Tohoku J. Exp. Med., 2022, **256**, 169-174

Total Hip Joint Replacement in a Patient with Colchicine-Resistant Familial Mediterranean Fever under Canakinumab Treatment

Haruki Matsumoto,[1] Hironori Ohashi,[2] Yuya Fujita,[1] Shuhei Yoshida,[1] Kohei Yokose,[1] Jumpei Temmoku,[1] Naoki Matsuoka,[1] Yumetaka Shinden,[3] Keigo Kusano,[3] Tatsuru Sonobe,[3] Yohei Nakamoto,[4] Makiko Yashiro-Furuya,[1] Tomoyuki Asano,[1] Shuzo Sato,[1] Eiji Suzuki,[5] Toru Yago,[1] Hiroshi Watanabe[1] and Kiyoshi Migita[1]

[1]Department of Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Fukushima, Japan
[2]Kaneko Clinic, Nishi shirakawa-gun, Fukushima, Japan
[3]Department of Orthopedics, Fukushima Medical University School of Medicine, Fukushima, Fukushima, Japan
[4]Department of General Internal Medicine, Fukushima Medical University, Fukushima, Fukushima, Japan
[5]Department of Rheumatology, Ohta Nishinouchi General Hospital Foundation, Koriyama, Fukushima, Japan

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent episodes of fever and serositis. Periodic febrile attack can be managed with biologic medication in colchicine-resistant FMF patients, however, no reports or guidelines exist regarding the postoperative management of elective joint surgery in these patients. Although it is not clear how FMF attacks are triggered, they may be precipitated by stress including anesthesia or surgery. This study reports the case of a 51-year-old FMF patient who received total hip replacement under canakinumab (a specific interleukin-1β monoclonal antibody) treatment. He had highly active FMF, which was resistant to colchicine; however, his recurrent febrile attack with serositis was successfully controlled with canakinumab. Four months later from the start of canakinumab treatment, his hip osteoarthritis was required for total hip replacement (THR) because of the traumatic fracture. THR was successfully done and FMF attack was not occurred after this elective surgery. Discontinuation of canakinumab 3 weeks before surgery and resumption 6 weeks after led to favorable outcome without complications. This case addresses the differential management concerning stopping and restating of canakinumab in the perioperative setting in contrast to the other biologics such as tumor necrosis factor-α (TNF-α) or interleukin-6 (IL-6) blocking agents. This case report suggests that canakinumab may represent a safe and effective therapy for the colchicine-resistant FMF, even in the patients requiring THR therapy.

Keywords: biologic; canakinumab; Familial Mediterranean fever; total hip replacement
Tohoku J. Exp. Med., 2022 February, **256** (2), 169-174.

Introduction

Biologics, such as tumor necrosis factor-α (TNF-α) inhibitors or interleukin-6 (IL-6) receptor antibodies are widely used in patients with rheumatic diseases. Although these biologics have improved the clinical outcome of rheumatic diseases, the numbers of patients receiving total joint arthroplasty under these treatments remain high (Goodman et al. 2016). Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease with the highest prevalence among monogenic autoinflammatory diseases (Fonnesu et al. 2009). The mainstream of therapy against FMF is colchicine (Ozturk et al. 2011). Approximately 90% of Japanese patients respond to colchicine (Migita et al. 2012). EULAR recommends IL-1 blockade therapy in FMF patients who fail to respond to colchicine (Ozen et al. 2016). In Japan there is currently only an IL-1 inhibitor, canakinumb, for clinical use, against colchicine-resistant

Received September 27, 2021; revised and accepted October 31, 2021. Published online ####, 2022; doi: 10.1620/tjem.256.169.
Correspondence: Kiyoshi Migita, M.D., Department of Rheumatology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima, Fukushima 960-1295, Japan.
e-mail: migita@fmu.ac.jp

FMF. However, information on canakinumab usage is lacking, including reducing dose or temporal withdrawal, during perioperative periods (Mulders-Manders et al. 2017). The present study reports a case of FMF who was successfully received the total hip arthroplasty under the use of pre- and postoperative canakinumab treatment.

