of 5 patients with PFM partially responding to corticosteroids, achieved a remarkable improvement after the first dose of anakinra. With the latter, the inflammatory markers declined and the corticosteroid dose was tapered within a month (81).

FMF patients may also display severe muscle pain, usually in the calf region. This exertional leg pain (ELP) is a relatively common feature of the disease, and is especially related to prolonged standing or walking; it is noteworthy that it appears despite colchicine therapy. (82, 83). Most patients with ELP

need complete rest and non-steroidal anti-inflammatory drugs (NSAIDs), in addition to colchicine. We have recently encountered two patients with ELP in whom treatment with canakinumab led to an excellent response and prevented additional events (unpublished data).

Take home message

- In cases of PFM and ELP where colchicine is not effective, anti-IL-1 agents may be beneficial, sparing the need for NSAIDs or corticosteroids, with their potential harmful side effects.

Colchicine-induced azoospermia

A rare but potential side effect of colchicine treatment is azoospermia. Discontinuation of the drug may lead to recovery of sperm production. In these cases, colchicine should be halted for a few months, in order to allow the male reproductive system to recover (57, 84). During this interim period, an alternative therapy is required.

We have an experience with three such patients, in whom we used anakinra in the interim period, with impressive recovery of sperm production and successful fertilisation; pregnancy outcome was normal too and colchicine treatment was resumed thereafter (Unpublished).

Take home message

- IL-1 blockers can replace colchicine transiently in the rare cases of colchicine-induced azoospermia.

FMF-associated amyloidosis

The main aims of therapy in FMF are to prevent the occurrence of attacks and the development of amyloidosis. While colchicine is able to achieve these goals, the question is whether anti-IL-1 agents may also provide the same benefit, especially relating to the prevention of amyloidosis. In some observational studies, anakinra and canakinumab have shown efficacy in patients who developed amyloidosis, with possible improvements in proteinuria and renal function (23, 26, 69-71, 85-91). In a systematic review about the long-term efficacy, safety, and tolerability of canakinumab in FMF patients, information about the presence of renal or systemic amyloidosis could be obtained from 121 patients in 11 of the assessed studies. There were 97 patients without amyloidosis before the initiation of therapy, and none of them developed it under treatment (40). Stankovic *et al*. described 4 patients with FMF and amyloidosis who were treated with anakinra. In one patient, proteinuria improved and renal function stabilised. The other 3 patients were with ESRD, with no change in renal function after treatment. However, the improvement in their general status made them eligible to undergo renal transplantation (69). Varan *et al*. also reported 17 cases of FMF patients complicated with amyloidosis. Except for 6 patients who were on haemodialysis, all the others had a reduction in proteinuria and a stabilisation of renal function under anakinra (70). In these two studies, anti-IL-1 treatment showed signs of efficacy in the treatment of gastrointestinal amyloidosis as well (69, 70). In a study by Kacar *et al*., 7 out of 14 patients who underwent kidney transplantation due to renal amyloidosis had evidence of amyloid deposition in the allograft, promoting the introduction of canakinumab. The transplants' function remained stable in all cases, with no improvement or exacerbation of proteinuria or significant changes in serum creatinine (45). On the other hand, one study with histopathologic renal evidence claimed that de novo vascular amyloid deposition was not prevented by anti-IL-1 therapy (92).

As for the prevention of amyloidosis as a monotherapy, there is no sufficient data on anti-IL-1 drugs in this regard. Some reports, however, described that the use of canakinumab or anakinra as a monotherapy led to a favourable response (19, 69, 93). Nevertheless, the follow-up time was short and further studies are still required. Therefore, conventional use of anti-IL-1 biologics in FMF patients with amyloidosis remains on a background of colchicine therapy.

Take home message

- Anti-IL-1 agents are excellent in replacing colchicine in the prevention of acute attacks of FMF. Observational studies are promising with respect to their effect in preventing or reducing the progression of amyloidosis. However, since no controlled trials are present in this regard, we use them concomitantly with colchicine in a minimal dose (1.5 mg daily) shown to be effective in halting amyloidosis.

Pregnancy and lactation

There are a few case reports, case series and retrospective studies describing the outcomes of pregnancy in FMF patients exposed to anti-IL-1 therapy. Most of our knowledge is derived from the experience with anti-IL-1 agents in other auto-inflammatory diseases, rather than in FMF.

