UNDERSTANDING AND IDENTIFYING AUTOINFLAMMATORY DISEASES

Learn more about the impact of IL-1β on autoinflammatory diseases such as Still's disease and Periodic Fever Syndromes, and which tools can help with diagnosis.

IL, interleukin.

INDICATIONS

ILARIS® (canakinumab) is an interleukin-1β blocker indicated for the treatment of the following autoinflammatory Periodic Fever Syndromes:

- Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and pediatric patients 4 years of age and older, including:
  - Familial Cold Autoinflammatory Syndrome (FCAS)
  - Muckle-Wells Syndrome (MWS)
- Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients
- Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients
- Familial Mediterranean Fever (FMF) in adult and pediatric patients

ILARIS is indicated for the treatment of active Still's disease, including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years of age and older.

ILARIS is indicated for the symptomatic treatment of adult patients with gout flares in whom nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ILARIS is contraindicated in patients with confirmed hypersensitivity to canakinumab or to any of the excipients.

WARNINGS AND PRECAUTIONS

Serious Infections

ILARIS has been associated with an increased risk of serious infections. Exercise caution when administering ILARIS to patients with infections, a history of recurring infections or underlying conditions, which may predispose them to infections.
Avoid administering ILARIS to patients during an active infection requiring medical intervention.
Discontinue ILARIS if a patient develops a serious infection.

Please see additional Important Safety Information throughout and full Prescribing Information, including Medication Guide, for ILARIS.

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(canakinumab)
150 mg subcutaneous injection

Key elements can help differentiate autoinflammatory and autoimmune diseases

Though frequently mistaken for one another, autoinflammatory and autoimmune diseases are different[1-7]

Autoinflammatory diseases

- Mediated by the **innate** immune system
- **IL-1β, in addition to IL-6, IL-18, and TNF**, is a critical driver of autoinflammatory disease

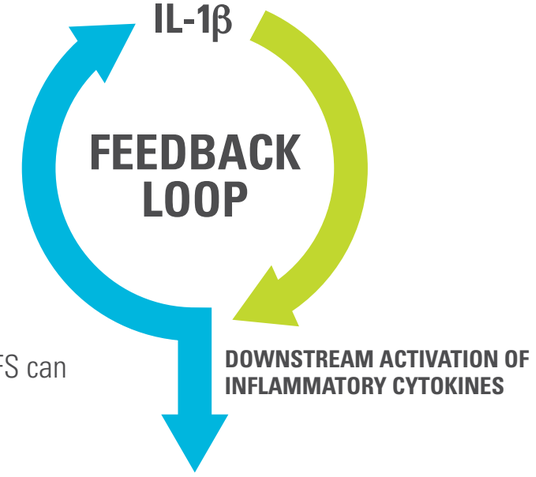
Autoimmune diseases

- Mediated by the **adaptive** immune system
- **IFN-γ and IL-17** are the drivers of autoimmune diseases

In certain autoinflammatory diseases, there is an excessive release of activated IL-1β[3,5,8]

This overabundance can[5,9-11]**:**

- Cause an **inflammatory cascade**
- Trigger a **feedback loop**, inducing the production of even more IL-1β



The inflammatory cascade in Still's disease and PFS can drive **fever and systemic inflammation.**[5,8,12-15]

IFN, interferon; PFS, periodic fever syndromes; TNF, tumor necrosis factor.

An excess of IL-1β contributes to these rare autoinflammatory diseases

Still's Disease[5,16]

SJIA: Systemic Juvenile Idiopathic Arthritis	**AOSD:** Adult-onset Still's Disease

PFS[2,3,5]

FMF: Familial Mediterranean Fever	**HIDS/MKD:** Hyperimmunoglobulin D Syndrome/ Mevalonate Kinase Deficiency
TRAPS: Tumor Necrosis Factor Receptor–associated Periodic Syndrome	**CAPS:** Cryopyrin-associated Periodic Syndrome **FCAS:** Familial Cold Autoinflammatory Syndrome **MWS:** Muckle-Wells Syndrome

Common features of these autoinflammatory diseases include[17-20]**:**

- **Fever**
- **Rash**
- **Arthritis/ Arthralgia**
- **High inflammatory markers**

Similarities in symptoms and features among autoinflammatory diseases and with other conditions can result in misdiagnosis or a delay in diagnosis.[17,18,20,21]

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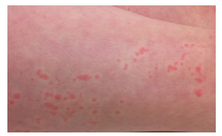
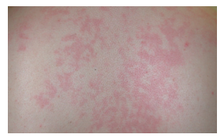
SJIA and AOSD, which often present similarly, are the juvenile and adult forms of Still's disease[14,16-18]

