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Off-label use of anti-IL-1 drugs in rheumatic diseases

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Abstract

Interleukin-1 (IL-1) plays a key role in the pathogenesis of different rheumatic diseases. There are now several agents available on the market capable of blocking IL-1. The proven effectiveness and excellent safety of these drugs makes them a possible therapeutic option in the treatment of IL-1 driven diseases, when previous therapies are contraindicated or ineffective. This article discusses the European wide off-label use of these drugs for the treatment of rheumatic diseases.

Keywords

anakinra, anti IL-1, canakinumab, off-label use, rheumatic diseases

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Introduction

Interleukin-1

IL-1 family is associated with innate immune responses, which occur in acute and chronic inflammatory conditions such as rheumatic diseases. IL-1 family is composed by seven pro-inflammatory molecules (IL-1α, IL-1β, IL-18, IL-33, e IL-36α, β e γ) and four anti-inflammatory ones (IL-1 receptor antagonist (IL-1RA), IL-36R antagonist (IL-36RA), IL-37 and IL-38). IL-1α and IL-1β have the greatest inflammatory activity. These Interleukins are encoded by two different genes and both bind the same receptor, therefore they result in the same biological activity. The receptor is IL-1 receptor type 1 (IL-1R), which recruits IL-1RAcP coreceptor, needed for signaling. IL-1α (also called alarmin) is present constitutively as a precursor in healthy individuals; it does not need to be synthesized or processed during a harmful event because it is biologically active and immediately available.[1,2] IL-1α is localized on epithelial cells of mucosa, skin, liver, kidneys, lungs, on platelets, endothelial cells and apoptotic bodies. The precursor IL-1α migrates on the cell surface activating its receptor placed on the adjacent cell.[3] IL-1β is not constitutively expressed within the cells, compared to IL-1α. IL-1β is produced by hematopoietic cells (monocytes, tissue macrophages, dendritic cells) as a result of stimuli, such as microbial products activating toll-like receptors (TLR) or intracellular NODlike receptors (NLRs), and cytokines such as TNF, IL-1α and IL-1β itself, which is responsible for self-maintaining inflammation. IL-1β precursor is inactive and needs to be cleaved by caspase 1, a cysteine protease that transforms it into its active form. The same caspase is active only within the inflammasome, an intracellular protein complex activated by pathogenic stimuli such as Pathogen Associated

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Molecular Patterns (PAMPS) and Damage-Associated Molecular Patterns (DAMPS). Once transformed into its active form, IL-1β is released from the cells and binds to the IL-1R, triggering the inflammatory cascade. This process consists in the activation of genes related to inflammation, such as COX2 and PLA2, and causes the synthesis of PGE2, the recall of acquired immunity, and the development of systemic events such as fever.[2,3] Thus, IL-1α and IL-1β differ dramatically in their compartmentalization within the producing cell or in the microenvironment, possibly proving their different physiological roles; therefore, the non-redundant roles of IL-1α and IL-1β in inflammation underscore the importance of a treatment that targets both cytokines. Another IL-1 binds on the same receptor and competes with IL-1α and IL-1β; IL-1Ra, which acts as an inhibitor, blocks the inflammatory cascade downstream. IL-1Ra is expressed on all nucleated cells. The genetic disease DIRA syndrome, characterized by the loss of function of the IL-1RA, highlights the role of IL-1 in determining inflammation.[1,2]

Anti-IL-1 drugs

Anti-IL-1 drugs are anakinra, canakinumab, rilonacept, gevokizumab; we discuss the off-label use only of the first two, the only ones approved in Europe.

Anakinra. Anakinra (Kineret) is the recombinant form of the natural IL-1antagonist. It prevents the link of IL-1α and IL-1β with IL-1R. Anakinra **is administered** subcutaneously on a daily basis. The drug is available in prefilled syringes of 100 mg per 0.67 mL, which allow for doses between 20 and 100 mg; its half-life is between 4 and 6 h, which makes the drug very manageable. A typical regimen is 100 mg subcutaneously (SC) each day.[4,5] Anakinra is currently approved in Italy to treat cryopyrin-associated periodic syndromes (CAPS), Adult Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA), refractory Rheumatoid Arthritis (RA), and Family Mediterranean Fever (FMF). Its off-label use is widely supported.[6]

Canakinumab. Canakinumab (Ilaris) is a humanized monoclonal antibody with high affinity for IL-1β; its action is to prevent its link with IL-1R. It has a half-life of 26 days and has intracellular catabolism, with little or no bile and kidney excretion. The dosage varies depending on weight in patients <2 years and in patients with a low body weight; the highest dose is 4 mg/die up to a max of 300 mg every 4 weeks. It is approved in Italy for the treatment of CAPS, Tumor Necrosis Factor Receptor-associated Periodic Syndrome (TRAPS), Mevalonate kinase deficiency/hyperimmunoglobulin D syndrome (MKD/HIDS), FMF, AOSD, sJIA, and Gout (the latter non-refundable by the National Health care Service).[2]

Retrospective studies have highlighted excellent safety profiles and tolerability of anti-IL-1 drugs. The adverse events emerged were mostly mild, such as reactions at the injection site, especially for anakinra, and an increased frequency of non-serious infections of the upper respiratory tract.[7,8] Off-label use is the use of drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration, when the previous treatment proved to be ineffective or contraindicated. We describe anti-IL-1 off-label use focusing only on those drugs allowed in Europe (Table 1).

Research strategy

PubMed and Google Scholar database were used to find articles treating European wide off-label use of anti-IL-1 for the treatment of rheumatic diseases, by using the terms "anakinra," "canakinumab," "anti interleukin-1 treatment," "off-label," "rheumatic diseases." We excluded articles about rilonacept and gevokizumab because both drugs are not approved in Europe, and we only took into consideration articles written in English.

Microcrystal arthropathies

Gout

Monosodium urate crystals can activate the NLRP3 inflammasome with excessive release of IL-1β through monocytes in the blood and synovial fluid. A 10 patients pilot study first showed that anakinra, when administered for three consecutive days at 100 mg dose, was effective in symptomatic control of acute gout arthritis.[9] A multicentric retrospective study confirmed the data. On the contrary, prolonged administration for the prevention of attacks was associated with an increased risk of infections, therefore not tolerated.[10] Resistant

Table 1. Main studies dailing with off-label use of anakinra and canakinumab in rheumatic diseases.