Case Presentation

A 51-year-old Japanese man with a family history of periodic fevers in his mother was admitted to our hospital for examination of fever of unknown origin (FUO). He had a history of left osteoarthritis of the hip and had been taking nonsteroidal anti-inflammatory drugs (NSAIDs), nerve block therapy, and intra-articular steroid injection for a long time (Fig. 1A). He had drug-induced nephropathy because of the long-term use of NSAIDs. He had recurrent fever during his teens, but with a decreased frequency and severity. At 47-year-old, he had fever, mild chest pain, and abdominal pain about once a month. Those symptoms were improved within a few days. The patient was admitted to our hospital for examination of FUO. Laboratory tests showed elevation of erythrocyte sedimentation rate 22 mm/h, CRP 6.01 mg/dL, and serum amyloid A 152 μg/mL (reference value < 8.0 μg/mL) (Table 1). Computed tomography and blood cultures showed no evidence of infection, and autoantibodies for various autoimmune diseases were negative. Gallium scintigraphy showed no pathological accumulative. FMF was suspected for the symptoms of recurrent fever, chest pain, and abdominal pain. He did not have the mutations of the *MEFV* exons that are genetic hallmarks of the disease, but the duration of fever and serositis was short (2-3 days). A clinical diagnosis typical of FMF was made since the patient met the Tel-Hashomer 1 major criteria (repeated febrile attack), and 1 minor criteria (peritoneal attack) (Livneh et al. 1997) in October 2018. The clinical course is summarized in Fig. 2. Colchicine treatment was begun in October 2018, but did not control the recurrent attacks of fever completely, and its dose could not be increased due to diarrhea. He was judged to have colchicine-resistant FMF, so treatment with canakinumab, a specific interleukin-1β monoclonal antibody (Ilaris 150 mg, subcutaneous injection every 4 weeks), was initiated in February 2021. Chest and abdominal pain with fever ceased after the administration of canakinumab. He fell down in his house while walking during the treatment of FMF. Clinical examination revealed the leg was in fixed flexion with adduction and internal rotation. X-rays revealed the progression of left hip osteoarthritis and fracture of the bone head (Fig. 1B). Computed tomography of the pelvis also showed the left hip fracture of the bone head (Fig. 3). The fracture made it difficult for him to walk independently, and he began to use a walking stick. Fentanyl tape was initiated as pain was not controlled with NSAID's, nerve block therapy, and intra-articular steroid injection. Left total hip arthroplasty (THA) was scheduled 2 months after the initiation of canakinumab. THA was performed after a 3-week break from the last canakinumab dose (Fig. 1C). There was no adverse event in the perioperative period, and the patient improved without FMF relapse. The wound was healed and there was no infection, so canakinumab was restarted 6 weeks after surgery. The pain improved postoperatively, and fentanyl tape was discontinued.

Informed consent was obtained from the patient. Because of a case report of single patient, ethical approval was waived for institutional review board in Fukushima Medical University.

Discussion

FMF is characterized by periodic febrile attack accompanied by sororities or arthritis (Fonnesu et al. 2009). Arthritis is present in 34% of the Japanese patients in a form of transient nonerosive monoarthritis affecting large joints (Migita et al. 2012). IL-1 plays a major role in the pathogenesis of FMF, and blockade of IL-1 provides therapeutic control of colchicine-resistant FMF (Roldan et al. 2008; Ben-Zvi and Livneh 2014). Canakinumab, a human IL-1 monoclonal antibody, has shown promising efficacy in