- In patients **younger than 16 years**, Still's disease is called SJIA (typical age of onset is 1 to 5 years old)
- In patients **16 years of age and older**, Still's disease is called AOSD (typical age of onset is 16 to 35 years old)

Recognizing the most common signs and symptoms—a triad of fever, rash, and arthritis/arthralgia—can help identify Still's disease[17,18]

	SJIA[17]	AOSD[18]
Fever	• Occurs daily or twice daily • Temperature can spike to ≥39 °C (≥102.2 °F) with a return to normal or to below baseline temperature	• Occurs daily or twice daily, lasting <4 hours • Temperature can spike to ≥39 °C (≥102.2 °F)
Rash	 • Transient, salmon colored, macular or maculopapular • Typically found on the trunk, neck, and proximal extremities	 • Evanescent, salmon-pink colored, maculopapular • Typically found on the trunk and proximal extremities
Arthritis/ Arthralgia	• Can range from oligoarticular to polyarticular patterns • Primarily affects wrists, knees, and ankles	• Arthritis may be symmetrical with most developing polyarthritis with fever spikes • Primarily affects wrists, knees, and ankles

Rash images credits: Courtesy of Pr Isabelle Koné-Paut (SJIA), DermNetNZ.org (AOSD).

Detailed classification criteria: SJIA and AOSD

Diagnosing SJIA Based on the ILAR Classification Criteria[22,23]

ARTHRITIS AFFECTING ≥1 JOINTS FOR ≥6 WEEKS

With or preceded by +

FEVER FOR ≥2 WEEKS OCCURRING DAILY FOR ≥3 DAYS

Plus 1 or more of the following +

1. **Evanescent (nonfixed) erythematous rash**
2. **Generalized lymphadenopathy**
3. **Hepatomegaly and/or splenomegaly**
4. **Serositis**

Exclusion criteria for ILAR[22]:

- Psoriasis or a history of psoriasis in the patient or first-degree relative
- Arthritis in male aged >6 years who is HLA-B27 positive
- Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative
- The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart

Common laboratory abnormalities[17]:

- Highly elevated inflammatory markers such as ESR and CRP are usually present in patients with SJIA

Diagnosing AOSD Based on the Yamaguchi Criteria[24]

(Requires ≥5 Criteria, Including ≥2 Major Criteria)

Major criteria[24]:

1. Fever ≥39 °C (≥102.2 °F) lasting for ≥1 week
2. Arthralgia for ≥2 weeks
3. Macular or maculopapular, nonpruritic salmon-pink–colored rash
4. Leukocytosis (≥10,000/microL), including 80% more of granulocytes

Minor criteria[24]:

1. Sore throat
2. Lymphadenopathy and/or splenomegaly
3. Abnormal liver function tests
4. Negative tests for rheumatoid factor and antinuclear antibody

Exclusions[24]:

- Infections
- Malignancies
- Rheumatic diseases

Several common laboratory abnormalities include[18,24]:

- Elevated ESR and CRP
- Leukocytosis
- Thrombocytosis
- Elevated ferritin levels, 5x upper limit of normal
  — Glycosylated ferritin is an important marker—in patients with AOSD, glycosylation of ferritin is often <20%

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IgM, immunoglobulin M; ILAR, International League of Associations for Rheumatology.

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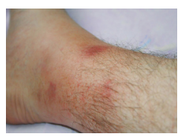
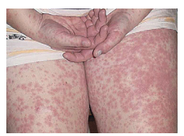
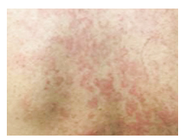
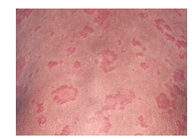
These PFS are hereditary and can emerge from early childhood to adulthood[19]

	FMF[2,19,20,25-28]	HIDS/MKD[2,19,20,25,29,30]
Predominant ethnic distribution	Turkish, Armenian, Arab, Jewish, Italian	Dutch or Northern European
Worldwide prevalence or number of cases	1 to 5 in 10,000	>180
Typical age at onset	<20 years	<1 year
Duration of attacks	12 hours to 3 days	3 to 7 days
Frequency of attacks	Irregular; once per week to once every 5 to 10 years	Irregular; 2- to 8-week intervals
Gene mutation	MEFV	MVK
Inheritance	Autosomal recessive	Autosomal recessive
		
Cutaneous findings	• Erysipelas-like erythema • Characterized by red, warm, and swollen areas • Lesions are tender to the touch, can be 10 cm to 15 cm in diameter, and usually occur below the knee on the anterior leg or top of foot	• Diffuse maculopapular eruption extending to the palms and soles, or nodular, urticarial, or morbilliform • Erythematous macules that are sometimes painful can occur
Other select clinical features	• Abdominal pain • Chest pain • Arthritis/monoarthritis	• Abdominal pain • Lymphadenopathy • Aphthous ulcers
High serology	Increase in CRP, ESR, and SAA	Increase in CRP, ESR, IgD, and SAA