Diseases	Studies	Drug	Efficacy	Safety
Microcrystals arthritis	Efficacy of anakinra in gouty arthritis: A retrospective study of 40 cases[10] Anakinra for the treatment of acute gout flares: a randomized, double-blind, placebo-controlled, active-comparator, non-inferiority trial[17] Efficacy of anakinra for refractory acute calcium pyrophosphate crystal arthritis[19] Efficacy of anakinra in acute hydroxyapatite calcification-induced joint pain: A retrospective study of 23 cases[22]	23 patients: ANA 100 mg for 3 days; 17 patients: ANA 100 mg > 3 days ANA 100 mg for 5 days versus treatment as usual ANA 100 mg for 3 days in five patients ANA 100 mg for 1–3 days	96% good response Anakinra was shown to be non-inferior to treatment as usual Four patients: rapid clinical response One patient: no response VAS pain score decreased rapidly. Size of calcifications not had significant change	Short-term use: one infectious event. Long term use: six infectious events One infectious event in the ANA group One injection-site skin reaction No adverse event
Behcet's disease	Anakinra treatment in drug-resistant Behcet's disease: a case series[25] Efficacy and safety profile of anti-interleukin-1 treatment in Behçet's disease: a multicenter retrospective study[27] Inhibition of interleukin-1 by canakinumab as a successful mono-drug strategy for the treatment of refractory Behçet's disease: A case series[32]	ANA 100 mg/day (one patient 150 mg/day) 30 patients who received ANA 100 mg/day or CAN 150 mg every 6 to 8 weeks (with any therapeutic adjustments and shift) CAN 150 mg every 6 weeks	Eight of nine patients: rapid clinical improvement (one patient with 150 mg/die) Complete remission in the patients who received at least 12 months anti-IL-1 drugs ($n = 13$) complete resolution of symptoms	Three of nine patients: injection-site skin reaction ANA: 16% local cutaneous reactions; CAN: no adverse event No adverse event
Uveitis	Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behçet's disease-related uveitis: a multicenter retrospective observational study[38] Clinical and transcriptional response to the long-acting interleukin-1 blocker canakinumab in Blau syndrome-related uveitis[41]	ANA 100 mg/day; CAN 150 mg every 4, 6, or 8 weeks CAN 2 mg/kg/month	Significant reduction of intraocular flares and frequency of retinal vasculitis Rapid involvement of uveitis	No adverse event No adverse event
Scleritis	Efficacy of the IL-1 receptor antagonist, anakinra, for the treatment of diffuse anterior scleritis in rheumatoid arthritis. Report of two cases[43] Anakinra in the treatment of patients with refractory scleritis: A pilot study[44]	ANA 100 mg/day ANA 100 mg/day	Remission of scleritis Clinical remission of the 90% of the patients at the end of the 19.4-months	No adverse event Four of Ten patients: injection-site skin reaction
Kawasaki Disease	The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: A retrospective cases series[48] Kawakinra: A phase IIa multicenter trial to assess the efficacy, and safety of anakinra in patients with intravenous immunoglobulin-resistant Kawasaki disease[49]	ANA from 2 mg/kg/day to 8 mg/kg/day ANA 2–6 mg/kg/die	Reduction of fever, CRP; in 10/11 patients reduction in coronary dilation Reduction of clinical and biological inflammation and coronary dilatation	Well tolerated Three severe adverse events: anakinra overdose, MAS and increase of coronary dilatation. Others AE cytolytic hepatitis (two patients), hypereosinophilia (1), injection site reaction (1) and pancreatitis (1)
Schnitzler syndrome	Treatment of Schnitzler's syndrome with anakinra: report of three cases and review of the literature[52] Efficacy and safety of canakinumab in Schnitzler's syndrome: a multi-center randomized placebo-controlled study[57]	ANA 100 mg/day Single CAN 150 mg or placebo injections for 7 days, followed by a 16-week open-label phase with CAN on demand	Complete and lasting resolution of symptoms; not influence in the course of monoclonal gammopathy Clinical responses in CAN group, along with improvement of quality of life, reduction of CRP and SAA	No adverse event Three severe adverse events: hypertension (two patients), severe lumbago (1) 22 mild or moderate adverse events: infectious events, gastrointestinal complaints, non-specific pain, skin symptoms, osteochondrosis, asthma and weight gain
Erdheim-Chester disease	Favorable radiological outcome of skeletal Erdheim-Chester disease involvement with anakinra[59] Treating heart inflammation with interleukin-1 blockade in a case of Erdheim-Chester disease[62]	ANA 100 mg/day ANA 100 mg/day	Complete clinical response. after 1 year: reduction in the uptake of radiopharmaceutical in the affected areas (PET-CT) Prompt reduction in pericardial effusion, inflammatory markers and general clinical improvement	No adverse event No adverse event

(Continued)

Table 1. (Continued)