A recent review summarising the data on anti-IL-1 biologic use in pregnancy was published by Brien et al. It included 22 studies, with 88 pregnancies. 85.2% (75/88) of the cases were on anakinra and 14.8% (13/88) were on canakinumab (94). The pregnancy outcomes included 3 miscarriages (2 of the same woman) and 1 elective termination of pregnancy. In 62.5% (55/88) of the cases, drug therapy was continued throughout pregnancy. In 9 patients, treatment was stopped after the first trimester, and in 2 after the second trimester. In 13 cases, treatment was started either during the second half of pregnancy (10 patients) or during the third trimester (3 patients). According to this review, neonatal complications appear in 13.6% of pregnancies exposed to anakinra and 10.0% of those exposed to canakinumab, totalling a 13.2% overall complication rate (94).

Take home message

- The available data regarding the use of anti-IL-1 agents during pregnancy is promising, but limited. Therefore, we do not recommend using canakinumab or anakinra during pregnancy.

On-demand treatment

FMF flares may be associated with tremendous pain, sometimes necessitating the administration of opioids. Anakinra may be used as an on-demand regimen either as the patient senses the typical prodrome preceding the attack or at

the very beginning of the flare. It may prevent the attack, shorten its duration, alleviate the symptoms, and normalise the inflammatory markers. In a retrospective analysis, 78 patients were treated with IL-1 inhibitors. Among those, 15 received an "on-demand" anakinra protocol, resulting in a significant improvement in terms of frequency, duration, and severity of the attacks (95). Another study described the successful use of anakinra only at the onset of flares (55). The patients in both studies received background colchicine therapy. The rationale for such use is the presence of characteristic prodromes or triggers already recognised by the patients (such as emotional or physical stress or cold exposure) (95). This approach has the advantage of reducing costs and side effects in selected patients with clear prodromes and controlled disease. However, this strategy does not prevent a possible inflammatory state in between attacks, which can lead to amyloidosis (type 2 FMF).

Take home message

- "On-demand" protocol can be considered in FMF patients who have clear prodromes or at the beginning of the attacks on the background of continuous colchicine treatment.

Switching between agents

In some FMF patients treated with anti-IL-1 agents, there may be a need to switch between the different formulas. For example, the ease of administration of canakinumab, loss of compliance to anakinra, inadequate response after long periods of use, and severe injection site reactions are some of the reasons to switch to canakinumab (12, 21, 24, 61, 96, 97). In fact, more cases of switching from anakinra to canakinumab are known, as the use of the former as a first line drug is much more common (older and cheaper). Druyan *et al*. reported a series of 46 patients who were prescribed canakinumab for FMF after previous anakinra treatment (98). Of those, 23/46 patients (50%) discontinued anakinra due to incomplete response. The frequency of flares was significantly decreased following the switch to canakinumab. A favourable response to anakinra after flares under canakinumab had also been reported (96).

Take home message

- Switching between anti IL-1 agents is possible and successful in cases of treatment failure or serious adverse events.

Concomitant biologic treatment with anti-IL-1 agents

There are no reports on combined biologic therapy in refractory FMF. In fact, anakinra had been tried in combination with etanercept in patients with rheumatoid arthritis (RA), with no added clinical benefit, but with a higher risk of adverse events, including infections (99). The combination of abatacept and anakinra in RA also resulted in a significantly higher risk of side effects (100).

Take home message

- We do not use an additional biologic agent concomitantly with IL-1 blockers in FMF patients.

Summary and conclusions

Colchicine is a cheap oral medication, effective in preventing FMF attacks and subsequent amyloidosis. Since its introduction as the treatment of choice for FMF in 1972, it improved the quality of life of many patients and saved their lives by obviating the development of amyloidosis. Nevertheless, as aforementioned, the drawbacks of colchicine include potential side effects (particularly gastrointestinal), non-compliance, inefficacy due to resistance, a narrow therapeutic window and many drug-drug interactions. Additional disadvantages are the rare occurrence of azoospermia/oligospermia in men, the lack of efficacy in cases of PFM or ELP, and the need for dose modifications in patients with renal or liver disease.

