

# The journey of canakinumab; on- and off-label indications

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## Abstract

The role of interleukin-1 (IL-1) has been studied in many diseases, ranging from auto-inflammatory diseases to malignancies, and much has been discovered. There are currently four IL-1 inhibitors available, but only two have been approved in Europe: the receptor antagonist anakinra, and the IL-1b selective inhibitor canakinumab. The aim of this paper is to summarize the on- and off-label use of canakinumab (ILARIS®).

## Introduction

In the 1940s, there were few people who could have imagined that biology, medicine, and the treatment of inflammatory diseases would have been revolutionized by the discovery of an endogenous fever-inducing protein that would have been successively called *granulocyte*, *leukocytic*, *endogenous pyrogen*, *lymphocyte activation factor* and finally (in 1979) interleukin (IL)-1.<sup>1-7</sup> The IL-1 family

belongs to the innate immune system and has 11 members: seven pro-inflammatory agonists (IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-33, and IL-36 $\alpha$ ,  $\beta$  and  $\gamma$ ) and four antagonists with anti-inflammatory activity (IL-1 receptor [IL-1R] antagonist [IL-1RA], IL-36R antagonist (IL-36RA), IL-37, and IL-38). IL-1-mediated inflammation has now been detected in diseases ranging from auto-inflammatory diseases to rheumatoid arthritis (RA), gout, cardiometabolic diseases and malignancies.

Given their greater biological activity, the most widely studied members of IL-1 family are IL-1 $\alpha$  and IL-1 $\beta$  which, although encoded by different genes, both bind to IL-1R1. The precursor of IL-1 $\alpha$  is an alarmin present in the epithelial layers of the gastrointestinal tract, lung, liver, kidney and endothelial cells that is fully active and is released by necrotic cells.<sup>8,9</sup> In addition, active monocytes present a membrane form of IL-1 $\alpha$ . Circulating IL-1 $\alpha$  is contained in apoptotic bodies released by endothelial cells,<sup>10</sup> whereas IL-1 $\beta$  is mainly produced by hematopoietic cells (blood monocytes, tissue macrophages and dendritic cells) in response to Toll-like receptor (TLR)-activated complement components, or by endogenous cytokines such as TNF- $\alpha$  and IL-1 itself.<sup>5</sup> It is this self-sustained induction that is the key to auto-inflammation.

The precursor of IL-1 $\beta$  is inactive and requires caspase-1 cleavage before the active cytokine is released into extra-cellular space and binds to the same receptor as IL-1 $\alpha$  (IL-1R1). This interaction starts a complex signaling cascade that leads to biological events ranging from the activation of the acquired immune system to the induction of fever,<sup>11</sup> a process that is highly regulated at different levels to prevent uncontrolled IL-1-mediated inflammation (Figure 1).

More precisely, numerous pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) activate the inflammasome, an intracellular protein complex. A wide variety of mechanisms seem to be involved in this activation, including potassium efflux secondary to ATP-gated channels, reactive oxygen species (ROS), and membrane perturbation. The inflammasome then activates caspase-1, which cleaves pro-IL-1 $\beta$  to its active form before it is released into extra-cellular space, where it binds to its receptor and initiates an inflammation cascade. There are numerous points along this pathway that can be targeted to inhibit IL-1-mediated inflammation: specific inflammasome triggers and components, common activation mechanisms, caspase 1, IL-1 $\beta$  release, the interaction between IL-1 $\beta$  and its receptor, and IL-1R signaling transduction.

Recent carcinogenetic findings have revealed that IL-1 is an important element in cancer-related inflammation. IL-1 $\beta$  correlates with tumor angiogenesis and metastatic spread as IL-1 $\alpha$ -deficient or wild-type mice develop more tumors than mice deficient in IL-1 $\beta$ . Clinical trials of IL-1 inhibitors have led to encouraging results in cachectic patients with terminal colon cancer and patients with lung cancer.<sup>12-16</sup>

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Key words: IL-1 $\beta$ ; inflammation; interleukin 1; rheumatic disease; IL-1 inhibitors; auto-inflammatory disease; CAPS; TRAPS; biological therapies; familial Mediterranean fever; adult-onset Still disease; SJA; HIDS; pregnancy.

