**Beyond pericarditis: a multicenter study on anakinra effectiveness in refractory polyserositis**

*Giuseppe Lopalco[1], *Vincenzo Venerito[1], Antonio Brucato[2], Giacomo Emmi[3], Roberto Giacomelli[4], Alberto Cauli[5], Matteo Piga[5], Paola Parronchi[6], Mariangela Nivuori[2], Danilo Malandrino[3], Piero Ruscitti[7], Gianfranco Vitiello[6], Claudia Fabiani[8], Luca Cantarini[8], Florenzo Iannone[1]

[1]Department of Emergency and Organ Transplantation, Rheumatology Unit, University of Bari, Bari, Italy; [2]Department of Medicine, Azienda Socio Sanitaria Territoriale (ASST) Fatebenefratelli-Sacco and Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milan, Milan, Italy; [3]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [4]Unit of Allergology, Immunology, Rheumatology, Department of Medicine, University of Campus Bio-Medico of Rome, Rome, Italy; [5]Rheumatology Unit, University of Cagliari and AOU University Clinic of Cagliari, Monserrato, Italy; [6]Department of Experimental and Clinical Medicine, Immunology and Cell Therapy Unit, Careggi University Hospital, Florence, Italy; [7]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy; [8]Research Centre of Systemic Autoinflammatory Diseases, Behçet's Disease Clinic and Rheumatology-Ophthalmology Collaborative Uveitis Centre, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy

*Both these authors equally contributed to this manuscript.

**Correspondence:** Giuseppe Lopalco, MD; Department of Emergency and Organ Transplantation, Rheumatology Unit, Polyclinic Hospital, Piazza G. Cesare 11, 70124 Bari, Italy; email: glopalco@hotmail.it

**Abstract**

Polyserositis is an inflammatory condition involving different serosal membranes at the same time, specifically the pericardium, pleura, and peritoneum with transudate in the respective cavities. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and glucocorticoids may be effective in patients with polyserositis, but relapses often occur when these drugs are tapered or discontinued. The interleukin (IL)-1 receptor antagonist anakinra has shown a beneficial effect in idiopathic recurrent pericarditis deriving from IL-1 blockade, mostly in unresponsive patients who develop steroid dependence and/or colchicine resistance. To date, there are no data suggesting the best therapy for managing acute episodes and/or relapses of polyserositis. On this basis, we performed a retrospective study aimed at evaluating the effectiveness and safety profile of anakinra in treating patients with refractory polyserositis.

Patients with idiopathic polyserositis or rheumatic diseases presenting inflammation of 2 or more serous membranes were included. Serositis had to be confirmed by imaging tests comprising either echocardiography, abdominal ultrasound, chest or abdomen computed tomography and/or chest x-ray scan. We included patients with polyserositis who started anakinra from January 2011 to January 2019 due to a poorly controlled disease despite treatment with NSAIDs, conventional immunosuppressant drugs, or the need to minimize oral corticosteroids intake. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), as well as eventual imaging tests to monitor serositis, were recorded at baseline and either at 3, 6 and 12-month follow-up. Patients with neoplastic and infectious diseases were excluded from the analysis.

Forty-five patients with recurrent polyserositis (mean age of 43.2 ± 15.8 years and mean disease duration of 23.1 ± 28 years) were analysed. Polyserositis was idiopathic in 26 (57.8%) patients. Combination treatment with colchicine and NSAIDs at anakinra baseline was administered in 38/45 (84.4%) and 37/45 (82.2%) patients, respectively. After starting anakinra, most patients experienced a resolution of serositis with a dramatic decrease in ESR and CRP ($p < 0.0001$, for both) already at 3 months, furthermore the same beneficial effect was observed up to 12 months. No relapse was seen

at 3 months, whereas the median number of relapses at 6 and 12 months was 0 (0-1). Glucocorticoids were discontinued in 22/45 patients (48.9%) already after 3 months (p=0.0006). After 12 months 32/37 (86.5%) patients were steroid-free. Similarly, NSAIDs use significantly was decreased at 3 months (7/45 patients 15.6%, p<0.0001), whereas at 12-month follow-up no patient was on NSAIDs. Urticarial rashes at anakinra injection site occurring in 3 patients were the most common adverse events.