Diseases	Studies	Drug	Efficacy	Safety
PFAPA	A case of resistant adult-onset periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome responsive to anakinra[64] Canakinumab efficacy in refractory adult-onset PFAPA syndrome[66]	ANA 100 mg/day CAN 150 mg every 8 weeks	Improvement of symptoms and decrease of CRP, ESR and SAA protein Improvement of the overall PFAPA symptoms	No adverse event No adverse event
CRMO/CNO	Anakinra in a cohort of children with chronic nonbacterial osteomyelitis[68] Efficacy of anti-IL-1 treatment in Majeed syndrome[70]	ANA at a median dose of 2 mg/kg/day ANA 1.7 mg/kg/day and then CAN 4 mg/kg/4 weeks	After 6 months in 5/9 patients favorable clinical outcome (none o minimal PGA score). Dramatic clinical and laboratory improvement with both drugs	No adverse event No adverse event
TRAPS	Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome[76] On-demand treatment with anakinra: A treatment option for selected TRAPS patients[77]	ANA 1.5 mg/kg/day ANA 2 mg/kg/day on demand (within 24 h of the first signs of an attack and for 5–7 days)	Clinical improvement, and reduction normalization of acute phase reagents Complete clinical remission and reduction of acute phase reagents	Few injection-site skin reaction Few injection-site skin reaction
MKD	On-demand anakinra treatment is effective in mevalonate kinase deficiency[81] Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency[82]	ANA 1 to 2 mg/kg/day for MA patients ANA on demand (100 mg/day or 1 mg/kg/day for 5–7 days) or continuous treatment for HIDS patients ANA 1 to 5 mg/kg/day CAN 2 to 7 mg/kg every 4 to 8 weeks	Partial remission in one MA patient complete remission in the HIDS patient with continuous treatment less intense and lasting attacks in HIDS patients with ANA on demand. Clinical improvement in the frequency and duration of attacks, reduction of CRP and SAA	Injection-site skin reaction; infectious events ($n = 2$) ANA and CAN: injection-site skin reaction, infectious event. ANA: hypothermia, shivers CAN: transient hepatitis
MAS	Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature[89] Refractory adult-onset still disease complicated by macrophage activation syndrome and acute myocarditis: A case report treated with high doses (8 mg/Kg/D) of Anakinra[93]	ANA 2 mg/kg/day ANA 80 mg/kg/day	Rapid remission of symptoms and normalization of laboratory findings Clinical remission with complete normalization of cardiac function	Injection-site skin reaction ($n = 1$) Transient pancytopenia
Osteoarthritis	Intraarticular injection of anakinra in osteoarthritis of the knee: A multicenter, randomized, double-blind, placebo-controlled study[100] Open-label use of anakinra (kineret) in the treatment of patients with osteoarthritis[103]	Single dose IA of anakinra 50 mg, anakinra 150 mg or placebo ANA 30 mg IA for small joints of hands, or 50 to 100 mg IA for medium joints of wrists or ankles, or 150 to 200 mg IA for large joints of knees or shoulder. ANA 100 mg/day SC for 30 days for erosive OA	Only pain reduction with 150 mg of anakinra compared to placebo on day 4 Only four patients responded, especially those who received anakinra injections in large joints. Only one patient with erosive OA had a slight improvement on day 30	Well tolerated. Few cases of arthralgia, headache, infectious events, extremity pain Well tolerated
Rheumatoid arthritis	Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: Results of a 12-week, phase ii, dose-finding study[106]	CAN 150 mg SC every 4 weeks, 300 mg SC every 2 weeks, a 600 mg IV loading dose of CAN followed by 300 mg SC every 2 weeks or placebo SC every 2 weeks	CA 150 mg SC every 4 weeks was effective to reach the primary endpoints (percentage of ACR 50 responders at 12 weeks significantly higher than placebo group). Higher doses of CAN did not result in higher efficacy	Few injection-site reactions, infectious events; elevations in transaminase (transient in most cases) with CAN 300 mg SC every 2 weeks and CAN 600 MG IV loading dose + 300 mg SC every 2 weeks

(Continued)

Table 1. (Continued)

Diseases	Studies	Drug	Efficacy	Safety
Ankylosing spondylitis	Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study[109]	ANA 100 mg/day for 3 months	Improvements in disease activity, function and quality of life; reduction in inflammatory markers. More than half of the inflammatory lesions in basal MRI regressed or disappeared after 3 months	Few injection-site skin reactions, headache
Psoriatic arthritis	An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate[112]	ANA 100 mg/day	Improvement of signs and symptoms in 9 out of 19 patients	Good safety profile, few injection-site skin reactions, rare infectious events
SLE	Preliminary results of safety and efficacy of the interleukin 1 receptor antagonist anakinra in patients with severe lupus arthritis[114]	ANA 100 mg/day	Subjective clinical response, reduction ECLAM score, and reduction in joint count and CRP after 12 weeks	Injection-site skin reaction, infectious events
Antiphospholipid antibodies syndrome	Disappearance of a strong triple positivity for antiphospholipid antibodies after treatment with anakinra[116]	ANA 100 mg/day	Disappearance of the strong positivity of aPLA	No adverse event
Sjogren asthenia and dry eye	Interleukin-1 inhibition and fatigue in primary Sjögren's syndrome—a double blind, randomized clinical trial[117]	ANA 100 mg versus placebo	No reduction in significant asthenia. But more than a 50% reduction in post-hoc fatigue in a statistically higher number of patients treated with anakinra than in the placebo group	Injection-site skin reaction, infectious events
Polymyalgia rheumatica	A 2-week single-blind, randomized, three-arm proof of concept study of the effects of secukinumab (anti-IL-17 mAb), canakinumab (anti-IL-1 b mAb), or corticosteroids on initial disease activity scores in patients with PMR, followed by an open-label extension[120]	Single dose (3 mg/kg/body weight) of either secukinumab or CAN, or daily oral prednisone	Only partial responses in patients treated with CAN	Well tolerated without Severe AEs or increased infections noted
Giant-cell arteritis	Interleukin-1 blockade in refractory giant cell arteritis[121]	ANA 100 mg/day	Improvement in inflammation biomarkers and/or in symptoms, as well as a disappearance of arterial inflammation in PET/CT of two out of three patients	Injection-site skin reaction
Urticarial vasculitis	Efficacy and safety of canakinumab in urticarial vasculitis: An open-label study[122]	Single dose of CAN 300 mg SC	Improvement of symptoms, quality of life, inflammatory markers; not all patients had a complete symptom control	Well tolerated: 3 respiratory tract infections, one fever, and five laboratory abnormalities
Pericarditis	Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: The AIRTRIP Randomized Clinical Trial[125]	ANA 2 mg/Kg/day SC up to 100 mg/ day	Reduction of the risk of recurrence over a median of 14 months	Injection-site skin reactions, few cases of elevation of transaminase

ANA: anakinra; CAN: canakinumab; SC: subcutaneous; IA: intraarticular; IV: intravenous; AE: adverse event; CRP: C-reactive protein; SAA: serum amyloid A; ESR: erythrocyte sedimentation rate; PGA: patient global assessment; OA: oateoarthritis; ACR: American College of Rheumatology; ECLAM: European Consensus Lupus Activity Measurement; aPLA: antiphospholipid antibodies; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; CRMO/CNO: chronic recurrent multifocal osteomyelitis/chronic non-bacterial osteomyelitis; TRAPS: tumor necrosis factor receptor-associated periodic syndrome; MKD: mevalonate kinase deficiency; HIDS: hyperimmunoglobulin D syndrome; MA: mevalonic aciduria; MAS: macrophage activation syndrome; SLE: systemic lupus erythematosus.