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## Canakinumab

Blocking IL-1 has allowed much to be discovered about its role in inflammation, and the reduction of IL-1 activity has changed the natural course of many inflammatory and non-inflammatory diseases such as type 2 diabetes and atherosclerosis.<sup>16-21</sup> Four IL-1 inhibitors are currently available, but only two have been approved in Europe: the receptor antagonist anakinra (ANA) and the selective IL-1b inhibitor canakinumab (CAN), a human monoclonal antibody that has a high degree of affinity to human IL-1 $\beta$ , is highly species-specific, and does not bind to any other member of the IL-1 family.<sup>22</sup> CAN is excreted by means of intra-cellular catabolism (it has a half-life of 26 days), with little or no renal or biliary excretion. Its high affinity and specificity to IL-1 $\beta$ , makes it very suitable for therapeutic purposes, and its biological activity has been evaluated *in vitro* and in animal models. A mouse model of joint inflammation<sup>23</sup> has shown that it protects against severe joint destruction and bone erosions,<sup>24</sup> and completely suppresses IL-1 $\beta$ -mediated joint inflammation and cartilage destruction.<sup>24,25</sup>

Marketed by Novartis under the trade name of ILARIS<sup>®</sup>, it is approved in more than 70 countries, including the European Union and the United States. The approved doses and regimens vary, with weight-based dosing being used in patients aged as young as two years and others with a low body weight; the highest approved doses are for patients with systemic juvenile idiopathic arthritis (SJIA), who receive 4 mg/kg (up to a maximum of 300 mg) every four weeks.

CAN is approved in Italy for the treatment of cryopyrin-associated periodic syndromes (CAPS), tumor necrosis factor receptor-associated

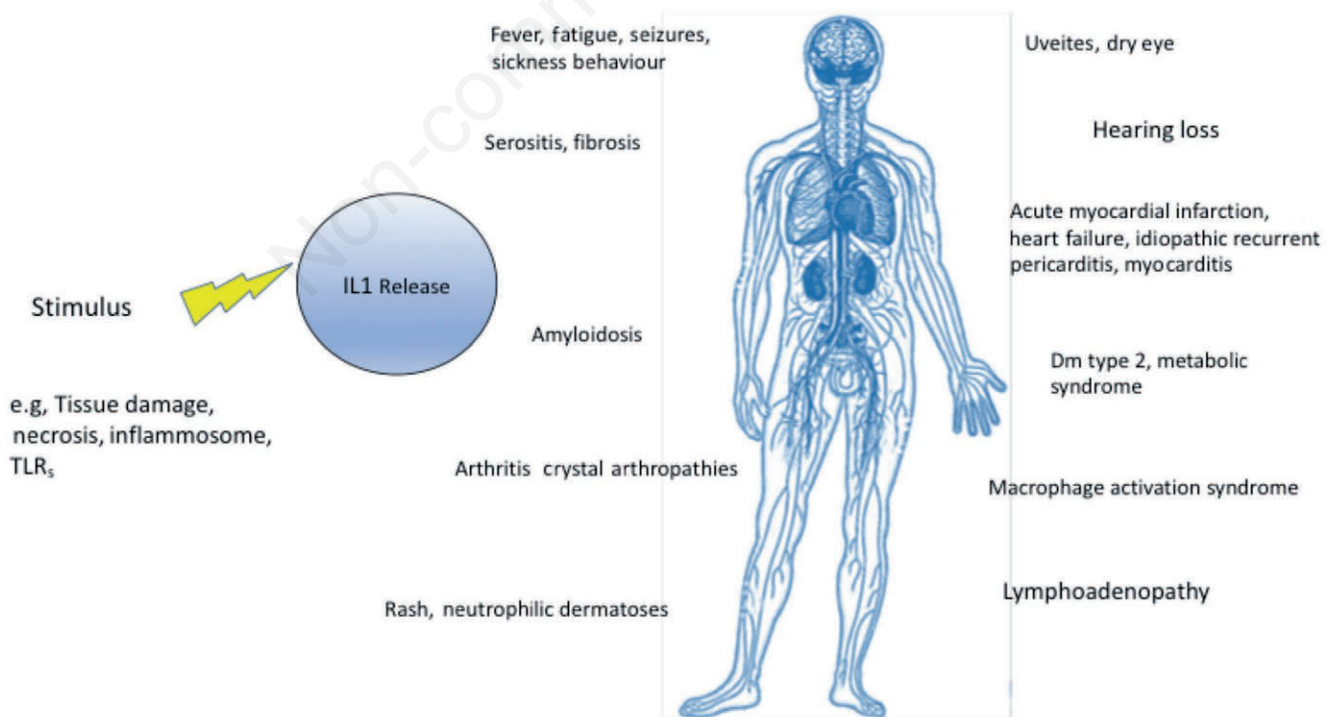
periodic syndrome (TRAPS), hyperimmunoglobulinemia D syndrome/mevalonate kinase deficiency (HIDS/MKD), familial Mediterranean fever (FMF), gout, and adult-onset Still's disease (AOSD). The treatment of all of these indications except gout is reimbursed by the Italian national health service (Figure 2).