Anakinra appeared to be a safe and useful therapeutic choice for patients refractory to optimal anti-inflammatory therapy (NSAIDs, colchicine and corticosteroids), allowing not only a dramatic reduction of recurrences but also of corticosteroids employment. Anakinra was effective both in the idiopathic forms of polyserositis and in those with an underlying rheumatic disease, suggesting a common pathogenetic pathway leading to serositis onset.

## Introduction

Polyserositis is an inflammatory condition involving different serosal membranes at the same time, specifically the pericardium, pleura, and peritoneum with transudate in the respective cavities [1]. This inflammatory disorder usually has a benign course but may become recurrent or even chronic if not adequately treated [2]. Different causes have been claimed to explain the etiology of polyserositis, with most of them including autoimmune, autoinflammatory, infectious and neoplastic diseases [3]. In this regard, it is well-known that several autoimmune diseases such as systemic lupus erythematosus (SLE) may have a high prevalence of serosa involvement, especially pericarditis which can occur in up to 50% of SLE patients [4]. Serositis may also arise as extra-articular manifestation of rheumatoid arthritis (RA) [5] and can be variably found in other autoimmune diseases such as systemic sclerosis (SSc) and [6] Sjogren syndrome (SS) [7]. Serosal involvement has also been demonstrated in different autoinflammatory diseases, a heterogeneous group of disorders marked by overexpression of several pro-inflammatory cytokines, especially IL-1, which plays a dominant role in driving the clinical manifestations of such diseases [8]. Polyserositis, mainly pericarditis, may be

the starting manifestation for patients with tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF) [9]. Regarding the infectious etiology of serositis, up to 25% of patients with *Mycobacterium tuberculosis* infection may present extrapulmonary involvement in the form of tuberculous pericarditis and pleural or peritoneal tuberculosis [10]. In addition, the occurrence of effusion in the serosal cavities is a frequent event in the clinical setting of cancer involving the pleural or peritoneal and, less often, the pericardial space [11]. However, a non-negligible percentage of cases can be defined as idiopathic polyserositis (IP), reflecting our uneasiness in disclosing the intimate mechanisms of such disorder [12]. The similitude of such cases with some clinical features of autoinflammatory diseases, namely serositis, high fever and increased inflammatory markers, suggests an analogous inflammasome-mediated pathogenesis [13]. More in detail, it is believed that some microbial agents, generally viruses, or their antigens, might lead to dysregulation of the inflammasome, a large intracellular multiprotein platform with a central role in innate immunity, promoting the production of large amounts of pro-inflammatory cytokines, especially IL-1[14]. No specific therapies for handling polyserositis exist; therefore its treatment has been borrowed from that adopted to manage recurrent pericarditis (RP) [15]. In this regard, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are the gold-standard therapies for treating RP, and they may be also employed for managing polyserositis. However, these drugs often fail in blocking inflammation [16]. Systemic glucocorticoids may also work in patients refractory to NSAIDs and colchicine, but disease relapses may occur when they are tapered [17]. Moreover, corticosteroids may cause severe long-term side effects such as diabetes and osteoporosis [18]. Growing experience with the short-acting IL-1 receptor antagonist anakinra has shown the beneficial approach in RP deriving from IL-1 blockade, mostly in unresponsive patients who develop steroid dependence and/or colchicine resistance [19]. Since there are no data suggesting the best therapy for treating acute episodes and/or relapses of polyserositis, we performed a retrospective multicenter study aimed at evaluating the effectiveness and safety profile of anakinra in managing patients with polyserositis.