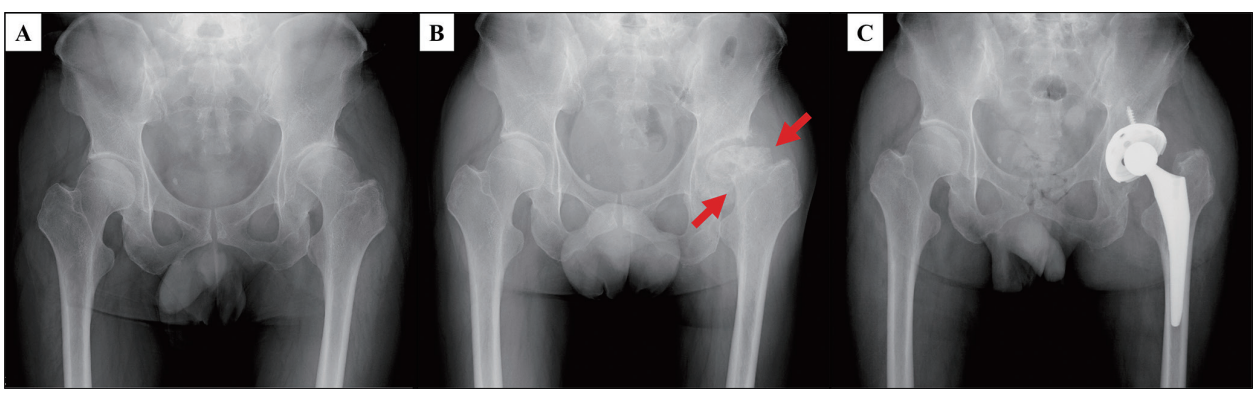

Fig. 1. Pelvic X-ray transition.
A: Pelvic X-ray at the admission to out hospital showed osteoarthritis of the left hip. B: Presurgery X-ray showed progression of osteoarthritis and fracture of femoral head (red arrows). C: Postsurgery X-ray showed artificial osteophyte head in left hip.

Table 1. Laboratory findings on admission.

Peripheral blood		Immunoserological tests	
Red blood cells	383 × 104/μL	C-reactive protein	6.01 mg/dL (< 0.30)
Hemoglobin	13.5 g/dL	Erythrocyte sedimentation rate	22 mm/hr (< 10)
Hematocrit	38.9%	Serum amyloid A	152 μg/mL (< 8.0)
Platelets	29.8 × 104/μL	sIL-2R	326 U/ml (121-613)
White blood cells	14,100/μL	IgG	716 mg/dL (861-1,747)
Neutriphil	78%	IgA	96 mg/dL (93-393)
Eosinophil	1%	IgM	57 mg/dL (50-269)
Monocyte	4%	Complement 3	128 mg/dL (73-138)
Lymphocyte	17%	Complement 4	33 mg/dL (11-31)
Basophil	0%	ANA	< × 80 (0-159)
Blood chemistry		MPO-ANCA	(−) (< 3.5 U/mL)
Total protein	7.2 g/dL (6.6-8.1)	PR3-ANCA	(−) (< 2.0 U/mL)
Total bilirubin	0.4 mg/dL (0.4-1.5)	HBs Ag	(−)
Albumin	4.5 g/dL (4.1-5.1)	Anti-HCV Antibody	(−)
Asparate aminotransferase	24 IU/L (13-30)	β-D glucan	< 6.0 (0-11.0)
Alanine aminotrans ferase	26 IU/L (10-42)	Procalcitonin	0.72 ng/mL (< 0.05)
Lactate dehydrogenase	219 IU/L (124-222)	Cytomegarovirus antigenemia	(0, 0)
Alkaline phosphatase	220 IU/L (106-322)	Coagulation	
Amylase	55 U/L (44-132)	PT	128%
Creatine kinase	73 IU/L (59-248)	PT-INR	0.88
Blood urea nitrogen	9 mg/dL (8-20)	APTT	25.6 sec
Creatinine	1.15 mg/dL (0.65-1.07)	Fibrinogen	391 mg/dL
Sodium	140 mEq/L (138-145)	FDP	< 2.5 μg/mL
Potassium	4.0 mEq/L (3.6-4.8)	D-dimer	0.5 μg/mL
Cloride	104 mEq/L (101-108)	Urinalysis	normal
Ferritin	515 ng/mL (50-200)	Blood culture	(−)

ANA, anti-nuclear antibody; APTT, activated partial thromboplastin time; FDP, fiburin/fibrinogen degradation products; HBs Ag, hepatitis B virus surface antigen; HCV, hepatitis C virus; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; PT; prothrombin time; PT-INR; prothrombin time-international normalized ratio; sIL-2R, soluble interleukin-2 receptor.
Reference values are shown in parentheses.