Anti-IL-1 agents allow us to cope with these clinical scenarios and colchicine drawbacks, providing a useful alternative. The gastrointestinal side effects of colchicine are extremely uncommon with anti-IL-1 biologics. Drug-drug interactions are also unlikely, and their therapeutic window is not narrow. No special dose adjustments are required in liver disease; however, the dosing frequency of anakinra is preferably reduced in ESRD to every-other day. The once daily injection of anakinra, the once weekly injection of rilonacept, and the once monthly injection of canakinumab result logically in a better compliance to therapy. Stabilisation of renal function in patients with amyloidosis, and even improvement in some, are other advantages of anti-IL-1 biologics. Furthermore, as opposed to the rare azoospermia reported with colchicine, cases where males were considered infertile, but terminated in successful fertilisation after the introduction of anti-IL-1 drugs have been described in cryopyrin-associated autoinflammatory syndrome (CAPS) (101). It should be mentioned however, that several drawbacks are also associated with anti-IL-1 therapy when compared to colchicine. The cost is a very important consideration in this regard, as colchicine pills are much cheaper. Since the latter is also given orally, injection-site reactions are irrelevant. In addition, as with other biologics, the occurrence of routine infections does increase with IL-1 blockers (102).

Can anti-IL-1 agents completely replace colchicine in FMF?

In our view, we still need controlled studies in order to justify a new policy of replacing colchicine by anti-IL-1 agents in preventing amyloidosis and in pregnancy. Moreover, the beneficial use of anakinra or canakinumab in the above clinical conditions should not encourage colchicine withdrawal when it is tolerated. Awaiting further RCTs, it seems that for the time being anti-IL-1 agents cannot replace colchicine completely in the treatment of FMF patients.

References

1. BEN-CHETRIT E, LEVY M: Familial Mediterranean fever. *Lancet* 1998; 351(9103): 659-64.
2. BEN-CHETRIT E, TOUITOU I: Familial mediterranean Fever in the world. *Arthritis Rheum* 2009; 61(10): 1447-53.
3. BEN-CHETRIT E, YAZICI H: Familial Mediterranean fever: different faces around the world. *Clin Exp Rheumatol* 2019; 37 (Suppl. 121): S18-22.
4. OZDOGAN H, UGURLU S: Familial Mediter-