Consider PFS when observing these common disease characteristics[19,20]:

- Fever with temperatures peaking >39 °C (>102.2 °F)
- Rash in varying forms
- Systemic inflammation often with arthralgia/arthritis
- Elevated inflammatory markers

	TRAPS[2,19,20,31-36]	CAPS: FCAS	CAPS: MWS[2,19,20,25,26,37,38]
Predominant ethnic distribution	All ethnicities	Mostly European	
Worldwide prevalence or number of cases	>1000	<1 in 1,000,000*	
Typical age at onset	Varies; <3 years to <20 years	<1 year	<20 years
Duration of attacks	7 to 28 days; nearly continuous in one-third of patients	12 to 24 hours	2 to 3 days
Frequency of attacks	Irregular; 5 weeks to months or years	Variable; triggered by generalized cold exposure	Variable; triggered by cold, stress, and exercise
Gene mutation	TNFRSF1A	NLRP3	
Inheritance	Autosomal dominant	Autosomal dominant	
		
Cutaneous findings	• Erythematous, migratory patch • Often overlies an area of myalgia and migrates together in a centrifugal pattern • Often found on the torso or extremity	• Urticaria-like appearance • Typically raised, erythematous, maculopapular, usually nonpruritic • Described by patients as feeling painful, tight, and/or warm • Severity worsening in the evening • Usually appears on the trunk and limb with individual migratory lesions
Other select clinical features	• Abdominal pain • Musculoskeletal pain • Eye manifestations, such as periorbital edema	• Headache • Arthralgia • Fatigue • Myalgia • Conjunctivitis	• Headache • Arthralgia • Fatigue • Conjunctivitis
High serology	Increase in CRP, ESR, and SAA	Increase in CRP, ESR, and SAA	

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with ILARIS. During clinical trials, no anaphylactic reactions attributable to treatment with canakinumab have been reported. It should be recognized that symptoms of the underlying disease being treated may be similar to symptoms of hypersensitivity. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), characterized by serious skin eruptions, has been reported in patients with autoinflammatory conditions treated with ILARIS. If a severe hypersensitivity reaction occurs, immediately discontinue ILARIS; treat promptly and monitor until signs and symptoms resolve.

Rash images credits: Reproduced with permission from Emedmd.com (FMF). Reproduced from *Annals of the Rheumatic Diseases*, Zhao M, Luo Y, Shen M, et al, vol. 78, page 587, 2019, with permission from BMJ Publishing Group Ltd (TRAPS). Reprinted from *Textbook of Pediatric Rheumatology*, 7th ed, Petty RE et al, Periodic Fever Syndromes and Other Inherited Autoinflammatory Diseases, page 617, 2016, with permission from Elsevier (HIDS/MKD; CAPS).

*Prevalence includes patients with FCAS, MWS, and NOMID.

IgD, immunoglobulin D; MEFV, Mediterranean fever; MVK, mevalonate kinase; NLRP3, NLR family pyrin domain containing 3; NOMID, neonatal onset multisystem inflammatory disease; SAA, serum amyloid A; TNFRSF1A, tumor necrosis factor receptor superfamily member 1A.

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PFS Eurofever/PRINTO classification criteria[39]*

Genetic and clinical variables†

FMF	HIDS/MKD	TRAPS	CAPS
Presence of confirmatory MEFV genotype‡ and at least 1 among the following:	**Presence of a confirmatory MVK genotype‡ and at least 1 among the following:**	**Presence of a confirmatory TNFRSF1A genotype‡ and at least 1 among the following:**	**Presence of a confirmatory NLRP3 genotype‡ and at least 1 among the following:**
• Duration of episodes 1 to 3 days • Arthritis • Chest pain • Abdominal pain	• Gastrointestinal symptoms • Cervical lymphadenitis • Aphthous stomatitis	• Duration of episodes ≥7 days • Myalgia • Migratory rash • Periorbital edema • Relatives affected	• Urticarial rash • Red eye (conjunctivitis, episcleritis, uveitis) • Neurosensorial hearing loss
OR		**OR**	**OR**
Presence of not confirmatory MEFV genotype§ and at least 2 among the following:		**Presence of not confirmatory TNFRSF1A genotype‖ and at least 2 among the following:**	**Presence of not confirmatory NLRP3 genotype‖ and at least 2 among the following:**
• Duration of episodes 1 to 3 days • Arthritis • Chest pain • Abdominal pain		• Duration of episodes ≥7 days • Myalgia • Migratory rash • Periorbital edema • Relatives affected	• Urticarial rash • Red eye (conjunctivitis, episcleritis, uveitis) • Neurosensorial hearing loss

Classification criteria were developed by experienced clinicians and geneticists using a multistep process with statistical analyses. Of the 360 patients randomly selected from the Eurofever Registry, consensus was achieved in 281 patients with MKD, TRAPS, PFAPA, FMF, CAPS, and undefined recurrent fevers. Genetic and clinical variables were reported for FMF, HIDS/MKD, TRAPS, and CAPS.