## Canakinumab for auto-inflammatory disorders

### Cryopyrin-associated periodic syndromes

CAN is approved for the treatment of cryopyrin-associated periodic syndromes (CAPS) in more than 40 countries. Cryopyrin (more frequently known as NLRP3) is a composite term describing the causative pyrin protein and the fact that the syndrome's clinical manifestations are triggered by exposure to cold.<sup>26-28</sup> CAPS refer to a continuum of three rare hereditary diseases with overlapping clinical phenotypes that are caused by single point mutations in the *NALP3/CIAS1* gene: their severity ranges from the mildest form of familial cold auto-inflammatory syndrome (FCAS), to Muckle-Wells syndrome (MWS), and the most severe neonatal-onset multi-inflammatory disease (NOMID) or chronic, infantile, neurological, cutaneous, articular (CINCA) syndrome. Their common characteristics are recurrent episodes of urticarial rash, fever and arthritis, but patients with Muckle-Wells syndrome may also experience progressive hearing loss or reduced kidney function due to secondary amyloidosis, and NOMID is also characterized by body rashes, joint destruction, hearing loss, and chronic sterile cerebral inflammation.

Studies have demonstrated that a complete clinical response to



**Figure 1. Interleukin (IL)1-mediated clinical manifestations.** TLR, Toll-like receptor; DM, diabetes mellitus. Modified from Cavalli G, Dinarello CA. Anakinra Therapy for Non-cancer Inflammatory Diseases. *Front Pharmacol* 2018;9:1157, doi: 10.3389/fphar.2018.01157.

CAN leads to rapidly improving symptoms and a reduction in Inflammatory markers (C-reactive protein [CRP] and serum amyloid-A [SAA]) within a few days. There are also fewer injection site reactions compared to those observed with the use of ANA.<sup>29</sup>

A phase II open-label study involving pediatric patients with CAPS found that a subcutaneous CAN dose of 2 mg/kg (for those with a body weight of  $\leq 40$  kg) or 150 mg (for those with a body weight off  $>40$  kg) led to a complete response within seven days in all cases (no or minimal disease activity and rash, and serum CRP and/or SAA levels within the normal range of  $<10$  mg/L). The improvement in symptoms occurred within 24 hours from the first dose. CAN was well tolerated: there was only one serious adverse event (vertigo), but it resolved during treatment.<sup>29</sup>

The ENVOLV study<sup>30</sup> found that CAN led to a marked reduction in healthcare consultations and the need for support from caregivers.

The approved CAN starting doses for CAPS patients are 150 mg in those with a body weight of  $>40$  kg, and 2 mg/kg in those with a body weight of  $\geq 15$  kg and  $\leq 40$  kg, both administered as a single subcutaneous dose every eight weeks.<sup>31,32</sup>

### Tumor necrosis factor receptor-associated periodic syndrome

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disorder caused by mutations in TNF receptor type 1 (TNFR1 or TNFRSF1A);<sup>33</sup> its clinical features are recurrent fever, rash, arthralgia, myalgia, and serositis.<sup>34</sup> The mutations disable the correct insertion of the receptor into the cell membrane, and the accumulation of mutated receptors inside the cells leads to an increase IL-1 levels as a result of the activation of ROS and other pathways.<sup>35,36</sup> The clinical efficacy of CAN is explained by the key role of IL-1 $\beta$  rather than TNF in the pathogenesis of TRAPS. Case studies and an open-label, single-arm, international multicenter phase II trial have demonstrated complete or nearly complete responses to CAN treatment.<sup>37</sup>