ranean Fever. *Presse Med* 2019; 48 (1 Pt 2): e61-e76.
5. ARAL O, OZDOGAN H, YAZICI H: The other physician behind the use of colchicine for the treatment of familial Mediterranean fever. *Clin Exp Rheumatol* 2001; 19 (Suppl. 24): S13-4.
6. CERQUAGLIA C, DIACO M, NUCERA G, LA REGINA M, MONTALTO M, MANNA R: Pharmacological and clinical basis of treatment of Familial Mediterranean Fever (FMF) with colchicine or analogues: an update. *Curr Drug Targets Inflamm Allergy* 2005; 4(1): 117-24.
7. TERKELTAUB RA: Colchicine update: 2008. *Semin Arthritis Rheum* 2009; 38(6): 411-9.
8. DAHAN A, AMIDON GL: Grapefruit juice and its constituents augment colchicine intestinal absorption: potential hazardous interaction and the role of p-glycoprotein. *Pharm Res* 2009; 26(4): 883-92.
9. ROZENBAUM M, BOULMAN N, FELD J *et al*.: Intravenous colchicine treatment for six months: adjunctive therapy in familial Mediterranean fever (FMF) unresponsive to oral colchicine. *Clin Exp Rheumatol* 2009; 27 (Suppl. 53): S105.
10. LIDAR M, KEDEM R, LANGEVITZ P, PRAS M, LIVNEH A: Intravenous colchicine for treatment of patients with familial Mediterranean fever unresponsive to oral colchicine. *J Rheumatol* 2003; 30(12): 2620-3.
11. SAHIN S, YALCIN I, SENEL S *et al*.: Assessment life quality of familial Mediterranean fever patients by short form-36 and its relationship with disease parameters. *Eur Rev Med Pharmacol Sci* 2013; 17(7): 958-63.
12. HENTGEN V, VINIT C, FAYAND A, GEORGIN-LAVIALLE S: The use of interleukine-1 inhibitors in familial Mediterranean fever patients: A narrative review. *Front Immunol* 2020 ;11: 971.
13. ALGHAMDI M: Familial Mediterranean fever, review of the literature. *Clin Rheumatol* 2017; 36(8): 1707-13.
14. KÖHLER BM, LORENZ H-M, BLANK N: IL1-blocking therapy in colchicine-resistant familial Mediterranean fever. *Eur J Rheumatol* 2018; 5(4): 230-4.
15. KALLINICH T, HAFFNER D, NIEHUES T *et al*.: Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. *Pediatrics* 2007; 119(2): e474-83.
16. SAG E, AKAL F, ATALAY E *et al*.: Anti-IL1 treatment in colchicine-resistant paediatric FMF patients: real life data from the HELIOS registry. *Rheumatology* (Oxford) 2020; 59(11): 3324-9.
17. GATTRINGER R, LAGLER H, GATTRINGER KB *et al*.: Anakinra in two adolescent female patients suffering from colchicine-resistant familial Mediterranean fever: effective but risky. *Eur J Clin Invest* 2007; 37(11): 912-4.
18. CALLIGARIS L, MARCHETTI F, TOMMASINI A, VENTURA A: The efficacy of anakinra in an adolescent with colchicine-resistant familial Mediterranean fever. *Eur J Pediatr* 2008; 167(6): 695-6.
19. LASKARI K, BOURA P, DALEKOS GN *et al*.: Longterm beneficial effect of canakinumab in colchicine-resistant familial Mediterranean fever. *J Rheumatol* 2017; 44(1): 102-9.
20. UGURLU S, ERGEZEN B, EGELI BH, SELVI O, OZDOGAN H: Anakinra treatment in patients with familial Mediterranean fever: a single-centre experience. *Rheumatology* (Oxford) 2021; 60(5): 2327-32.
21. AKAR S, CETIN P, KALYONCU U *et al*.: Nationwide experience with off-label use of interleukin-1 targeting treatment in familial Mediterranean fever patients. *Arthritis Care Res* (Hoboken) 2018; 70(7): 1090-4.
22. GÜLEZ N, MAKAY B, SÖZERI B: Long-term effectiveness and safety of canakinumab in pediatric familial Mediterranean fever patients. *Mod Rheumatol* 2020; 30(1): 166-71.
23. SARGIN G, KOSE R, SENTURK T: Anti-interleukin-1 treatment among patients with familial Mediterranean fever resistant to colchicine treatment. Retrospective analysis. *Sao Paulo Med J* 2019; 137(1): 39-44.
24. EROGLU FK, BEŞBAŞ N, TOPALOGLU R, OZEN S: Treatment of colchicine-resistant Familial Mediterranean fever in children and adolescents. *Rheumatol Int* 2015; 35(10): 1733-7.
25. ALPA M, ROCCATELLO D: Canakinumab as rescue therapy in familial Mediterranean fever refractory to conventional treatment. *Drug Des Devel Ther* 2015; 9: 1983-7.
26. CETIN P, SARI I, SOZERI B *et al*.: Efficacy of interleukin-1 targeting treatments in patients with familial Mediterranean fever. *Inflammation* 2015; 38(1): 27-31.