tophaceous gout also responds to on demand administration of anakinra, in combination with sub-optimal doses of allopurinol, with faster steroids tapering.[11,12] There were excellent results in patients burdened by multiple comorbidities, whose gout attacks benefited from anakinra continuous treatment,[13] and in complex hospitalized patients, thanks to the drug's short half-life, rapidity of action and good tolerability.[14,15] Clinical improvements also occurred in patients with chronic kidney failure at the 4–5 stage and in patients with kidney transplantation.[16] A randomized, double-blind, placebo-controlled, non-inferiority-related study highlighted the non-inferiority of anakinra in the treatment of gout exacerbations compared to conventional drugs (Colchicine, Naproxen, or Corticosteroids).[17]

Pseudogout

By acting on NALP3, inflammasome calcium pyrophosphate crystals increase IL-1β production, activating metalloproteinase, inhibiting collagen 2, and synthesizing proteoglycans in the cartilage matrix, thus promoting joint damage. Anakinra can be a highly valuable drug in the prevention of joint damage and in changing the outcome of this disease.[18,19] A patient with end-stage renal failure successfully responded to 100 mg of anakinra administered as a preventive therapy 3 days at week after each session of hemodialysis; after 8 months of follow-up, the patient did not show any serious episode of arthritis.[20]

Hydroxyapatite crystal deposition disease

Acute inflammation is mainly due to crystals dissolution which also causes macrophages activation. Similarly to the gout and pseudogout, microcrystalline-induced inflammation involves mainly IL-1. The Inflammation is often self-limiting but can last up to 2 or 3 weeks with the need to take NSAIDs or glucocorticoids infiltration which may result insufficient, or contraindicated. An open study of five patients proved the effectiveness of anakinra in treating acute shoulder calcific periarthritis. Anakinra 100 mg was administered SC for three consecutive days with a prompt reduction in pain and inflammatory markers. Total crystals dissolution was not obtained, as the 6-week follow-up period was too short.[21] A retrospective 23 patients study confirmed the effectiveness and speed of action of anakinra 100 mg on pain resolution, when administered 1–3 consecutive days.[22]

Behcet's disease

Behcet's disease (BD) is a chronic multi-systemic inflammatory disease. It is characterized by the presence of recurrent oral and genital ulcers, skin lesions, and uveitis, a state of hypercoagulability, cerebral or gastrointestinal vasculitis. It shares some features with autoinflammatory diseases such as the lack of autoantibodies, recurrent episodes of inflammation, and mucocutaneous manifestations characterized by neutrophil infiltrations. It is characterized by an important activation of both innate and adaptive immunity. Many cytokines participate in the pathogenesis of the disease, among which IL-1 plays a key role, opening up new scenarios for Bechet's disease's treatment. Elevated IL-1β levels can be found in serum and synovial fluid of BD patients, although they do not correlate with the disease activity.[23] Botsios et al.[24] described the first case of multidrug resistant BD successfully treated with anakinra. Subsequently, a case series (nine patients with refractory BD) showed seven patients with rapid clinical improvement after 100 mg of daily anakinra, one responding to the dose of 150 mg, and another not responding. After an initial clinical remission, almost all patients showed exacerbations of the disease after a few months.[25] Anakinra was effective in inducing sacroiliitis resolution related to BD.[26] A retrospective study assessed the effectiveness of anakinra and canakinumab in 30 BD patients. Some patients who had a low response to daily administration of anakinra 100 mg, showed clinical improvement under a higher dose (150 mg), or by switching to canakinumab. Closer doses of canakinumab (150 mg every 6 weeks) also determined positive results if 150 mg every 8 weeks proved ineffective. Anakinra was partially effective in treating mucocutaneous lesions.[27] Anakinra was a safe treatment in a patient with refractory BD and latent tuberculosis.[28] A 2-step adaptive clinical trial concluded that a 200 mg/die dose of anakinra is partially effective in reducing oral and resistant genital ulcers.[29] Canakinumab demonstrated excellent results in various BD cases, after multiple failed therapies, including anakinra.[30–32] However, there were no encouraging results from

canakinumab use in the control of neurological manifestations.[33] Anakinra appeared to be more effective in treating skin, joint, and intestinal mucosa, while canakinumab showed relevant efficacy in BD ocular involvement, evidently linked to different pharmacokinetics and cytochemical expression in the different organs.[34,35]

Uveitis

IL-1 can have a pivotal role in inflammatory eye diseases such as uveitis. IL-1β produced in the retina by dendritic cells, macrophages, and neutrophils may be the protagonist of the local inflammatory process, and this would explain the great effectiveness of anti-IL-1 drugs.[36] Canakinumab has been successfully employed in a case of BD-related uveitis which was refractory to conventional treatment and anakinra. At the beginning of canakinumab therapy, a low-grade papillary bladder carcinoma was found and surgically excised. Canakinumab therapy continued once the excision led to a complete resolution of the symptoms and the absence of cancer recurrence was assured.[37] A multicenter retrospective study of 19 patients with refractory or long-standing BD-related uveitis showed that canakinumab and anakinra are both viable treatment options: after 12 months of follow-up there was a reduction in eye inflammations attacks and an improvement in retinal vasculitis, which allowed for a reduction in corticosteroid use. There were no differences in efficacy between the treatment with anti-IL-1 naive and the previously treated with anti-TNF. There was a higher rate of inflammatory flare in patients co-administered with DMARDS than in patients administered with anti-IL-1 in monotherapy. These results confirm the recent evidence indicating the role of IL-1β, produced by myeloid cells in the retina, in uveitis pathogenesis.[38] There were significant clinical improvements in BD uveitis with a longer duration of the disease.[39] Moreover, Anakinra and Canakinumab also showed excellent results in the treatment of Blau syndrome, a rare genetic disease characterized by triad arthritis, rash and uveitis.[40,41]