In a study Gattorno observed 20 patients aged 7-78 years

treated with CAN 150 mg or 2 mg/kg (for those weighing  $\leq 40$  kg) every four weeks for four months, after which the treatment was withdrawn for up to five months; upon relapse, treatment was resumed every four weeks and then every eight weeks for 24 months. Nineteen patients achieved the primary efficacy endpoint of a rapid response, with a median time to clinical remission of four days. All of the patients relapsed after CAN was withdrawn, with a median time to relapse of 91.5 days. The clinical and serological responses to the resumption of CAN were similar to those observed during the first period of treatment, and were sustained until the end of the study. CAN was well tolerated, and the clinical responses were accompanied by a rapid and sustained improvement in the patients' health-related quality of life. The most frequent adverse events were nasopharyngitis, abdominal pain, headache and oropharyngeal pain; they were all mild and none required treatment discontinuation. Seven patients experienced serious adverse events (pericarditis, abdominal pain, diarrhea, intestinal obstruction, vomiting, upper respiratory tract infection, meniscus injury, hypertriglyceridemia, hyperkalemia, foot deformity) but none were suspected to be drug related. There were no meaningful changes in laboratory data or vital signs, and no neutralizing anti-CAN antibodies were identified.<sup>38</sup>

This study substantially confirmed previous data.<sup>39</sup>

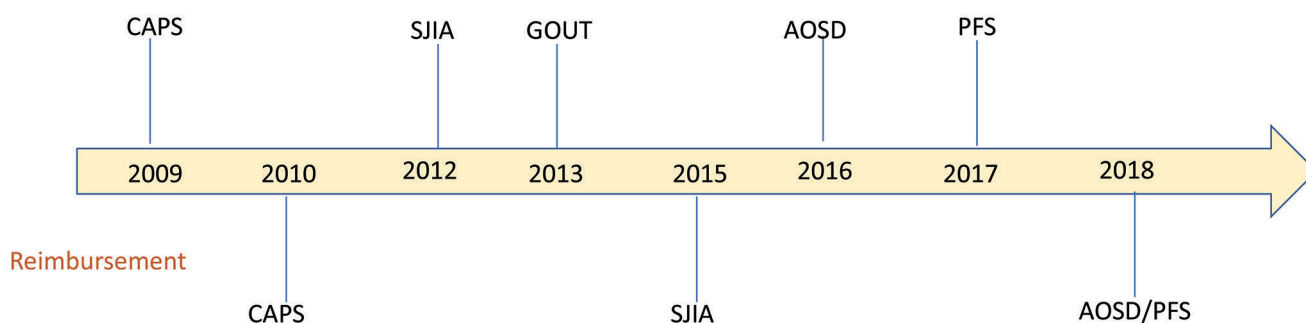
### Hyperimmunoglobulinemia D syndrome

Recurrent fever, myalgia, skin rash, gastrointestinal symptoms, lymphadenopathy, splenomegaly, arthralgia, pharyngitis, aphthosis are some of the features of mevalonate kinase (MVK) deficiency or hyperimmunoglobulinemia D syndrome (HIDS), an autosomal recessive auto-inflammatory disorder related to mutations in the *MVK* gene. MVK deficiency deregulates the release of IL-1.

The efficacy and safety of CAN in HIDS patients are supported by observational registries, some case reports and two clinical trials,<sup>40</sup> although some data suggest the need for a higher dose or shorter dosing interval to achieve and maintain complete clinical and laboratory responses in comparison with other auto-inflammatory disorders.<sup>41</sup> The reported adverse events have been mild.

## TIMELINE OF EMA APPROVAL AND REIMBURSEMENT IN ITALY

### APPROVAL



AOSD = ADULT ONSET STILL DISEASE SJIA=SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS  
CAPS=CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES PFS=PERIODIC FEVER SYNDROME

Figure 2. The timeline highlights the years of European Medicines Agency (EMA) approval and Italy reimbursement of canakinumab in all indications.