27. MEINZER U, QUARTIER P, ALEXANDRA JF, HENTGEN V, RETORNAZ F, KONÉ-PAUT I: Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. *Semin Arthritis Rheum* 2011; 41(2): 265-71.
28. ALPAY N, SUMNU A, CALIŞKAN Y, YAZICI H, TÜRKMEN A, GÜL A: Efficacy of anakinra treatment in a patient with colchicine-resistant familial Mediterranean fever. *Rheumatol Int* 2012; 32(10): 3277-9.
29. ROLDAN R, RUIZ AM, MIRANDA MD, COLLANTES E: Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. *Joint Bone Spine* 2008; 75(4): 504-5.
30. SORIANO A, VERECCHIA E, AFELTRA A, LANDOLFI R, MANNA R: IL-1β biological treatment of familial Mediterranean fever. *Clin Rev Allergy Immunol* 2013; 45(1): 117-30.
31. OZKAN S, ATAS B: Canakinumab treatment in four children with colchicine resistant familial mediterranean fever. *J Pak Med Assoc* 2017; 67(6): 945-7.
32. DE BENEDETTI F, GATTORNO M, ANTON J *et al*.: Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N Engl J Med* 2018; 378(20): 1908-19.
33. OZEN S, BILGINER Y, AKTAY AYAZ N, CALGUNERI M: Anti-interleukin 1 treatment for patients with familial Mediterranean fever resistant to colchicine. *J Rheumatol* 2011; 38(3): 516-8.
34. OZEN S, BEN-CHERIT E, FOELDVARI I *et al*.: Long-term efficacy and safety of canakinumab in patients with colchicine-resistant familial Mediterranean fever: results from the randomised phase III CLUSTER trial. *Ann Rheum Dis* 2020; 79(10): 1362-9.
35. KURT T, AYDIN F, NILÜFER TEKGÖZ P, SEZER M, UNCU N, ÇELIKEL ACAR B: Effect of anti-interleukin-1 treatment on quality of life in children with colchicine-resistant familial Mediterranean fever: A single-center experience. *Int J Rheum Dis* 2020; 23(7): 977-81.
36. HASHKES PJ, SPALDING SJ, GIANNINI EH *et al*.: Rilonacept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. *Ann Intern Med* 2012; 157(8): 533-41.
37. ÇAKAN M, KARADAĞ Ş, AYAZ NA: Canakinumab in colchicine resistant familial Mediterranean fever and other pediatric rheumatic diseases. *Turk J Pediatr* 2020; 62(2): 167-74.
38. BEN-ZVI I, KUKUY O, GIAT E *et al*.: Anakinra for colchicine-resistant familial Mediterranean fever: A randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2017; 69(4): 854-62.
39. HENNIG S, BAYEGAN K, UFFMANN M, THALHAMMER F, WINKLER S: Pneumonia in a patient with familial Mediterranean fever successfully treated with anakinra--case report and review. *Rheumatol Int* 2012; 32(6): 1801-4.
40. GÜL A, OZDOGAN H, ERER B *et al*.: Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. *Arthritis Res Ther* 2015; 17(1): 243.
41. PECHER AC, IGNEY-OERTEL A, KANZ L, HENES J: Treatment of familial Mediterranean fever with anakinra in patients unresponsive to colchicine. *Scand J Rheumatol* 2017; 46(5): 407-9.
42. HACIHAMDIOGLU DO, OZEN S: Canakinumab induces remission in a patient with resistant familial Mediterranean fever. *Rheumatology* (Oxford) 2012; 51(6): 1041.
43. BRIK R, BUTBUL-AVIEL Y, LUBIN S *et al*.: Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study. *Arthritis Rheumatol* 2014; 66(11): 3241-3.
44. BERDELI A, ŞENOL Ö, TALAY G: Treatment of familial Mediterranean fever with canakinumab in patients who are unresponsive to colchicine. *Eur J Rheumatol* 2019; 6(2): 85-8.
45. KACAR M, SAVIC S, VAN DER HILST JCH: The efficacy, safety and tolerability of Canakinumab in the treatment of familial Mediterranean Fever: A systematic review of the literature. *J Inflamm Res* 2020; 13: 141-9.
46. YAZILITAŞ F, AYDOĞ Ö, ÖZLÜ SG *et al*.: Canakinumab treatment in children with familial Mediterranean fever: report from a single center. *Rheumatol Int* 2018; 38(5): 879-85.
47. ESPÍLDORA-HERNÁNDEZ J, ABARCA-COSTALAGO M: Familial mediterranean fever treated with anakinra: A case report. *Reumatol Clin* 2017; 13(2): 120-1.
48. EREN AKARCAN S, DOGANTAN S, EDEER KARACA N, AKSU G, KUTUKCULER N: Successful management of colchicine resistant familial Mediterranean fever patients with a standardized canakinumab treatment protocol: a case series and literature review.