**Methods**

We carried out a retrospective study to investigate whether treatment with anakinra had a beneficial effect in Caucasian adult patients with polyserositis. Patients were followed in four specialized Rheumatologic Centers and two Internal Medicine Units in Italy (Bari, Cagliari, Firenze, L'Aquila, Milano, Siena) from January 2011 to January 2019. We included patients with a diagnosis of IP or systemic rheumatic diseases presenting inflammation of 2 or more serous membranes (pericarditis, pleuritis and/or peritonitis with effusion). Serositis had to be confirmed by imaging tests including either echocardiography, abdominal ultrasound, chest or abdomen computed tomography and/or chest x-ray scan. Retrieved data encompassing gender, ethnicity, etiology of polyserositis, comorbidities, body mass index, disease duration, number of relapses in the 3 months before anakinra starting and ongoing medications on anakinra were collected. Included patients had a poorly controlled disease despite treatment with NSAIDs, conventional immunosuppressant drugs, or the need to minimize oral corticosteroids intake. For patients in whom an autoimmune disease was suspected, rheumatoid factor test, anti-cyclic citrullinated peptide antibodies, anti-nuclear antibodies, anti-extractable nuclear antigens, as well as anti-dsDNA antibodies were carried out, whereas tuberculin skin test or QuantiFERON-TB assay, human immunodeficiency virus serology and blood cultures were performed to rule out infectious diseases. If the clinical history and physical examination suggested the presence of malignancy, appropriate additional tests were also evaluated. Clinical assessment and routine laboratory tests including complete blood count, kidney liver function, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), as well as eventual imaging tests were carried out at baseline and either at 3, 6 and 12 months or when required during the time span of study. ESR was considered increased if > 25 mm/h, whereas CRP when > 5 mg/L. Patients with clinical features suggestive for monogenic autoinflammatory diseases were tested for mutations in the *MEFV* and *TNFRSF1A* genes involved in FMF and TRAPS, respectively. The study was approved and reviewed by the local Ethical Committee (GISEA registry, IRB approval number DG-624, ClinicalTrial.Gov NCT01543594 - AOUB, Azienda Ospedaliera Universitaria di Bari) and

was conducted according to the declaration of Helsinki. Moreover off-label use of anakinra was authorized by each hospital involved in this study. All patients provided a written informed consent. To test differences among variables at different follow-up periods Student's t-test for matched pairs, Wilcoxon matched pairs signed rank-test or McNemar's test were used as appropriate. Statistical significance was considered for $\alpha$=0.05. Stata 16 (StataCorp, Texas, USA) was used for statistical analysis.

**Results**

Twenty-three women and twenty-two men (mean age 43.2 ± 15.8 years) with a disease duration of 23.1 ± 28 years were followed for 12 months while they received anakinra treatment (Table 1). Twenty-six (57.7%) subjects were diagnosed as IP, whereas an underlying systemic rheumatic disease was found in the remaining 19 (42%) patients. Among the latter, 9 (20%) patients suffered from monogenic autoinflammatory diseases: 5 of them were diagnosed with TRAPS and the other 4 had FMF. Moreover, AOSD was found in 4 patients and SLE in 2. The remaining 3 patients were affected with Behçet's diseases (BD) [1 patient], SSc (1 patient) and undifferentiated connective tissue disease (1 patient) (Figure 1). Over time, all the patients had received treatment with systemic glucocorticoids (up to 50 mg/daily), NSAIDs (ibuprofen 600 mg three times a day or indomethacin from 25 to 50 mg three times a day) and colchicine (up to 2 mg/daily) (data not shown). Other treatments such as methotrexate were employed in 5 patients: 4 with AOSD and 1 with RA, respectively. Data up to 12 months were available for 37/45 patients. Combination treatment with colchicine and NSAIDs at anakinra baseline was administered in 38/45 (84.4%) and 37/45 (82.2%) patients, respectively. All patients except 6 (13.3%) took oral glucocorticoid therapy at baseline. More in detail, prednisone ≥ 25 mg/daily were employed in 18 (40%) patients, dosage from 7.5 mg to 25 mg/daily was given to 16 (36.6%) subjects and only 5 (11%) patients underwent prednisone ≤ 7.5 mg/daily (Table 1; Figure 3). After starting anakinra, inflammatory markers, including ESR and CRP, dramatically dropped to normal levels in the first 3 months of treatment ($p < 0.0001$) and were normal