## Familial Mediterranean fever

The most frequent hereditary auto-inflammatory syndrome is familial Mediterranean fever (FMF), which is caused by mutations in the *MEFV* gene that encodes the pyrin protein involved in regulating IL-1 $\beta$ . It is characterized by recurrent attacks of fever and serositis, and may be complicated by amyloidosis if left untreated. The mainstay of treatment is colchicine, but 10-20% of patients fail to respond or cannot tolerate colchicine and the European League Against Rheumatism (EULAR) recommend anti-IL-1 drugs in second line<sup>41</sup> as they have proved to be effective in treating colchicine-resistant FMF patients and improving their quality of life.<sup>42,43</sup> One case series and two trials suggest that anti-IL-1 treatment prevents the progression of FMF-associated amyloidosis,<sup>41,44,45</sup> and a recent study has investigated its effects on the quality of life. This study enrolled a total of 44 patients who received ANA 100 mg/day or CAN 150 mg/month and were monitored for the frequency, duration and severity of attacks. Laboratory and SF-36 parameters were compared before and after treatment, and the patients recorded their global assessments using a visual analogue scale (VAS). Both groups experienced significant improvements in physical function, role limitations due to physical difficulties and emotional problems, emotional well-being, social function, pain and overall health.<sup>46</sup>

Many studies have demonstrated that CAN leads to rapid, sustained and complete disease control in FMF patients,<sup>47-49</sup> making it the first and only biological FMF treatment option approved and reimbursed in Italy.

The phase III Canakinumab Pivotal Umbrella Study evaluated the efficacy and safety of CAN in 63 patients with colchicine-resistant FMF, 46 with TRAPS, and 72 with MVK deficiency. The primary endpoint of the resolution of index flares by day 15 with no new flares during the 16 weeks of treatment was achieved by all three disease cohorts. CAN 150 mg was found to be superior to placebo in all cases, with 55% more responders to CAN in the FMF cohort. Up-titration to 300 mg every four weeks in patients inadequately responding to the initial dose improved flare control. There were no opportunistic infections, cases of tuberculosis or deaths. The most frequent adverse events were infections (particularly respiratory infections), abdominal pain, headaches and injection site reactions.<sup>49</sup>

## Adult-onset Still's disease and systemic juvenile idiopathic arthritis

There is evidence suggesting that Adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) are not distinct entities but different manifestation of the same disease occurring at different ages.<sup>50-51</sup> The current treatments for SJIA include non-steroidal anti-inflammatory drugs, glucocorticoids, synthetic disease-modifying anti-rheumatic drugs (DMARD) and biological DMARDs inhibiting IL-6 and IL-1. The efficacy and safety of CAN in patients with SJIA has been demonstrated in an extension of a phase III trial, which documented a rapid and marked improvement in the patients' condition that was maintained for up to five years.<sup>51</sup> Furthermore, the majority of patients can have their glucocorticoid treatment discontinued (44%) or tapered. The limited therapeutic benefit of methotrexate (MTX) in SJIA has been confirmed by the similar response rates of CAN-treated patients regardless whether or not they were also taking MTX. Therefore, it cannot be expected that the combination of CAN and MTX would

offer any advantage over CAN alone. An early response to CAN correlates with a more favorable long-term outcome, and no new adverse event has been associated with the long-term use of CAN.<sup>49</sup>

On the basis of the concept that SJIA and AOSD are manifestations of the same underlying disease,<sup>50</sup> the European Medicines Agency (EMA) approved the use of CAN in the treatment of AOSD in 2016. Feist *et al.* used a population-based pharmacokinetic-binding model of Still's disease to show the comparability of the effects of CAN exposure at all ages,<sup>52</sup> and the largest retrospective observational study of the efficacy and safety of IL-1 inhibitors in AOSD patients confirmed the efficacy of anti-IL-1 treatment.<sup>53</sup>

The recommended dose in patients with a body weight of >7.5 kg is 4 mg/kg (up to a maximum of 300 mg) every four weeks.

## Gout

Gout is the most frequent form of arthritis in adults and the fact that it is often associated with co-morbidities can contraindicate the use of conventional therapies. At the start of a flare of acute gout, monosodium urate crystals activate inflammasome NLRP3, thus leading to the release of IL-1 $\beta$  and an inflammatory response with vasodilation and the recruitment of immune cells (particularly neutrophils) at the site of crystal deposition. Knowledge of the role of IL-1 $\beta$  in orchestrating this crystal-induced inflammatory response offered new therapeutic perspective to patients who are refractory to standard treatments or in whom such treatments are contraindicated.