Rheumatol Int 2020; 40(1): 161-8.
49. KISLA EKINCI RM, BALCI S, DOGRUEL D, ALTINTAS DU, YILMAZ M: Canakinumab in children with familial Mediterranean fever: A single-center, retrospective analysis. *Paediatr Drugs* 2019; 21(5): 389-95.
50. BELKHIR R, MOULONGUET-DOLERIS L, HACHULLA E, PRINSEAU J, BAGLIN A, HANSLIK T: Treatment of familial Mediterranean fever with anakinra. *Ann Intern Med* 2007; 146(11): 825-6.
51. BABAOGLU H, VARAN O, KUCUK H *et al*.: Effectiveness of canakinumab in colchicine- and anakinra-resistant or -intolerant adult familial Mediterranean fever patients: A single-center real-life study. *J Clin Rheumatol* 2020; 26(1): 7-13.
52. MARKO L, SHEMER A, LIDAR M *et al*.: Anakinra for colchicine refractory familial Mediterranean fever: a cohort of 44 patients. *Rheumatology* (Oxford) 2021; 60(6): 2878-83.
53. ATAS N, EROGLU GA, SODAN HN *et al*.: Long-term safety and efficacy of anakinra and canakinumab in patients with familial Mediterranean fever: a single-centre real-life study with 101 patients. *Clin Exp Rheumatol* 2021; 39 (Suppl. 132): S30-6.
54. MITROULIS I, SKENDROS P, OIKONOMOU A, TZIOUFAS AG, RITIS K: The efficacy of canakinumab in the treatment of a patient with familial Mediterranean fever and long-standing destructive arthritis. *Ann Rheum Dis* 2011; 70(7): 1347-8.
55. MITROULIS I, PAPADOPOULOS VP, KONSTANTINIDIS T, RITIS K: Anakinra suppresses familial Mediterranean fever crises in a colchicine-resistant patient. *Neth J Med* 2008; 66(11): 489-91.
56. WEBB DI, CHODOS RB, MAHAR CQ, FALOON WW: Mechanism of vitamin B12 malabsorption in patients receiving colchicine. *N Engl J Med* 1968; 279(16): 845-50.
57. BEN-CHETRIT E: Colchicine. *In*: HASHKES PJ, LAXER RM, SIMON A (Eds.): Textbook of Autoinflammation. *Springer Nature Switzerland AG* 2018; 729-49.
58. BEN-CHETRIT E, AAMAR S: About colchicine compliance, resistance and virulence. *Clin Exp Rheumatol* 2009; 27 (Suppl. 53): S1-3.
59. KARAASLAN Y, DOGAN Ị, OMMA A, SANDIKCI SC: Compliance to colchicine treatment and disease activity in Familial Mediterranean Fever (FMF) patients in Middle/Black Sea Region of Turkey (in Çorum region). *Pediatr Rheumatol Online J* 2015; P81.
60. BERKUN Y, WASON S, BRIK R *et al*.: Pharmacokinetics of colchicine in pediatric and adult patients with familial Mediterranean fever. *Int J Immunopathol Pharmacol* 2012; 25(4): 1121-30.
61. ROSSI-SEMERANO L, FAUTREL B, WENDLING D *et al*.: Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey. *Orphanet J Rare Dis* 2015; 10: 19.
62. TAYLOR SA, VITTORIO JM, MARTINEZ M *et al*.: Anakinra-induced acute liver failure in an adolescent patient with Still's disease. *Pharmacotherapy* 2016; 36(1): e1-4.
63. MURRAY GM, NG SK, BEASLEY D, JOHANSEN L, RAMANAN AV: Severe hepatotoxicity as a rare side effect of anakinra in a patient with systemic JIA. *Rheumatology* (Oxford) 2021; 60(9): e307-e8.
64. CANNA S, FRANKOVICH J, HIGGINS G *et al*.: Acute hepatitis in three patients with systemic juvenile idiopathic arthritis taking interleukin-1 receptor antagonist. *Pediatr Rheumatol Online J* 2009; 7: 21.
65. VERGIS N, PATEL V, BOGDANOWICZ K *et al*.: IL-1 Signal Inhibition In Alcoholic Hepatitis (ISAIAH): a study protocol for a multicentre, randomised, placebo-controlled trial to explore the potential benefits of canakinumab in the treatment of alcoholic hepatitis. *Trials* 2021; 22(1): 792.
66. AFSAR B, COVIC A, ORTIZ A, AFSAR RE, KANBAY M: The future of IL-1 targeting in kidney disease. *Drugs* 2018; 78(11): 1073-83.
67. YANG B-B, BAUGHMAN S, SULLIVAN JT: Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther* 2003; 74(1): 85-94.
68. MOSER C, POHL G, HASLINGER I *et al*.: Successful treatment of familial Mediterranean fever with Anakinra and outcome after renal transplantation. *Nephrol Dial Transplant* 2009; 24(2): 676-8.
69. STANKOVIC STOJANOVIC K, DELMAS Y, TORRES PU *et al*.: Dramatic beneficial effect of interleukin-1 inhibitor treatment in patients with familial Mediterranean fever complicated with amyloidosis and renal failure. *Nephrol Dial Transplant* 2012; 27(5): 1898-901.