up to 12 months (Figure 2). Only 1 patient with SLE and another one with IP continued to have an increase in CRP at 3 and 12-month follow-up, respectively (Table 2). However, no relapse was seen at 3 months, instead the median number (interquartile range) of relapses at 6 and 12 months was 0 (0-1) (Table 2). Of note, glucocorticoids were discontinued in 22/45 patients (48.9%) already at 3 months ($p=0.0006$). At 12 months 32/37 (86.5%) patients were steroid-free, whereas only 5 (13.5%) patients took prednisone ($\leq$ 7.5 mg/daily) yet (Figure 3). Similarly, at 3 months 7/45 (15.6%) patients underwent NSAIDs, whereas at 12 months no patient was on treatment with these drugs (Figure 4). Regarding conventional treatments, 29/45 (64.4%) patients took still colchicine at 3 months, whereas 28/43 (51.4%) and 19/37 (51.4%) continued to be on colchicine at 6 and 12 months, respectively (Figure 4). Most patients experienced a resolution of serositis already at 3 months, with a beneficial effect lasting up to 12 months. However, at 3 months, pericarditis was still present in 3 patients (2 IP and 1 SSc), pleuritis in 3 subjects with IP as well as ascitis in one IP. Moreover, pericarditis and pleuritis were found each in 2 different IP, whereas ascitis in 2 IP at 6 months. Finally, at 12 months 3 IP had still pericarditis and one IP pleuritis. None of them had ascitis (Table 1). Anakinra was not tapered throughout the whole observation period. No difference about the response to treatment among patients after stratification according to age, gender and aetiology of IP was seen. Among adverse events, urticarial rashes at anakinra injection site were seen in 3 patients, whereas 1 patient experienced uncomplicated respiratory infection. One discontinuation due to the occurrence of macrophage activation syndrome in a patient with AOSD after 6 months of anakinra was recorded as well.

**Discussion**

Polyserositis is not uncommon clinical entity and is often related to different rheumatological diseases [3]. Dysregulation of either adaptive and innate immune responses together with unidentified tissue/organ milieus may promote the activation of one or the other immune system, leading to disease onset [13]. In our study we found that more than half of patients was diagnosed as idiopathic form,

mirroring our awkwardness in unveiling the authentic pathogenic mechanism of this disorder. The main findings of this study are that anakinra dramatically reduced flares of polyserositis allowing a steroid sparing effect. This remark is mainly significant because side effects from corticosteroids can be severe and affect up to 25% of chronically treated patients [20]. Although anakinra has been successfully used in the treatment of RA and several monogenic and polygenic autoinflammatory diseases, our results support the hypothesis that IL-1 may play a critical role in the pathogenesis of polyserositis, irrespective of the underlying rheumatic disease. In this regard we found that 5 (11%) patients had an autoimmune disease and 2 of them were diagnosed as SLE. Serositis in SLE, especially recurrent pericarditis, has a prevalence ranging from 11 to 50% [21]. Findings of high neutrophil count in the pericardial effusion of SLE patients [22] may suggest an involvement of IL-1 as the driver of inflammation in SLE serositis [23]. Of note, neutrophils are critical at the site of inflammation for the recruitment of macrophages producing large amount of IL-1β and TNF-α [24] which set back neutrophil apoptosis and consequently further spread inflammation [25]. Moreover IL-1 has been found to be increased in glomerulonephritis and in the serum and cerebrospinal fluid of SLE patients with central nervous system involvement, corroborating that IL-1 might be a therapeutic target in SLE [26]. We also found that 30% of patients included in our study was affected by monogenic (TRAPS and FMF) and polygenic (BD, AOSD) autoinflammatory diseases. Mostly FMF and TRAPS can be marked by the recurrence of serositis combined with fever and other clinical features which show a dramatic response to IL-1 blocking [9]. FMF also known as “periodic peritonitis” or “familial paroxysmal polyserositis”, is the most common of all periodic fever syndromes [27]. Peritonitis occurs in almost 90% of the patients during their disease course [28], whereas about half of patients may complain chest pain due to pleural involvement, usually unilateral [29]. Moreover, pleuritis may arise simultaneously with peritonitis and rarely with pericarditis, which commonly appears late in the course of the disease [30]. A significant improvement of abdominal and chest inflammatory attacks has been reported in colchicine-resistant FMF subjects who underwent anakinra, suggesting the pivotal role of IL-1 in such patients [31]. Similarly, polyserositis