A number of studies have demonstrated the efficacy of anti-IL-1 treatment<sup>54-57</sup> and, in 2013, the EMA approved CAN for the symptomatic treatment of adult patients with frequent gout attacks (at least three in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated or do not provide an adequate response, and in whom repeated corticosteroid cycles are inappropriate.<sup>57</sup>

The recommended dose is 150 mg, to be administered subcutaneously as a single dose during an attack. In order to optimize its effect, the drug should be administered as soon as possible after the onset of the attack. Non-responders should not be re-challenged; responding patients requiring further treatment should leave an interval of at least 12 weeks before re-administration.<sup>57</sup>

## Diabetes, cardiovascular diseases, and malignancies

Early studies showed decreased levels of atherosclerotic plaque in IL-1-deficient mice,<sup>58</sup> and extensive research has demonstrated the role of IL-1 in cardio-metabolic diseases. IL-1 exposure in pigs leads to intimal arterial wall thickening.<sup>59</sup>

A large multicenter, randomized, placebo-controlled clinical trial called the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) has demonstrated that inflammation (especially IL-1 $\beta$ -dependent inflammation) is an independent risk factor for cardiovascular events.<sup>60,61</sup> It involved 10,061 patients with a previous myocardial infarction and persistent inflammation (CRP levels of >2 mg/L) who were randomized to receive CAN at doses of 50 mg, 150 mg or 300 mg every three months. The 150 mg group reached the primary efficacy endpoint of a 15% reduction in the risk of non-fatal

myocardial infarction, non-fatal stroke, or cardiovascular death.<sup>62</sup> Data from a secondary analysis showed an additional 10% reduction in those patients whose CRP levels decreased to <2 mg/L three months after the first administration of CAN.<sup>63</sup>

Another interesting finding of this trial is that CAN reduced cardiovascular events without reducing lipid levels. In a specific subset of patients in whom lipid-lowering therapy is not enough, CAN may therefore be used as a complementary treatment.

An unexpected finding in a *post hoc* safety analysis of CANTOS, was a significantly lower incidence of lung cancer in the 300 mg group,<sup>64,65</sup> and Novartis is now testing CAN in phase III studies of lung cancer patients.

The first studies of possible anti-IL-1 treatments for diabetes used ANA,<sup>66</sup> but multicenter randomized and controlled trials have also shown the clinical efficacy and safety of CAN in patients with diabetes mellitus (DM) type 2<sup>67,68</sup> and, given the significant reduction in hemoglobin A1C levels and improved glycemic control shown in these studies, the incidence of new-onset diabetes was included as a secondary endpoint in CANTOS. However,

although the incidence of DM was higher in those patients with high PCR levels, CAN did not reduce the incidence of DM, thus confirming the multifactorial etiology of the development and progression of the disease.

## Miscellaneous

Table 1 shows case reports of the use of CAN in other conditions.

### Canakinumab during pregnancy

Uncontrolled inflammatory disease carries a potential risk for fertility, embryogenesis and pregnancy outcomes. Pre-term delivery, a low birth weight, and a slight increase in fetal loss and Caesarean sections are associated with poorly controlled FMF,<sup>69</sup> and chronic inflammation is related to reduced male fertility, testicular amyloidosis and azoospermia.