Scleritis

Non-infectious scleritis refers to a wide spectrum of ocular conditions associated with a high risk of irreversible visual impairment and the potential to threaten the anatomical integrity of the eye. It often occurs in the context of systemic disorders such as RA, vasculitis or SLE. Therefore, early recognition and timely treatment are critical for a successful management of this sight-threatening condition. In this regard, refractory cases unresponsive to conventional Disease Modifying Antirheumatic Drugs (cDMARDs) may take advantage of biotechnologic agents that have revolutionized many rheumatic diseases. More in detail, encouraging results have been reported with anakinra.[42] IL-1, together with other cytokines, is produced by the local inflammatory cell infiltrate, and it is involved in sclera damage. Anakinra was successful in two patients with anterior scleritis and RA resulting in a rapid response with the reduction of eye inflammation. However, the reduction of the dose caused symptoms reactivation in a patient, which resolved only after the restoration of the previous dose of anakinra.[43] A pilot study was carried out to evaluate the effectiveness of anakinra 100 mg daily in severe anterior refractory scleritis. Ten patients were enrolled, six of whom had scleritis associated with autoimmune and autoinflammatory diseases (Relapsing Polychondritis, BD, Psoriatic Arthritis, and RA). Ninety percent of the patients presented clinical remission at the end of the 19.4-months follow-up, corticosteroid therapy was reduced, immunosuppressants were discontinued (except in one case). Most patients responded after 1 month and only three patients experienced recurrence of scleritis which was successfully treated with corticosteroids. Only one patient was refractory to anakinra. In addition, patients with scleritis associated with systemic rheumatological diseases also showed improvement in extraocular symptoms.[44]

Kawasaki disease

Kawasaki syndrome (KD) is a vasculitis of medium and small arteries, which characteristically affects coronary arteries generating ectasia or aneurysms in 15%–20% of untreated children and can lead to heart dysfunction and death. It is characterized by fever, skin rash, conjunctivitis, interest in the buccal mucosa and lips, lymphadenopathy. IL-1 recall inflammatory cells in the vasal walls in particular it facilitates the inflammatory infiltration, the smooth muscle cells proliferation and the myofibroblasts formation into the coronary arterial wall inducing endothelial damage, vasodilatation with subsequent aneurysm formation. Despite conventional

therapies, a relapsed KD patient showed progressive cardiac deterioration and evolution to giant coronary artery aneurysm, which normalized after anakinra administration (1 mg/kg/die).[45] Two case reports documented the partial coronary aneurysms regression in KD after treatment with anakinra,[46] and another case reported the positive response in a 16-year-old KD.[47] Patients who started taking anakinra (variable dosage from 2 to 8 mg/kg/day) on average 15 days after the onset of the disease showed rapid clinical improvement: reduction of fever, C-reactive Protein (CRP), and 10/11 patients showed reduction in coronary dilation. The complete clinical and cardiac resolution verified in 6/10 patients.[48] A phase IIA multicenter trial assessing the effectiveness and safety of the 15-day anakinra immediately after the failure of IVIG treatment, found that when administered within the 2–6 mg/kg/die dose, anakinra is rapidly effective in reducing clinical and biological inflammation and coronary dilatation.[49]

Schnitzler syndrome

Schnitzler syndrome is a rare inflammatory multisystemic disease with late onset, it is characterized by chronic urticaria and monoclonal gammopathy (often IgM), often associated with fever, myalgia and polyarthralgia, lymphadenopathies, and increased inflammatory markers. Patients have a higher risk of developing Waldenström macroglobulinemia and lymphoma. Clinical similarities with autoinflammatory diseases, the increase in proinflammatory cytokines such as IL-1 and the effectiveness of IL-1 blocking agents suggest the central role of IL-1 in the etiopathogenesis of this rare disease, which is not yet entirely known. Several case reports highlighted how anakinra induced remission of the disease.[50,51] It is also assumed that anakinra does not influence the course of monoclonal gammopathy.[52] In a retrospective study 29 patients treated with anakinra responded significantly to treatment, with no loss of effectiveness after a median follow-up of 3-years of treatment ensuring steroids sparing. Cases of non-response to anakinra are rare and may be linked to a subtype of disease or even misdiagnosis.[53] Canakinumab has also been tested in three Schnitzler patients inducing prompt clinical benefit.[54] Vanderschueren and Knockaert describe a significant and long-lasting clinical and biological response, with the disappearance of fever, arthritis, skin rash, asthenia and reduction of CRP levels in a patient treated with canakinumab 150 mg every 8 weeks for 6 months. After discontinuation of the drug the disease reappeared, with its remission after the reintroduction of the drug.[55] An open study of eight patients, treated with canakinumab 150 mg every month for 6 months, confirmed the rapidly inducing clinical and biological remission of the disease, except for a single patient who had a relapse after the initial clinical remission. After the discontinuation of treatment, the patients experienced reactivation of symptoms.[56] A randomized phase 2, placebo-controlled, multicenter study on 20 patients to evaluate canakinumab effectiveness was carried out. At day 7, patients who received 150 mg had clinical responses unlike the placebo group, and these results, along with the improvement of quality of life and the reduction of CRP, continued up to 16 weeks with on demand administration.[57]

Erdheim-Chester disease

Erdheim-Chester disease (ECD) is a non-Langerhans cell histiocytosis, characterized by fibroinflammatory lesions in retroperitoneal, periureteral areas or in bone, determined by infiltration of macrophages CD68, CD1a-. It is a rare disease that manifests with bone pain, fever, asthenia, involvement of cardiocirculatory and central nervous systems. The etiopathogenesis is still unclear, but IL-1 and IL-6 seem to have a relevant role; in fact, the IL-1 signaling appears overstimulating in ECD. Two patients with ECDs had a rapid clinical and biological response after anakinra administration, with disappearance of fever and bone pain, and reduction of IL-1, IL-6 and CRP and the expression of the IL-1α on monocytes. Pulmonary fibrosis also partially regressed.[58] The radiological response in an ECD patient with refractory bone infiltration treated with anakinra was assessed: after 1 year of treatment, PET-CT showed a significant reduction in the uptake of radiopharmaceutical for the affected areas.[59] Two case reports highlighted the clinical and biological success of anakinra, with no significant improvement in radiological images.[60,61] Anakinra, thanks to its rapid action and excellent tolerance, was particularly suitable for this rapidly progressive condition; a patient with severe pericarditis, risk of cardiac

buffering and secondary heart failure, refractory to NSAIDS, colchicine and pericardial window, showed prompt reduction in pericardial effusion, inflammatory markers and general clinical improvement after anakinra.[62]