treating colchicine-resistance FMF (De Benedetti et al. 2018). Clinical trial data demonstrated that canakinumab induced the clinical remission against colchicine-resistant FMF patients (De Benedetti et al. 2018; Ozen et al. 2020). Post-marketing survey also demonstrated that canakinumab induced clinical improvement with limited adverse effects, including infections, leukopenia, and thrombocytopenia in patients with colchicine-resistant FMF (Kuemmerle-Deschner et al. 2020). However, evidence regarding the appropriate dose reduction or discontinuation of canakinumab in colchicine-resistant FMF patients receiving major surgery because of the rarity of this disease (Mulders-Manders et al. 2017).

This case report highlights the administration of canakinumab in an FMF patient receiving total joint replacement therapy. An unusual case of FMF has been described here who progressed to end-stage hip joint destruction because of long-standing osteoarthritis and traumatic fracture. Clinical remission of FMF was maintained during 4 months from the start of canakinumab treatment; however, the hip joint damage because of traumatic fracture progressed to requiring a total hip joint replacement. The assessment of postoperative complications is of great significance in patients receiving major orthopedic surgery since these complications can affect the postoperative recovery (Healy et al. 2016). Biologic agents, such as TNF-α blockers, are considered to increase the risk of infections, depending on their half-lives (den Broeder et al. 2007; Ruyssen-Witrand et al. 2007). The half-life of canakinumab is about 3 weeks. Therefore, it is recommended that administration of these biologics should be withheld two half-lives (about 6 weeks) before surgery, and the clinical status of patients should be considered to restart the administration of these drugs (den Broeder et al. 2007).

Clinical remission was maintained in most colchicine-resistant FMF patients who were randomized to receive either 4 mg/kg or 150 mg canakinumab every 4 weeks (De Benedetti et al. 2018). Furthermore, the dose of canakinumab can be increased to either 8 mg/kg or 300 mg ever 4 weeks in FMF patients with inadequate response to