**Table 1. Canakinumab off-label use.**

Canakinumab off-label use	Studies
Schnitzler syndrome	Efficacy and safety of canakinumab in Schnitzler syndrome: A multicenter randomized placebo-controlled study. Krause K, Tsianakas A, Wagner N, Fischer J, Weller K, Metz M, Church MK, Maurer M. <i>J Allergy Clin Immunol.</i> 2017;139:1311-20.
Behçet's disease	The right place of interleukin-1 inhibitors in the treatment of Behçet's syndrome: a systematic review. Bettiol A, Silvestri E, Di Scala G, Amedei A, Becatti M, Fiorillo C, Lopalco G, Salvarani C, Cantarini L, Soriano A, Emmi G. The Presence of Uveitis Is Associated with a Sustained Response to the Interleukin (IL)-1 Inhibitors Anakinra and Canakinumab in Behçet's Disease. Fabiani C, Vitale A, Rigante D, Emmi G, Lopalco G, Di Scala G, Sota J, Orlando I, Franceschini R, Frediani B, Galeazzi M, Iannone F, Tosi GM, Cantarini L. <i>Ocul Immunol Inflamm.</i> 2018 Aug 27:1-7
PAPA	Disease activity accounts for long-term efficacy of IL-1 blockers in pyogenic sterile arthritis pyoderma gangrenosum and severe acne syndrome. Omenetti A. <i>et al.</i> <i>Rheumatology (Oxford)</i> 2016;55:1325-35
Hidradenitis suppurativa	Canakinumab for Severe Hidradenitis Suppurativa: Preliminary Experience in 2 Cases. Houriet C, Seyed Jafari SM, Thomi R, Schlapbach C, Borradori L, Yawalkar N, Hunger RE. <i>JAMA Dermatol</i> 2017;153:1195-7
Macrophage activation syndrome	Refractory Macrophage Activation Syndrome in the setting of Adult Onset Still's Disease with Hemophagocytic Lymphohistiocytosis Detected on Skin Biopsy treated with Canakinumab and Tacrolimus. Chamseddin B, Marks E, Dominguez A, Wysocki C, Vandergriff T. <i>J Cutan Pathol.</i> 2019 Mar 30
Pyoderma gangrenosum	Pyoderma gangrenosum and concomitant hidradenitis suppurativa--rapid response to canakinumab (anti-IL-1β). Jaeger T, Andres C, Grosber M, Zirbs M, Hein R, Ring J, Traidl-Hoffmann C. <i>Eur J Dermatol</i> 2013;23:408-10.
Renal amyloidosis	The experience of canakinumab in renal amyloidosis secondary to familial Mediterranean fever. Sozeri B, Gulez N, Ergin M, Serdaroglu E. <i>Mol Cell Pediatr</i> 2016;3:33
Pericarditis	Canakinumab for recurrent rheumatic disease-associated pericarditis: a case series with long-term follow-up. Kougkas N, Fanouriakis A, Papanopoulos I, Bertsias G, Avgoustidis N, Repa A, Sidiropoulos P. <i>Rheumatology (Oxford)</i> 2018;57:1494-5
Myocardial infarction	Antiinflammatory therapy with canakinumab for atherosclerotic disease. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, <i>et al.</i> <i>N Engl J Med</i> 2017;377:1119-3
Fatigue	Interleukin-1 as a mediator of fatigue in disease: a narrative review Roerink ME <i>et al.</i> <i>Neuroinflammation</i> 2017;14:16

There is only limited clinical experience concerning men and women exposed to IL-1-inhibitors before conception and during pregnancy and breastfeeding, but reassuring data concerning paternal and maternal exposure have been collected in an international multicenter retrospective study of the outcomes of 43 pregnancies exposed to ANA or CAN.<sup>70</sup> Data concerning CAN related to 14 exposed pregnancies (eight cases of maternal and five of previous paternal exposure to one miscarriage) and four newborns breastfed by mothers taking canakinumab. The median follow-up was 18 months (range one week to 10 years). All of the 13 pregnancies reached full term and normal birth weights were recorded; there were no serious adverse events. No growth or developmental abnormalities were observed in the long term [median 24 months, range 6-73 months], and the authors suggested that paternal use of IL-1 antagonists at the time of conception seems to be safe.<sup>70</sup>

CAN is well tolerated during pregnancy but the safety data remain limited. One theoretical concern is the possibility of the placenta-active transport of IgG monoclonal antibodies from gestation week 30 and so, given the prolonged half-life of immunoglobulins in neonates, the EULAR guidelines recommend not to administer CAN after 22 weeks of gestation and totally avoid using it if possible.

### Canakinumab safety

Clinical trials demonstrate the overall safety of CAN, whose good tolerability profile is characterized by very few treatment discontinuations, few injection site reactions, and a marginally increased rate of non-serious upper respiratory tract infections. Vertigo was reported in CAPS patients, but this has no medical significance.<sup>71,72</sup>

A long-term phase III study evaluating the safety and efficacy of CAN in CAPS patients with differently severe phenotypes confirmed its safety and tolerability.<sup>73</sup> The low immunogenic potential of CAN is indicated by clinical studies in which none of the subjects treated developed anti-CAN antibodies.

Table 2 summarizes the most relevant adverse events observed in patients with CAPS, TRAPS, HIDS/MVK, FMF, SJIA, and gout.

### Drug interactions

No drug interaction studies have been published.