A patient with (1) evidence of elevation of acute phase reactants (ESR or CRP or SAA) in correspondence to the clinical flares and (2) careful consideration of possible confounding diseases (neoplasms, infections, autoimmune conditions, other inborn errors of immunity) and a reasonable period of recurrent disease activity (at least 6 months) is classified as having hereditary recurrent fever if the criteria are met.

*Currently, no US-based guidelines exist.
†There are 2 sets of validated classification criteria. One set includes genetic and clinical variables shown above. The second set is based solely on clinical criteria to be used as a potential tool to indicate a need for molecular analysis or if genetic testing is not available.
‡Pathogenic or likely pathogenic variants (heterozygous in autosomal dominant diseases, homozygous or in trans [or biallelic] compound heterozygous in autosomal recessive diseases).
§In trans compound heterozygous for 1 pathogenic MEFV variants and 1 VUS, or biallelic VUS, or heterozygous for 1 pathogenic MEFV variant.
‖Variant of uncertain significance (VUS). Benign and likely benign variants should be excluded.

PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; PRINTO, Paediatric Rheumatology International Trials Organisation.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Immunizations

Avoid administration of live vaccines concurrently with ILARIS. Update all recommended vaccinations prior to initiation of therapy with ILARIS. In addition, because ILARIS may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ILARIS.

Canakinumab, like other monoclonal antibodies, is actively transported across the placenta mainly during the third trimester of pregnancy and may cause immunosuppression in the *in utero* exposed infant. The risks and benefits should be considered prior to administering live vaccines to infants who were exposed to ILARIS *in utero* for at least 4 to 12 months following the mother's last dose of ILARIS.

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ILARIS® (canakinumab)
150 mg subcutaneous injection

ILARIS IS INDICATED TO TREAT 8 AUTOINFLAMMATORY DISEASES ACROSS STILL'S DISEASE (SJIA AND AOSD), PFS,* AND GOUT FLARES[40]

- **ILARIS is dosed every 4 weeks in Still's disease, FMF, HIDS/MKD, and TRAPS**
- **ILARIS is dosed once every 8 weeks in CAPS (including FCAS and MWS)**
- **ILARIS is dosed as a single dose at the time of a gout flare**
  - **In patients who require re-treatment, there should be an interval of at least 12 weeks before a new dose of ILARIS may be administered**
- **Injections may be administered by a nurse in the comfort of the patient's home**

*ILARIS is indicated for FMF, HIDS/MKD, TRAPS, and CAPS (including FCAS and MWS).

For more information about ILARIS and to learn about ILARIS Companion, visit **www.ILARISHCP.com**.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Macrophage Activation Syndrome

Macrophage Activation Syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still's disease, and should be aggressively treated. Physicians should be attentive to symptoms of infection or worsening of Still's disease as these are known triggers for MAS. Eleven cases of MAS were observed in 201 SJIA patients treated with canakinumab in clinical trials. Based on the clinical trial experience, ILARIS does not appear to increase the incidence of MAS in Still's disease patients, but no definitive conclusion can be made.

ADVERSE REACTIONS

Serious adverse reactions reported with ILARIS in the CAPS clinical trials included infections and vertigo. The most common adverse reactions greater than 10% associated with ILARIS treatment in CAPS patients were nasopharyngitis, diarrhea, influenza, rhinitis, headache, nausea, bronchitis, gastroenteritis, pharyngitis, weight increased, musculoskeletal pain, and vertigo.

The most common adverse reactions greater than or equal to 10% reported by patients with TRAPS, HIDS/MKD, and FMF treated with ILARIS were injection site reactions and nasopharyngitis.

The most common adverse drug reactions greater than 10% associated with ILARIS treatment in SJIA patients were infections (nasopharyngitis and upper respiratory tract infections), abdominal pain, and injection site reactions.

The most common adverse reactions greater than 2% reported by adult patients with gout flares treated with ILARIS in clinical trials were nasopharyngitis, upper respiratory tract infections, urinary tract infections, hypertriglyceridemia, and back pain.

Please see additional Important Safety Information throughout and full Prescribing Information, including Medication Guide, for ILARIS.

NOVARTIS

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ILARIS® (canakinumab) 150 mg subcutaneous injection