70. VARAN Ö, KUCUK H, BABAOGLU H *et al*.: Efficacy and safety of interleukin-1 inhibitors in familial Mediterranean fever patients complicated with amyloidosis. *Mod Rheumatol* 2019; 29(2): 363-6.
71. SOZERI B, GULEZ N, ERGIN M, SERDAROGLU E: The experience of canakinumab in renal amyloidosis secondary to Familial Mediterranean fever. *Mol Cell Pediatr* 2016; 3(1): 33.
72. YILDIRIM T, YILMAZ R, UZERK KIBAR M, ERDEM Y: Canakinumab treatment in renal transplant recipients with familial Mediterranean fever. *J Nephrol* 2018; 31(3): 453-5.
73. RADIN A, MARBURY T, OSGOOD G, BELOMESTNOV P: Safety and pharmacokinetics of subcutaneously administered rilonacept in patients with well-controlled end-stage renal disease (ESRD). *J Clin Pharmacol* 2010; 50(7): 835-41.
74. TUFAN A, LACHMANN HJ: Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. *Turk J Med Sci* 2020; 50(SI-2): 1591-610-
75. DAHAN A, SABIT H, AMIDON GL: Multiple efflux pumps are involved in the transepithelial transport of colchicine: combined effect of p-glycoprotein and multidrug resistance-associated protein 2 leads to decreased intestinal absorption throughout the entire small intestine. *Drug Metab Dispos* 2009; 37(10): 2028-36.
76. TERKELTAUB RA, FURST DE, DIGIACINTO JL, KOOK KA, DAVIS MW: Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. *Arthritis Rheum* 2011; 63(8): 2226-37.
77. ALTIPARMAK MR, PAMUK ON, PAMUK GE, HAMURYUDAN V, ATAMAN R, SERDENGECTI K: Colchicine neuromyopathy: a report of six cases. *Clin Exp Rheumatol* 2002; 20 (Suppl. 26): S13-6.
78. SCHWIER NC, CORNELIO CK, BOYLAN PM: A systematic review of the drug-drug interaction between statins and colchicine: Patient characteristics, etiologies, and clinical management strategies. *Pharmacotherapy* 2022; 42(4): 320-33.
79. TUFAN G, DEMIR S: Uncommon clinical pattern of FMF: protracted febrile myalgia syndrome. *Rheumatol Int* 2010; 30(8): 1089-90.
80. AMITAL H, BEN-CHETRIT E: Therapeutic approaches to familial Mediterranean fever. What do we know and where are we going to? *Clin Exp Rheumatol* 2004; 22 (Suppl. 34): S4-7.
81. YILDIRIM DG, BAKKALOGLU SA, BUYAN N: Protracted febrile myalgia as a challenging manifestation of familial Mediterranean fever: case-based review. *Rheumatol Int* 2019; 39(1): 147-52.
82. ESHED I, ROSMAN Y, LIVNEH A *et al*.: Exertional leg pain in familial Mediterranean fever: a manifestation of an underlying enthesopathy and a marker of more severe disease. *Arthritis Rheumatol* 2014; 66(11): 3221-6.
83. OZTURK MA, KANBAY M, KASAPOGLU B *et al*.: Therapeutic approach to familial Mediterranean fever: a review update. *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S77-86.
84. MERLIN HE: Azoospermia caused by colchicine--a case report. *Fertil Steril* 1972; 23(3): 180-1.
85. SEVILLANO ÁM, HERNANDEZ E, GONZALEZ E *et al*.: Anakinra induce la remisión completa del síndrome nefrótico en un paciente con fiebre mediterránea familiar y amiloidosis. *Nefrologia* 2016; 36(1): 63-6.
86. ÖZÇAKAR ZB, ÖZDEL S, YILMAZ S, KURTŞÜKÜR ED, EKIM M, YALÇINKAYA F: Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis. *Clin Rheumatol* 2016; 35(2): 441-6.
87. ÖZÇAKAR ZB, KEVEN K, ÇAKAR N, YALÇINKAYA F: Transplantation within the era of anti-IL-1 therapy: case series of five patients with familial Mediterranean fever-related amyloidosis. *Transpl Int* 2018; 31(10): 1181-4.
88. UGURLU S, ERGEZEN B, EGELI BH, SELVI O, OZDOGAN H: Safety and efficacy of anti-interleukin-1 treatment in 40 patients, followed in a single centre, with AA amyloidosis secondary to familial Mediterranean fever. *Rheumatology* (Oxford) 2020; 59(12): 3892-9.
89. KUCUKSAHIN O, YILDIZGOREN MT, ILGEN U *et al*.: Anti-interleukin-1 treatment in 26 patients with refractory familial mediterranean fever. *Mod Rheumatol* 2017; 27(2): 350-5.
90. SCARPIONI R, RIGANTE D, CANTARINI L *et al*.: Renal involvement in secondary amyloidosis of Muckle-Wells syndrome: marked improvement of renal function and reduction of proteinuria after therapy with human anti-interleukin-1β monoclonal antibody canakinumab. *Clin Rheumatol* 2015; 34(7): 1311-6.
91. BILGINER Y, AYAZ NA, OZEN S: Anti-IL-1 treatment for secondary amyloidosis in an