PFAPA

PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy) is an autoinflammatory disease, often with its onset in childhood. The etiopathogenesis remains unclear, but the disease is considered an inflammasome disorder, characterized by elevated production of IL-1β in PFAPA. Stojanov et al.[63] treated five patients with anakinra, with satisfactory results. Anakinra can be a valid option, especially in late-onset PFAPA.[64] Canakinumab also reduced adult disease activity, improving symptoms and biological reduction of inflammatory markers when anakinra was not effective[65] or lost its efficacy.[66] Child PFAPA attacks do not always respond to canakinumab. Higher or closer doses of canakinumab may be needed to control PFAPA attacks.[67]

Chronic recurrent multifocal osteomyelitis/chronic non-bacterial osteomyelitis

Chronic Recurrent Multifocal Osteomyelitis/ Chronic Non-Bacterial Osteomyelitis (CRMO/ CNO) is a chronic inflammatory syndrome characterized by multiple sterile bone inflammation, very painful, that arises in childhood–adolescent age. The overactivation of innate immune systems with an abnormal production of IL-1β may be involved in pathogenesis, which still remains poorly understood. The effectiveness of anakinra was assessed in nine patients with CNO resistant to NSAIDs and bisphosphonates. Five out of nine patients reported a positive clinical response during 6 months of treatment at a median dose of 2 mg/kg/day.[68] Many authors argue that CRMO/CNO has a counterpart in adulthood, SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis), in which positive responses were also described.[69] There are family monogenic forms of CNO: Majeed syndrome, PAPA syndrome, and DIRA syndrome. Satisfactory responses were observed under the administrations of anakinra and canakinumab also in these hereditary diseases.[70–74]

Tumor necrosis factor receptor-associated periodic syndrome

TRAPS is a rare autoinflammatory dominant autosomal disease caused by the mutation of TNF type 1 receptor gene, characterized by recurrent fever, migrant myalgias, and painful skin lesions, often associated with abdominal pain, headaches, arthritis, and significant increase in inflammatory markers. The overactivation of TNF signaling is the protagonist of the excessive inflammation which characterized the disease, but a dysregulation of IL-1 production also seems to participate in pathogenesis. Case reports showed how anakinra promptly induced into remission refractory TRAPS.[75] Then a study conducted on five patients with severe form of TRAPS showed, already after 2 days of treatment, clinical improvement, and reduction of CRP levels, normalized within the first fortnight in all patients. At the end of the fortnight, therapy was suspended with exacerbation of the disease; anakinra was reintroduced inducing remission during the next 11 months of follow up.[76] Another study investigated the effects of on-demand anakinra on two TRAPS pediatric patients. The drug was administered within 24–48 h of the symptoms' onset and it was continued for 5 days with rapid complete clinical remission and reduction of acute phase reagents in 24/48 H. After 2 years of treatment the number of attacks increased in one patient, requiring more lasting anakinra treatment, perhaps owed to the natural development of the disease rather than to the effectiveness of the drug.[77]

Mevalonate kinase deficiency/ hyperimmunoglobulin D syndrome

MKD is a rare autosomal recessive disease caused by the mutation of the MVK gene, which results in an altered isoprenoid and cholesterol production. IL-1 is involved in pathogenesis since the lack of isoprenoid products results in an increased production of IL-1β. It is an autoinflammatory disease and it includes a less severe form consisting of partial deficiency of Mevalonate Kinase or Hyperimmunoglobulinemia D with periodic fever (HIDS), and a more severe form with complete deficiency of Mevalonate Kinase, or Mevalonic Aciduria (MA).[78] Canakinumab is the only anti-IL-1 drug approved in Europe to treat this disease.

Studies showed that Anakinra is able to reduce significantly the severity of fever attacks in refractory HIDS. Anakinra effectiveness was also assessed on demand in regressing fever attacks in patients with HIDS after vaccinations,[79,80] and in atypical MKD, with refractory erosive arthritis.[81] A prospective study assessed the effects (1–2 mg/kg/day) of anakinra in patients with MKD; one of the two MA patients responded partially to continuous administration, 8/9 patients with HIDS chose to be treated on demand (in order to avoid daily injections on days free from symptoms), and only one chose continuous treatment. Patients receiving anakinra within 24 h of the onset of attacks, had less intense and shorter attacks. Continuous administration gave clinical remission for 7 months, after which the patient discontinued the drug due to its side effects.[82] In a retrospective study anakinra (1–5 mg/kg/day) and canakinumab (2–7 mg/kg every 4–8 weeks) were administered in 11 patients (five received anakinra, two canakinumab, and four switched from anakinra to canakinumab). All patients experienced clinical improvements in the frequency and duration of attacks, with reduced CRP and Serum Amyloid A (SAA) protein. The complete clinical remission took place in one patient treated with anakinra and in three patients treated with canakinumab. Continuous drug administration, unlike on-demand administration, also led to a reduction in the frequency of attacks, as well as duration and intensity. Further research is necessary to assess the benefits of both strategies in preventing long-term complications such as amyloidosis.[78]