in the form of pericarditis and pleuritis may be clinical hallmarks of TRAPS, especially in patients with adult-onset disease [32]. Anakinra has been shown to be useful in TRAPS leading to improvement of symptoms and inflammatory parameters, even when employed on-demand [33, 34]. Pericarditis and pleurisy may also be found in up to 38% and 53%, respectively of patients with AOSD [35]. Data from the literature showed that in most patients, both clinical features and laboratory parameters resolved within a few days with anakinra, albeit a quicker action in controlling inflammation may be seen when this agent is employed as soon as after AOSD onset [36]. In our cohort, IP presented the same clinical phenotype of autoinflammatory diseases, marked by serositis, fever and a remarkable increase in inflammatory parameters. Most patients showed prompt resolution of symptoms with anakinra, thus advocating an underlying involvement of innate immunity. At 12-month follow-up, pleuritis and pericarditis were still present only in 11% of patients (Table 1). Our results are in line with those from the AIRTRIP trial showing a pericarditis recurrence rate of 18% in the arm of patients assigned to anakinra [37]. As regard conventional treatments, a steroid-sparing effect was seen in our patients, so much so that at 12 months, 86.5% of subjects were steroid-free. Similarly, none of the patients was on NSAIDs at the end of of the observation period. Otherwise, 19 patients, remained on colchicine at 12-month follow-up. Some studies showed that colchicine can concentrate itself in white blood cells, especially granulocytes, hindering tubulin polymerization which is critical for several cellular functions, including phagocytosis, degranulation and chemotaxis [38]. Moreover, colchicine is also able to attenuate bacterial toxin-induced caspase-1 activation, IL-1 release and pyroptosis [39]. This evidence may substantiate the use of colchicine in our patients, despite its previous failure, to enhance the anti-inflammatory effect of anakinra in such subjects, thus preventing potential serositis recurrences [40]. The safety profile of anakinra is also encouraging in this study. Most adverse events were mild, mostly related to local skin reactions. These adverse events had a low incidence (6.6%) in our cohort and could be mitigated by the application of topical hydrocortisone or antihistamine cream [41]. Patients were taught in advance about the possible occurrence of such reactions to avoid drug withdrawal. Noteworthy infections, mostly respiratory and

soft-tissue infections during treatment with anakinra may occur [42]. In our study, we observed one infectious adverse event (2%), involving the respiratory system, which resolved with proper treatment without needing anakinra cessation. The observational design as well as the small sample size may be regarded as limitations of this study. Therefore, wider controlled trials of anakinra in patients with refractory polyserositis are needed to confirm our findings. Overall, our results provide evidence that anakinra may be a worthwhile therapeutic option for refractory polyserositis suggesting that the activation of innate immune system might be predominant of such condition irrespective of underlying disease.

**Take-home messages**

- Polyserositis is not uncommon clinical entity and is often related to different rheumatological diseases including autoimmune and autoinflammatory diseases
- Dysregulation of either adaptive and innate immune responses together with unidentified tissue/organ milieus may promote the activation of one or the other immune system, leading to polyserositis onset
- Treatment with non-steroidal anti-inflammatory drugs, colchicine and glucocorticoids may be effective in patients with polyserositis, but relapses often occur when these drugs are tapered or discontinued
- The interleukin (IL)-1 receptor antagonist anakinra may be a useful therapeutic option for refractory polyserositis suggesting that the activation of innate immune system might be predominant in this disorder irrespective of underlying disease

**REFERENCES**

1. Hoffman FG. Idiopathic polyserositis. Arch Intern Med. 1961 Dec;108:872-83. doi: 10.1001/archinte.1961.03620120056009

2. Brucato A, Emmi G, Cantarini L, Di Lenarda A, Gattorno M, Lopalco G, Marcolongo R, Imazio M, Martini A, Prisco D. Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism. Intern Emerg Med. 2018 Jun;13(4):475-489. doi: 10.1007/s11739-018-1842-x