Monoclonal antibodies are not metabolized by the cytochrome P450 (CYP) system and their elimination mainly occurs mainly via catabolism. Theoretically, it is not expected that any of the most widely used concomitant medications (paracetamol, NSAIDs, systemic corticosteroids, antibacterial agents, iron supplements) would have any effect on CAN pharmacokinetics, which are known to be unaffected by the co-administration of MTX.<sup>74,75</sup>

However, there are theoretically less obvious interaction pathways. During chronic inflammation, increased levels of pro-inflammatory cytokines suppress the formation of CYP<sup>75,76</sup> and drugs such as CAN that target and neutralize these pro-inflammatory cytokines or their receptors are capable of indirectly restoring CYP enzymes to normal levels,<sup>74</sup> and up-regulated levels can lead to high clearance rates of co-administered drugs that are CYP substrates.

### Long-term remission of systemic juvenile idiopathic arthritis

Only one study has evaluated the maintenance of treatment responses by reducing the dose of Ilaris<sup>®</sup> or extending the dosing interval in patients with SJIA who were being treated with Ilaris<sup>®</sup> 4 mg/kg every four weeks. Seventy-five patients aged 2-22 years with inactive disease for at least six consecutive months (clinical remission) as a result of treatment with CAN alone (including some who had discontinued concurrent corticosteroid and/or MTX treatment for at least four weeks) were randomized to receive Ilaris<sup>®</sup> 2 mg/kg every four weeks or Ilaris<sup>®</sup> 4 mg/kg every eight weeks. After 24 weeks, 71% of the patients who had received 2 mg/kg every four weeks and 84% of those who had received 4 mg/kg every eight weeks maintained their inactive disease status.

**Table 2. Summary of adverse events (data from Ilaris<sup>®</sup> Summary of Product Characteristics).**

System	Adverse event
<i>Infections and infestations</i>	
Very common	Respiratory tract infection (cellulitis, pharyngitis, sinusitis cellulites, influenza), ear infection, urinary tract infection, gastroenteritis, nasopharyngitis viral infection
<i>Nervous system disorders</i>	
Common	Dizziness/vertigo
<i>Gastrointestinal disorders</i>	
Common	Abdominal pain (upper)
Uncommon	Gastro-esophageal reflux disease
<i>Skin and subcutaneous tissue disorders</i>	
Common	Injection site reaction
<i>Musculoskeletal and connective tissue disorders</i>	
Very common	Arthralgia
Common	Musculoskeletal pain back pain
<i>Laboratory investigations</i>	
Common	Decreased renal creatinine clearance*, proteinuria <sup>o</sup> , leukopenia
Very common	Neutropenia
<i>General disorders and administration site conditions</i>	
Common	Fatigue/asthenia

\*Based on estimated creatinine clearance; most were transient; <sup>o</sup>from transient traces to 1+ positive urinary protein dipstick assay.

Of the patients in clinical remission who continued with a further dose reduction (1 mg/kg every four weeks) or a further extension of the dosing interval (4 mg/kg every 12 weeks), respectively 93% and 91% maintained their inactive disease status after six months, and were allowed to discontinue Ilaris® treatment. A total of 33% of patients in the dose reduction or interval extension arm discontinued treatment with Ilaris® and maintained their inactive disease status for six months.<sup>77</sup>

## Conclusions

The pharmacological targeting of IL-1 $\beta$  may lead to symptom relief or radically modify the natural course of a number of inflammatory diseases. The currently approved drugs are injectable protein-based *biological* agents that inhibit IL-1 $\beta$  or the IL-1 receptor. The anti-inflammatory CAN human monoclonal antibody has a high affinity to and neutralises the biological activity of human IL-1 $\beta$ .

This review describes the pre-clinical and clinical journey of development of CAN from rare auto-inflammatory genetic diseases to juvenile systemic arthritis, rare periodic fever syndromes, and non-orphan diseases such as myocardial infarction, lung cancer and gout.

The dose-response efficacy of CAN was first demonstrated in a small number of patients with four rare, mainly chronic, auto-inflammatory genetic disorders characterized by an overactive IL-1 $\beta$  pathway (CAPS). This initial dose-response model was then used to design a single phase III clinical trial involving patients with HIDS, TRAPS or colchicine-resistant FMF, all of which are characterized by an irregular flare pattern that makes very difficult to establish a dose-pharmacodynamic relationship *de novo*.

CAN has also been tested in small studies of Behçet's disease, chronic obstructive pulmonary disease, type I diabetes, heart failure, pyoderma gangrenosum, sarcoidosis, Schnitzler's syndrome, and urticarial vasculitis.

The CAN development program has so far been a remarkably successful 20-year journey and who can say when or where it will come to an end?

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