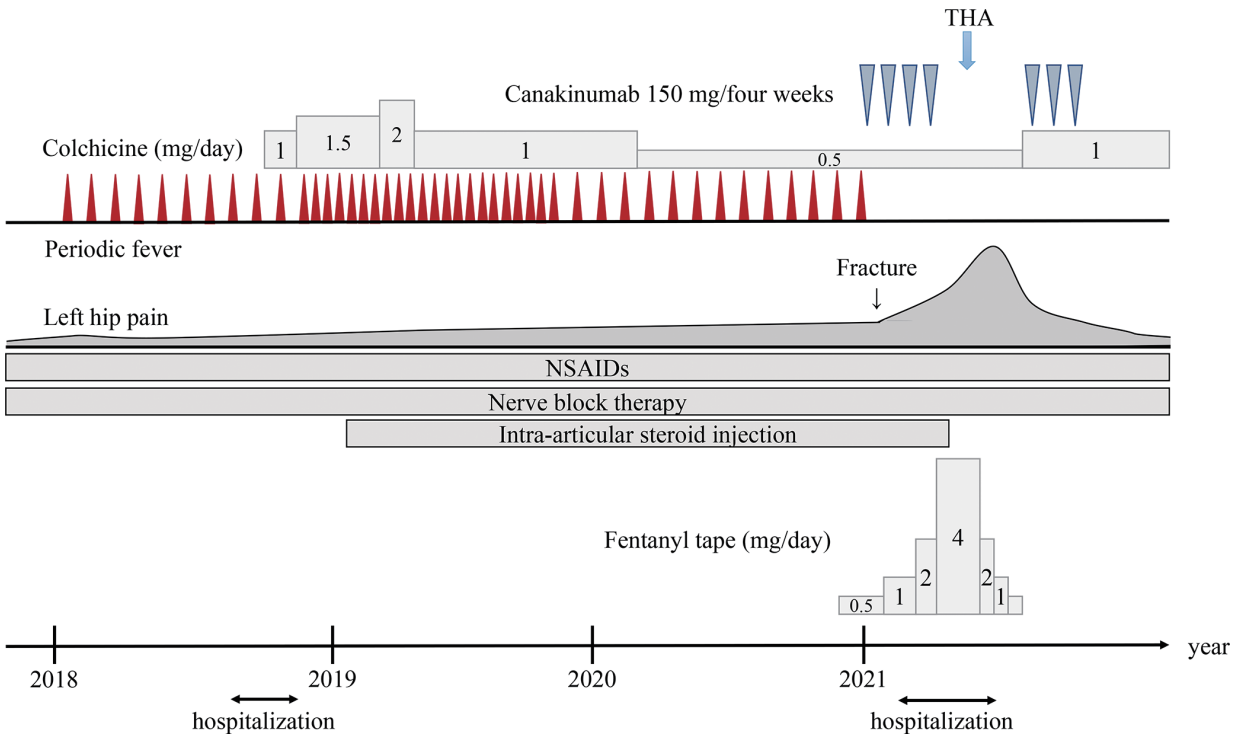

Fig. 2. Clinical course.
For colchicine-resistant Familial Mediterranean fever (FMF), treatment with canakinumab was initiated. During the treatment of FMF, the patient fell and broke the left femoral head. Two months after the initiation of canakinumab, because of the inability to control pain, left total hip arthroplasty (THA) was scheduled. THA was performed after a 3-weeks break from the last canakinumab dose, and canakinumab was restarted 6 weeks after THA. NSAIDs, nonsteroidal anti-inflammatory drugs.

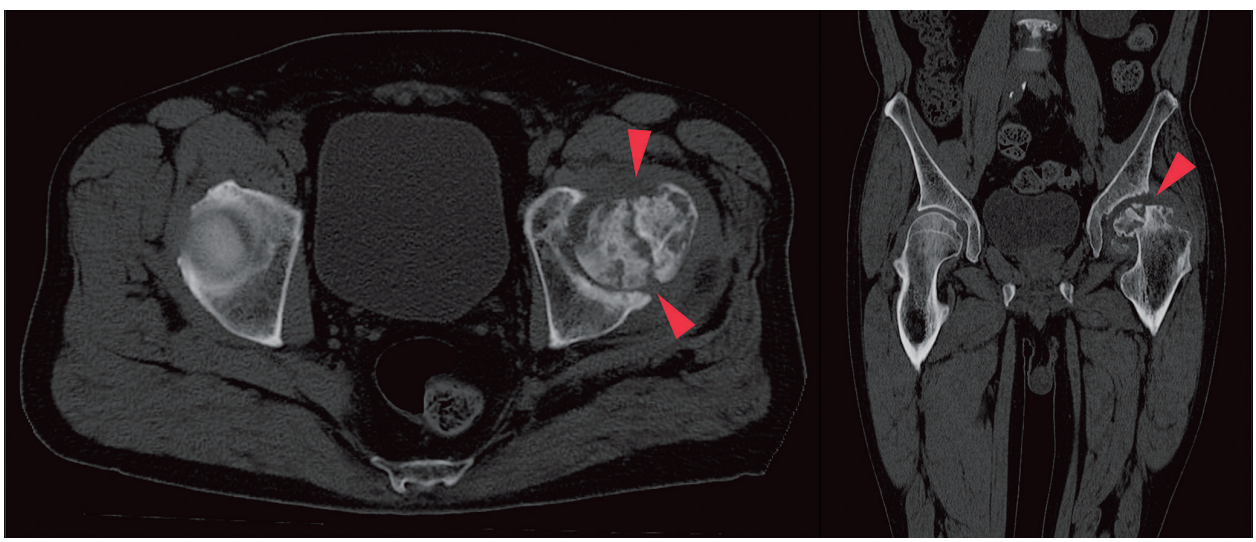

Fig. 3. Computed tomography of the pelvis.
Computed tomography, as well as X-rays, showed the left hip fracture of the bone head (red arrowheads).