3. Losada I, González-Moreno J, Roda N, Ventayol L, Borjas Y, Domínguez FJ, Fernández-Baca V, García-Gasalla M, Payeras A. Polyserositis: a diagnostic challenge. Intern Med J. 2018 Aug;48(8):982-987. doi: 10.1111/imj.13966

4. Miner JJ, Kim AH. Cardiac manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am. 2014 Feb;40(1):51-60. doi: 10.1016/j.rdc.2013.10.003

5. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular Manifestations in Rheumatoid Arthritis. Maedica (Bucur). 2010 Dec;5(4):286-91

6. Thompson AE, Pope JE. A study of the frequency of pericardial and pleural effusions in scleroderma. Br J Rheumatol. 1998 Dec;37(12):1320-3. doi: 10.1093/rheumatology/37.12.1320

7. Hosoda C, Hosaka Y, Ryu K, Kinoshita A, Saito K, Kuwano K. Pleuritis associated with primary Sjogren syndrome. Respirol Case Rep. 2017 Dec 22;6(2):e00285. doi: 10.1002/rcr2.285

8. Rigante D, Lopalco G, Vitale A, Lucherini OM, Caso F, De Clemente C, Molinaro F, Messina M, Costa L, Atteno M, Laghi-Pasini F, Lapadula G, Galeazzi M, Iannone F, Cantarini L. Untangling the web of systemic autoinflammatory diseases. Mediators Inflamm. 2014;2014:948154. doi: 10.1155/2014/948154

9. Cantarini L, Lopalco G, Selmi C, Napodano S, De Rosa G, Caso F, Costa L, Iannone F, Rigante D. Autoimmunity and autoinflammation as the yin and yang of idiopathic recurrent acute pericarditis. Autoimmun Rev. 2015 Feb;14(2):90-7. doi: 10.1016/j.autrev.2014.10.005

10. Vaid U, Kane GC. Tuberculous Peritonitis. Microbiol Spectr. 2017 Jan;5(1). doi: 10.1128/microbiolspec.TNMI7-0006-2016

11. Davidson B. Malignant effusions: from diagnosis to biology. Diagn Cytopathol. 2004 Oct;31(4):246-54. doi: 10.1002/dc.20133

12. Massaro MG, Rigante D, Sicignano LL, Verrecchia E, De Vito F, Gasbarrini A, Manna R. Therapeutic management of idiopathic recurrent serositis: a retrospective study. Eur Rev Med Pharmacol Sci. 2020 Mar;24(6):3352-3359. doi: 10.26355/eurrev_202003_20703

13. Lopalco G, Rigante D, Cantarini L, Imazio M, Lopalco A, Emmi G, Venerito V, Fornaro M, Frediani B, Nivuori M, Brucato A, Iannone F. The autoinflammatory side of recurrent pericarditis: Enlightening the pathogenesis for a more rational treatment. Trends Cardiovasc Med. 2021 Jul;31(5):265-274. doi: 10.1016/j.tcm.2020.04.006

14. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell. 2002 Aug;10(2):417-26. doi: 10.1016/s1097-2765(02)00599-3

15. Emmi G, Urban ML, Imazio M, Gattorno M, Maestroni S, Lopalco G, Cantarini L, Prisco D, Brucato A. Use of Interleukin-1 Blockers in Pericardial and Cardiovascular Diseases. Curr Cardiol Rep. 2018 Jun 14;20(8):61. doi: 10.1007/s11886-018-1007-6

16. Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, Moratti M, Gaschino G, Giammaria M, Ghisio A, Belli R, Trinchero R. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation. 2005 Sep 27;112(13):2012-6. doi: 10.1161/CIRCULATIONAHA.105.542738

17. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J et al (2015) ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC) endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 36(42):2921-64. doi: 10.1093/eurheartj/ehv318

18. Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther. 2002 Oct;96(1):23-43. doi: 10.1016/s0163-7258(02)00297-8