adolescent with FMF and Behçet's disease. *Clin Rheumatol* 2010; 29(2): 209-10.
92. SIMSEK C, KARATAS M, TATAR E, YILDIRIM AM, ALKAN FT, USLU A: The efficacy of interleukin-1 antagonist drugs in combination with colchicine in patients with FMF-AA with colchicine resistance after kidney transplantation: A study with histopathologic evidence. *Clin Transplant* 2021; 35(6): e14309.
93. JESENAK M, HRUBISKOVA K, KAPUSTOVA L, KOSTKOVA M, BANOVCIN P: Canakinumab as monotherapy for treatment of familial Mediterranean fever - first report in Central and Eastern Europe region. *Bratisl Lek Listy* 2018; 119(4): 198-200.
94. BRIEN ME, GAUDREAULT V, HUGHES K, HAYES DJL, HEAZELL AEP, GIRARD S: A systematic review of the safety of blocking the IL-1 system in human pregnancy. *J Clin Med* 2021; 11(1).
95. BABAOGLU H, VARAN O, KUCUK H *et al*.: On demand use of anakinra for attacks of familial Mediterranean fever (FMF). *Clin Rheumatol* 2019; 38(2): 577-81.
96. BAŞARAN Ö, UNCU N, ÇELIKEL BA, TAKTAK A, GÜR G, CAKAR N: Interleukin-1 targeting treatment in familial Mediterranean fever: an experience of pediatric patients. *Mod Rheumatol* 2015; 25(4): 621-4.
97. SENDOGAN DO, SARITAS H, KUMRU G *et al*.: Outcomes of canakinumab treatment in recipients of kidney transplant with familial Mediterranean fever: A case series. *Transplant Proc* 2019; 51(7): 2292-4.
98. DRUYAN A, GIAT E, LIVNEH A, GROSSMAN C, BEN-ZVI I, LIDAR M: Effect of interleukin-1 inhibition in a cohort of patients with colchicine-resistant familial Mediterranean fever treated consecutively with anakinra and canakinumab. *Clin Exp Rheumatol* 2021; 39 (Suppl. 132): S75-9.
99. GENOVESE MC, COHEN S, MORELAND L *et al*.: Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004; 50(5): 1412-9.
100. WEINBLATT M, COMBE B, COVUCCI A, ARANDA R, BECKER JC, KEYSTONE E: Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006; 54(9): 2807-16.
101. YOUNGSTEIN T, HOFFMANN P, GÜL A *et al*.: International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors. *Rheumatology* (Oxford) 2017; 56(12): 2102-8.
102. FLEISCHMANN RM, SCHECHTMAN J, BENNETT R *et al*.: Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; 48(4): 927-34.