the initial dose of canakinumab (De Benedetti et al. 2018). Patients with colchicine-resistant FMF receiving canakinumab treatment are very few, and there is no comprehensive protocol for the interval between the last canakinumab injection and operation. FMF crisis can be triggered by stress factors such as anesthesia and surgery (Khosroshahi et al. 2006; Sert et al. 2009; Korkmaz et al. 2020). Therefore, in patients undergoing elective orthopedic surgery, the presence of IL-1 mediated autoinflammatory disease may require IL-1 inhibiting treatment to prevent the operative stress-triggered autoinflammation. In patient with cryopyrin-associated periodic syndrome

(CAPS) receiving canakinumab, it is recommended to switch IL-1 inhibition to the short-acting anakinra when surgery is scheduled (Kuemmerle-Deschner and Haug 2013), but anakinra is not covered by insurance in Japan. The present case was regularly administrated with canakinumab preoperatively to prevent operative stress-induced FMF crisis. The pharmacokinetic characteristics of canakinumab have been previously described, and canakinumab has a long half-life of 21-28 days (Dhimolea 2010; Landmann and Walker 2017). Thus, discontinuation of canakinumab with only a half-life (3 weeks) before arthroplasty and resumption after 6 weeks (twice of half-life) lead to favorable results. In this patient canakinumab treatment before total arthroplasty was safe and well tolerated and stress-induced febrile or serosal attacks were not complicated after surgery. Adequate inflammatory control using IL-1 blocker may protect against stress-triggered autoinflammation including febrile serositis or synovitis attacks. After joint replacement, the dose or interval of canakinumab injection should be adjusted to prevent surgical site infection (SSI) (Antonelli and Chen 2019).

In conclusion, the present case suggests that adequate canakinumab treatment may prevent the operative stress-induced autoinflammatory responses, such as febrile attacks with serositis or synovitis in FMF patients receiving elective orthopedic surgery. Although SSI in joint surgery may not be few, in patients receiving canakinumab, the flare of autoinflammatory responses triggered by operative stress can be reduced by the pre-scheduled canakinumab treatment in these patients. Prospective studies of adjusting the length of anti-IL-1 therapy or withholding are needed to confirm the influence of this therapy against SSI risk degree.

Acknowledgments

The authors are grateful to Enago (http://www.enago.jp) for the English language review.

Conflict of Interest

The authors declare no conflict of interest.

References

Antonelli, B. & Chen, A.F. (2019) Reducing the risk of infection after total joint arthroplasty: preoperative optimization. *Arthroplasty*, **1**, 4.

Ben-Zvi, I. & Livneh, A. (2014) Colchicine failure in familial Mediterranean fever and potential alternatives: embarking on the anakinra trial. *Isr. Med. Assoc. J.*, **16**, 271-273.

De Benedetti, F., Gattorno, M., Anton, J., Ben-Chetrit, E., Frenkel, J., Hoffman, H.M., Kone-Paut, I., Lachmann, H.J., Ozen, S., Simon, A., Zeft, A., Calvo Penades, I., Moutschen, M., Quartier, P., Kasapcopur, O., et al. (2018) Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N. Engl. J. Med.*, **378**, 1908-1919.

den Broeder, A.A., Creemers, M.C., Fransen, J., de Jong, E., de Rooij, D.J., Wymenga, A., de Waal-Malefijt, M. & van den Hoogen, F.H. (2007) Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. *J. Rheumatol.*, **34**, 689-695.

Dhimolea, E. (2010) Canakinumab. *MAbs*, **2**, 3-13.

Fonnesu, C., Cerquaglia, C., Giovinale, M., Curigliano, V., Verrecchia, E., de Socio, G., La Regina, M., Gasbarrini, G. & Manna, R. (2009) Familial Mediterranean Fever: a review for clinical management. *Joint Bone Spine*, **76**, 227-233.

Goodman, S.M., Menon, I., Christos, P.J., Smethurst, R. & Bykerk, V.P. (2016) Management of perioperative tumour necrosis factor alpha inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis. *Rheumatology* (*Oxford*), **55**, 573-582.