19. Blank N, Lorenz HM. Idiopathic Pericarditis-an Autoinflammatory Disease? Curr Rheumatol Rep. 2019 Mar 9;21(5):18. doi: 10.1007/s11926-019-0820-2

20. Imazio M, Brucato A, Cumetti D, Brambilla G, Demichelis B, Ferro S, Maestroni S, Cecchi E, Belli R, Palmieri G, Trinchero R. Corticosteroids for recurrent pericarditis: high versus low doses: a nonrandomized observation. Circulation. 2008 Aug 5;118(6):667-71. doi: 10.1161/CIRCULATIONAHA.107.761064

21. Dein E, Douglas H, Petri M, Law G, Timlin H. Pericarditis in Lupus. Cureus. 2019 Mar 1;11(3):e4166. doi: 10.7759/cureus.4166

22. Rao S, Siddaraju N, Mishra P, Muthalagan E, Toi PC, Rajesh NG. Significance of lupus erythematosus (LE) cell detection in pericardial fluid in an era of sophisticated techniques. Cytopathology. 2015 Jun;26(3):200-2. doi: 10.1111/cyt.12152

23. Cafarelli F, Coladonato L, Lopalco G, Cacciapaglia F, Cantarini L, Iannone F. Successful treatment with anakinra of refractory pericarditis in systemic lupus erythematosus. Clin Exp Rheumatol. 2021 Jan-Feb;39(1):227

24. Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. Science. 2015 Jul 17;349(6245):316-20. doi: 10.1126/science.aaa8064
25. van den Berg JM, Weyer S, Weening JJ, Roos D, Kuijpers TW. Divergent effects of tumor necrosis factor alpha on apoptosis of human neutrophils. J Leukoc Biol. 2001 Mar;69(3):467-73

26. Takemura T, Yoshioka K, Murakami K, Akano N, Okada M, Aya N, Maki S. Cellular localization of inflammatory cytokines in human glomerulonephritis. Virchows Arch. 1994;424(5):459-64. doi: 10.1007/BF00191429

27. Ozdogan H, Ugurlu S. Familial Mediterranean Fever. Presse Med. 2019 Feb;48(1 Pt 2):e61-e76

28. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore). 2005 Jan;84(1):1-11. doi: 10.1097/01.md.0000152370.84628.0c

29. Ben-Chetrit E, Levy M. Familial Mediterranean fever. Lancet. 1998 Feb 28;351(9103):659-64. doi: 10.1016/S0140-6736(97)09408-7

30. Kees S, Langevitz P, Zemer D, Padeh S, Pras M, Livneh A. Attacks of pericarditis as a manifestation of familial Mediterranean fever (FMF). QJM. 1997 Oct;90(10):643-7. doi: 10.1093/qjmed/90.10.643

31. Ben-Zvi I, Kukuy O, Giat E, Pras E, Feld O, Kivity S, Perski O, Bornstein G, Grossman C, Harari G, Lidar M, Livneh A. Anakinra for Colchicine-Resistant Familial Mediterranean Fever: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Rheumatol. 2017 Apr;69(4):854-862. doi: 10.1002/art.39995

32. Gaggiano C, Vitale A, Obici L, Merlini G, Soriano A, Viapiana O, Cattalini M, Maggio MC, Lopalco G, Montin D, Jaber MA, Dagna L, Manna R, Insalaco A, Piga M, La Torre F, Berlengiero V, Gelardi V, Ciarcia L, Emmi G, Ruscitti P, Caso F, Cimaz R, Hernández-Rodríguez J, Parronchi P, Sicignano LL, Verrecchia E, Iannone F, Sota J, Grosso S, Salvarani C, Frediani B, Giacomelli R, Mencarelli MA, Renieri A, Rigante D, Cantarini L. Clinical Features at Onset and Genetic Characterization of Pediatric and Adult Patients with TNF-α Receptor-Associated Periodic Syndrome (TRAPS): A Series of 80 Cases from the AIDA Network. Mediators Inflamm. 2020 Aug 7;2020:8562485. doi: 10.1155/2020/8562485