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a hyperinflammation condition caused by excessive activation and proliferation of T lymphocytes and macrophages. This activation generates a cytokine storm, where IL-1 and IL-6 have a central role. The macrophages engulf normal hematopoietic cells and injure the organs in which they are located, for example liver, spleen, lymph nodes, and bone marrow. There are still many uncertainties concerning etiopathogenesis. This disease represents a dangerous complication of diseases such as SJIA and AOSD, but also SLE, KD[83,84]; it is classified as hemophagocytic lymphohistiocytosis (HLH), secondary to rheumatic diseases. It manifests with fever, hepatosplenomegaly, progressive pancytopenia, coagulopathy, high increase in serum ferritin, encephalopathy, and even multi-organ failure. A bone marrow biopsy is often required to arrive at a clear diagnosis, since the clinical features are confused with those of sepsis.[84] Anakinra was successfully administered for the first time in a patient with cytophagic histiocytic panniculitis who developed HLH.[85] Conflicting data comes from a study affirming that anakinra can act as a potential trigger for the development of MAS, since a patient with SJIA developed MAS following anakinra treatment.[86] Out of 46 patients with SJIA treated with anakinra at doses of 1–2 mg/kg, five have developed MAS, which was controlled from higher doses of anakinra.[87] In a multicenter study evaluating the long-term effectiveness of anakinra in AOSD and SJIA, out of 137 patients only one developed MAS.[88] Anakinra and canakinumab are approved for the treatment of AOSD and SJIA, and they have proven effective on many patients with related MAS.[84,89] MAS also affects patients with SLE, although more rarely, and there is evidence that shows the effectiveness of anakinra in this condition.[90,91] More frequent dosing times are often necessary to reach the required efficacy,[92] and sometimes higher doses of anakinra are essential to reduce hyperinflammation. Parisi et al.[93] described a patient with AOSD complicated by MAS and fulminant myocarditis who quickly responded to 400 mg/day of anakinra, after failed therapies such as steroids, cyclosporine and 100 mg/day of anakinra. In addition to the aforementioned SJIA case, canakinumab was also held responsible for the onset of MAS in a patient who developed AOSD 10 days after the second injection.[94] Other evidence declares that canakinumab does not increase the risk of MAS in patients under treatment for SJIA; it does not provide protection from MAS, although it induces clinical SJIA remission.[95] Shakoory et al.[96] reanalyzed data from phase III randomized trial about the effectiveness of anakinra in severe sepsis; in patients showing MAS characteristics anakinra led to an improvement in survival at 28 days compared to placebo. Hence, it is important to identify them in order to start immediately anti-IL-1 treatment. A recent retrospective study on sHLH/MAS patients associated with rheumatological diseases showed how anakinra reduces its mortality rate, especially when administered early.[97]

Osteoarthritis

IL-1α and IL-1β are more expressed on cartilage and synovial fluid in osteoarthritis (OA); in particular IL-1β induces an increases production and activation of proteolytic enzymes, an inhibition of collagen and proteoglycan synthesis and an increase production of inflammatory mediators like cytokines, prostaglandins, nitric oxide which result in tissue damage.[98] Some studies showed both Intra Articular (IA) and Subcutaneous (SC) administration of anakinra in OA. In a double-blind, multicenter, prospective study Chevalier et al.[99] demonstrated that a single dose of 150 mg anakinra IA administered in 13 patients with knee OA was absolutely well tolerated. A later 170 patients study described no clinical benefit from 50 mg or 150 mg of anakinra IA compared to placebo in patients with knee OA, from baseline to week 4; only pain reduction was seen with 150 mg of anakinra compared to placebo on day 4.[100] Case reports showed a clinical improvement in patients with refractory erosive OA regarding overall pain and disability after 3 months of SC anakinra injections.[101,102] In a prospective study, 9 out of 11 patients received anakinra IA injections (an average of two over a 2–3 months period) and 2/11 patients with erosive polyosteoarthritis received anakinra 100 mg SC injections daily for 30 days. Only four patients responded, especially those who received anakinra injections in large joints, probably due to the major drug dose (150–200 mg than 100 mg) that can be administered in large joints. Only one patient with erosive polyarthritis had a slight improvement from SC administration of anakinra on day 30.[103] A post-hoc survey of a randomized placebo study dealing with the canakinumab anti-inflammatory thrombosis outcomes study (CANTOS) reported a reduction in the incidence of OA in patients treated with canakinumab.[104] Nevertheless some patients with erosive OA treated with a single injection of canakinumab SC did not report positive results.[105]

Other diseases

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease. Alongside TNFα, the dysregulation of IL-1β plays an important role in pathogenesis by fueling inflammatory processes that result in synovial pannus formation, cartilage destruction, and bone erosion. In fact, elevated levels of IL-1β were detected in synovial fluid of RA patients. In a 12-week, phase II, dose-finding study Canakinumab showed excellent results in patients with active RA despite maximum tolerated doses of MTX. The SC dose of 150 mg every 4 weeks was effective to reach the primary endpoints with a percentage of ACR 50 responders at 12 weeks significantly higher than the placebo group. Higher doses of canakinumab (600 mg intravenous -IV- plus 300 mg SC every 4 weeks, or 300 mg SC every 2 weeks) did not result in higher efficacy.[106] These results were also confirmed in another study in which 150 mg SC of canakinumab improved ACR 50, unlike higher doses or more frequent administrations which did not lead to more benefit. Total canakinumab and IL-1β measurements were compared with serum markers (CRP) and clinical outcomes (ACR 20, 50, 70). Therefore, it could be assumed that the lack of a clear dose-effect characterization could be due to the limited role of IL-1β in RA pathogenesis compared to the role of other cytokines, such as TNFα and IL-6. Indeed, it is also possible that therapy led to differential up-or down-regulation of receptors and soluble receptors, including IL-1 type 2 decoy receptor which is involved in regulation of IL-1β activity, thereby resulting in paradoxical effects.[107] A case report showed how canakinumab administration, after failure of previous treatments (MTX, Leflunomide, anti-TNFα, anti-CD20, and Anakinra), brought the disease into remission in a girl with rapidly destructive RA.[108]

Ankylosing spondylitis

Ankylosing spondylitis (AS) is the prototype of spondyloarthritis, characterized mainly by enthesitis/osteitis. The IL-1 is overexpressed in AS patients, and it contributes to the inflammatory state amplification and to joint damage by stimulating macrophage and osteoclast activity, and fibroblast proliferation. An open label study of nine patients with active AS refractory to NSAIDs highlighted how anakinra 100 mg SC for 3 months led to significant improvements in disease activity (BASDAI), function (BASFI) and quality of life (ASQoL), as well as a reduction in inflammatory markers. In addition, more than half of the inflammatory lesions in basal MRI regressed or

disappeared after 3 months.[109] However, the encouraging clinical, biochemical and radiologic success observed in the first months was not confirmed by long-term data.[110,111]

Psoriatic arthritis

It is an inflammatory chronic disease that involves skin and joints. Alongside TNF, IL-1 also participates in the pathogenesis of the disease by inducing chronic inflammation. There is little data on anti-IL-1 use in Psoriatic Arthritis (PA); in a pilot study 9 out of 19 PA patients responded to anakinra therapy. However, the clinical benefit received by 30% of the patients should be not underestimated. Thus, larger randomized controlled trials could better define the role of Anakinra in PA.[112]

Systemic lupus erythematosus (SLE)