Healy, W.L., Iorio, R., Clair, A.J., Pellegrini, V.D., Della Valle, C.J. & Berend, K.R. (2016) Complications of total hip arthroplasty: standardized list, definitions, and stratification developed by The Hip Society. *Clin. Orthop. Relat. Res.*, **474**, 357-364.

Khosroshahi, H.T., Tubbs, R.S. & Shoja, M.M. (2006) Familial Mediterranean fever triggered by renal transplantation. *Nephrol. Dial. Transplant.*, **21**, 3000-3001.

Korkmaz, C., Cansu, D.U. & Cansu, G.B. (2020) Familial Mediterranean fever: the molecular pathways from stress exposure to attacks. *Rheumatology* (*Oxford*), **59**, 3611-3621.

Kuemmerle-Deschner, J.B., Gautam, R., George, A.T., Raza, S., Lomax, K.G. & Hur, P. (2020) A systematic literature review of efficacy, effectiveness and safety of biologic therapies for treatment of familial Mediterranean fever. *Rheumatology* (*Oxford*), **59**, 2711-2724.

Kuemmerle-Deschner, J.B. & Haug, I. (2013) Canakinumab in patients with cryopyrin-associated periodic syndrome: an update for clinicians. *Ther. Adv. Musculoskelet. Dis.*, **5**, 315-329.

Landmann, E.C. & Walker, U.A. (2017) Pharmacological treatment options for cryopyrin-associated periodic syndromes. *Expert Rev. Clin. Pharmacol.*, **10**, 855-864.

Livneh, A., Langevitz, P., Zemer, D., Zaks, N., Kees, S., Lidar, T., Migdal, A., Padeh, S. & Pras, M. (1997) Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum.*, **40**, 1879-1885.

Migita, K., Uehara, R., Nakamura, Y., Yasunami, M., Tsuchiya-Suzuki, A., Yazaki, M., Nakamura, A., Masumoto, J., Yachie, A., Furukawa, H., Ishibashi, H., Ida, H., Yamazaki, K., Kawakami, A. & Agematsu, K. (2012) Familial Mediterranean fever in Japan. *Medicine* (*Baltimore*), **91**, 337-343.

Mulders-Manders, C.M., Baas, M.C., Molenaar, F.M. & Simon, A. (2017) Peri- and postoperative treatment with the interleukin-1 receptor antagonist anakinra is safe in patients undergoing renal transplantation: case series and review of the literature. *Front. Pharmacol.*, **8**, 342.

Ozen, S., Ben-Cherit, E., Foeldvari, I., Amarilyo, G., Ozdogan, H., Vanderschueren, S., Marzan, K., Kahlenberg, J.M., Dekker, E., De Benedetti, F. & Kone-Paut, I. (2020) 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.*, **79**, 1362-1369.

Ozen, S., Demirkaya, E., Erer, B., Livneh, A., Ben-Chetrit, E., Giancane, G., Ozdogan, H., Abu, I., Gattorno, M., Hawkins, P.N., Yuce, S., Kallinich, T., Bilginer, Y., Kastner, D. & Carmona, L. (2016) EULAR recommendations for the management of familial Mediterranean fever. *Ann. Rheum. Dis.*, **75**, 644-651.

Ozturk, M.A., Kanbay, M., Kasapoglu, B., Onat, A.M., Guz, G., Furst, D.E. & Ben-Chetrit, E. (2011) Therapeutic approach to familial Mediterranean fever: a review update. *Clin. Exp. Rheumatol.*, **29**, S77-86.

Roldan, R., Ruiz, A.M., Miranda, M.D. & Collantes, E. (2008) Anakinra: new therapeutic approach in children with Familial Mediterranean Fever resistant to colchicine. *Joint Bone Spine*, **75**, 504-505.

Ruyssen-Witrand, A., Gossec, L., Salliot, C., Luc, M., Duclos, M., Guignard, S. & Dougados, M. (2007) Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers. *Clin. Exp. Rheumatol.*, **25**, 430-436.

Sert, H., Muslu, B., Usta, B. & Gozdemir, M. (2009) Familial Mediterranean fever abdominal pain during spinal anaesthesia. *Br. J. Anaesth.*, **103**, 139.