33. Gattorno M, Pelagatti MA, Meini A, Obici L, Barcellona R, Federici S, Buoncompagni A, Plebani A, Merlini G, Martini A. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum. 2008 May;58(5):1516-20. doi: 10.1002/art.23475

34. Grimwood C, Despert V, Jeru I, Hentgen V. On-demand treatment with anakinra: a treatment option for selected TRAPS patients. Rheumatology (Oxford). 2015 Sep;54(9):1749-51. doi: 10.1093/rheumatology/kev111

35. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. J Autoimmun. 2018 Sep;93:24-36. doi: 10.1016/j.jaut.2018.07.018. Epub 2018 Aug 1. PMID: 30077425

36. Vitale A, Cavalli G, Ruscitti P, Sota J, Colafrancesco S, Priori R, Valesini G, Argolini LM, Baldissera E, Bartoloni E, Cammelli D, Canestrari G, Cavallaro E, Massaro MG, Cipriani P, De Marchi G, De Vita S, Emmi G, Frassi M, Gerli R, Gremese E, Iannone F, Fornaro M, Paladini A, Lopalco G, Manna R, Mathieu A, Montecucco C, Mosca M, Piazza I, Piga M, Pontikaki I, Romano M, Rossi S, Rossini M, Silvestri E, Stagnaro C, Talarico R, Frediani B, Tincani A, Viapiana O, Vitiello G, Galozzi P, Sfriso P, Gaggiano C, Grosso S, Rigante D, Dagna L, Giacomelli R, Cantarini L. Comparison of Early vs. Delayed Anakinra Treatment in Patients With Adult Onset Still's Disease and Effect on Clinical and Laboratory Outcomes. Front Med (Lausanne). 2020 Feb 21;7:42. doi: 10.3389/fmed.2020.00042

37. Brucato A, Imazio M, Gattorno M, Lazaros G, Maestroni S, Carraro M, Finetti M, Cumetti D, Carobbio A, Ruperto N, Marcolongo R, Lorini M, Rimini A, Valenti A, Erre GL, Sormani MP, Belli R, Gaita F, Martini A. Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence: The AIRTRIP Randomized Clinical Trial. JAMA. 2016 Nov 8;316(18):1906-1912. doi: 10.1001/jama.2016.15826

38. mazio M. Colchicine for pericarditis. Trends Cardiovasc Med. 2015 Feb;25(2):129-36. doi: 10.1016/j.tcm.2014.09.011

39. Imazio M, Lazaros G, Brucato A, Gaita F. Recurrent pericarditis: new and emerging therapeutic options. Nat Rev Cardiol. 2016 Feb;13(2):99-105. doi: 10.1038/nrcardio.2015.115

40. Imazio M, Andreis A, De Ferrari GM, Cremer PC, Mardigyan V, Maestroni S, Luis SA, Lopalco G, Emmi G, Lotan D, Marcolongo R, Lazaros G, De Biasio M, Cantarini L, Dagna L, Cercek AC, Pivetta E, Varma B, Berkson L, Tombetti E, Iannone F, Prisco D, Caforio ALP, Vassilopoulos D, Tousoulis D, De Luca G, Giustetto C, Rinaldi M, Oh JK, Klein AL, Brucato A, Adler Y. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis: The IRAP (International Registry of Anakinra for Pericarditis) study. Eur J Prev Cardiol. 2020 Jun;27(9):956-964. doi: 10.1177/2047487319879534

41. Bettiol A, Lopalco G, Emmi G, Cantarini L, Urban ML, Vitale A, Denora N, Lopalco A, Cutrignelli A, Lopedota A, Venerito V, Fornaro M, Vannacci A, Rigante D, Cimaz R, Iannone F. Unveiling the Efficacy, Safety, and Tolerability of Anti-Interleukin-1 Treatment in Monogenic and Multifactorial Autoinflammatory Diseases. Int J Mol Sci. 2019 Apr 17;20(8):1898. doi: 10.3390/ijms20081898

42. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis. 2009 Jan;68(1):25-32. doi: 10.1136/ard.2007.083188