Despite the paucity of data on IL-1 inhibition in SLE, its pivotal role in the inflammatory cascade may provide the biologic rationale for the use of IL-1 blockers, at least in certain areas such as articular/musculoskeletal involvement. Three patients refractory to conventional treatment received anakinra. The drug was effective in lupus arthritis, while there were no improvements in myositis.[113] Another study on active polyarthritis secondary to SLE revealed, after 3 months of 100 mg/day anakinra, subjective clinical response, reduction of European Consensus Lupus Activity Measurement (ECLAM) score, and a reduction in joint count and CRP in all its four patients. The clinical response was short-lived in two patients, one patient showed remission after treatment and another continued the treatment.[114] The drug was also effective on general symptoms; a patient with increased CRP and recurrent fever, after anakinra treatment, had no more fever and CRP significantly decreased during a follow up of 26 months.[115]

Antiphospholipid antibodies syndrome

A patient with primary aPLA syndrome, after treatment with anakinra 100 mg daily for the onset of relapsed pericarditis refractory to conventional therapies, showed symptoms of improvement after 2 weeks and the disappearance of the strong positivity of aPLA too, confirmed repeatedly during quarterly follow-up. The physiopathogenetic mechanism that binds the IL-1 blockage to the disappearance of above autoantibodies remains poorly understood. The hypothesis is that blocking the activity of IL-1 could determine an increase in regulatory T-cells which can suppress the production of autoantibodies by B-cells, containing the production of antiphospholipid antibodies (aPLA) too.[116]

Sjogren asthenia and dry eye

A randomized, double-blind, placebo-controlled study was conducted to assess the effectiveness of anakinra on asthenia in Sjogren's syndrome. The hypothesis that IL-1 could participate, at the level of the central nervous system, in the genesis of asthenia associated with Sjogren's syndrome, moved the basis of this study. Although there was no reduction in significant asthenia after anti-IL-1 treatment, there was more than a 50% reduction in post-hoc fatigue in a statistically higher number of patients treated with anakinra than in the placebo group.[117] A study documented the effectiveness of topical treatment with anakinra 2.5% in patients with Dry Eye Syndrome, pointing out the role of IL-1 which recalls and activates inflammatory cells, stimulates the production of other cytokines and thus participates to the production of ocular surface inflammation.[118] A subsequent randomized, double-controlled, placebo-controlled study showed no positive results after a single intravenous dose of canakinumab in patients with dry eye.[119]

Polymyalgia rheumatica

The role of IL-1 and its blockage with IL-1 inhibitors is poorly understood. A single-blinded, double-dummy, randomized, active-controlled, parallel-group study was conducted to assess the effects of canakinumab compared to prednisone in patients with newly onset untreated polymyalgia rheumatica. Patients treated with prednisone had quick and meaningful responses to pain, and one patient got a full response, while patients treated with canakinumab had only partial responses. However, patients treated with biologics switched to glucocorticoids, requiring reduced doses.[120]

Giant-cell arteritis (GCA)

IL-1β is highly expressed in inflamed arterial walls of patients with giant cell arteritis and may

contribute to the pathogenesis of this disease; in addition, GCA patients showed high levels of IL-1. Case reports showed the positive response of two out of three patients refractory to multiple therapies. Anakinra yielded improvements in inflammation biomarkers and/or in symptoms, as well as a disappearance of arterial inflammation in PET/CT in two of the three patients; it also had steroid sparing effect.[121]

Urticarial vasculitis

Urticarial Vasculitis is a chronic disease characterized by recurrent attacks of urticaria and histopathological leukocytoclastic vasculitis. Often, the lesions are joined with burden, pain or pruritus, but also joint pain, gastrointestinal and pulmonary involvement. The use of IL-1 inhibitors is based on the hypothesis that IL-1 participates in the vascular inflammation process. In a refractory patient with non-complementary Urticarial Vasculitis (NUV), after 2 weeks of daily anakinra treatment, the symptoms resolved. It was decided to administer anakinra on alternate days, with the reappearance of urticaria and fever; so daily therapy was restored with lasting remission; disappearance of fever, urticaria, and reduction of inflammatory markers.[122] Canakinumab was studied on 10 patients with NUV assessing its effects on symptoms, quality of life, inflammatory markers. All factors improved after administration of a single dose of canakinumab, although not all patients had a complete symptom control.[123]

Pericarditis

Pericarditis is a debilitating condition that results from profound inflammation of the pericardial tissue. Between 10% and 15% of first episodes of acute pericarditis are followed by several episodes refractory to conventional therapy (high-dose non-steroidal anti-inflammatory drugs, colchicine, and systemic corticosteroids, each associated with potentially severe toxicities too). The causes of pericarditis vary widely and most cases are considered idiopathic recurrent pericarditis (IRP). Anakinra was highly effective in treating IRP.[124–126] Its impressive effectiveness is due to the autoinflammatory pathogenesis, in which IL-1 (in particular IL-1β) plays a pivotal role. Pericarditis is initiated by an irritant itself or by the release of necrotic cellular debris and then amplified through the activation of the Nod-like receptor 3 (NLRP3) inflammasome. This process leads to the intensification of the inflammatory response through the release of mature IL-1β.[127] The presence of pro-inflammatory cytokines in the pericardial fluid supports this hypothesis. Moreover, IRP can be associated with a procession of symptoms such as fever, myalgias, arthralgias, polyserositis, increased inflammatory markers, with a remitting chronic trend similar to those of autoinflammatory diseases, like FMF and TRAPS. The effectiveness of anti-IL-1 drugs in treating pericarditis associated with autoinflammatory and autoimmune rheumatic diseases is well known.[128,129]

The use of anakinra and canakinumab has also been considered in other diseases such as urticarial,[130–132] suppurative hidradenitis,[133–138] pyoderma gangrenosum,[139–147] panniculite neutrophila,[148] sweet syndrome.[149,150]

Conclusions

Anti-IL-1 drugs are successfully used off-label in a wide variety of rheumatological diseases, suggesting the important role of IL-1 in their pathogenesis. Off-label prescription is crucial in clinical settings when therapies are limited or research is scarce. The problems arising from the use of off-label drugs in clinical practice are the difficulty to define the optimal dosage or the duration of treatment, the patient population, as well as the high costs. Therefore, since the majority of these are low-prevalence diseases, it would be necessary to obtain evidence from multicenter national and international studies in order to assess their effectiveness and safety.

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