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DISEASE MANAGEMENT

Include rare, treatable IL-1-mediated autoinflammatory diseases in differential diagnosis of chronic or periodic inflammation

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Abstract
Four very rare interleukin (IL)-1-mediated systemic autoinflammatory diseases [cryopyrin-associated periodic syndromes, tumour necrosis factor-associated periodic syndrome, mevalonate kinase deficiency and deficiency of the IL-1 receptor antagonist (DIRA)] can now be definitively diagnosed and effectively treated, potentially transforming patients' quality of life. First-line therapies are three subcutaneously administered IL-1 blockers: anakinra, rilonacept and canakinumab. Anakinra and rilonacept block IL-1α/β and are preferred in DIRA and for neurological or bone symptoms, but canakinumab offers the advantage of monthly or bimonthly injections. Lifelong therapy and monitoring aim to control inflammation, limit consequent organ damage and optimise life quality.

Remember rare systemic autoinflammatory diseases

The mixed bag of systemic autoinflammatory diseases (SAIDs) includes a subgroup of four exceedingly rare interleukin (IL)-1 mediated syndromes, which can now be definitively diagnosed with genetic testing [1]. These SAIDs: cryopyrin-associated periodic syndromes (CAPS); tumour necrosis factor (TNF)-associated periodic syndrome (TRAPS); mevalonate kinase deficiency (MKD); and deficiency of the IL-1 receptor antagonist (DIRA), are diagnosed in fewer than one in a million people [1]. Underdiagnosis, however, is likely, as both knowledge of these SAIDs and the availability of genetic screening are limited [2]. Despite the term "periodic syndrome", the systemic and organ-specific inflammation in all four IL-1-mediated SAIDs is usually constant [3].

Recent advances in genetic testing and pharmacological therapies, particularly biologicals, provide life-changing opportunities for people with IL-1-mediated SAIDs [3]. This article summarises current recommended management of these four syndromes, as reviewed by Cetin Gedik et al. [1], with additional data sourced from the 2021 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) consensus [3] and a literature review by Li et al. [2]. Familial Mediterranean fever, another common IL-1-mediated autoinflammatory disease, is discussed elsewhere [3] and is outside the scope of this article.

Hyperinflammatory effects from various variations

The otherwise inexplicable symptoms characteristic of IL-1-mediated SAIDs stem from unwarranted increases in IL-1β, and IL-1α in DIRA [2]. Despite overlapping symptoms, different gain- or loss-of-function genetic mutations cause the four IL-1-mediated SAIDs (Table 1) [1–3]. Elevated IL-1β results from either its overproduction (CAPS and TRAPS) or reduced immune response inhibition (MVD) [1, 2]. In DIRA, a loss-of-function mutation affects the IL-1 receptor antagonist, leaving unopposed proinflammatory IL-1α and -1β activity [2]. While pathophysiology is not always clear, abnormal inflammasomes play a key role in some IL-1-mediated SAIDs [1].

In suspected IL-1-mediated SAIDs, the diagnostic process, similar for all four syndromes, begins with the basics, but may progress to genetic testing [1, 3]. The starting point is a standard laboratory workup to confirm systemic inflammation and (especially for CAPS [2] and TRAPS) any suspected systemic amyloid A (AA) amyloidosis [1, 3]. Investigations need to assess likely ocular, neurological, skeletal or other organ damage, then

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Table 1 Key characteristics of interleukin-1-mediated systemic autoinflammatory diseases, as reviewed by Cetin Gedik et al. [1] and Romano et al. [3]

SAID	Characteristics
Cryopyrin-associated periodic syndromes	
Subgroups	Range from intermittent mild familial cold autoinflammatory syndrome, through moderate childhood-onset MWS, to almost constant severe early onset NOMID/CINCA
Presentation	Cold/stress-induced episodes, an urticaria-like rash, fever, joint pain and ocular symptoms, often with decreased hearing and arthritis in MWS, and chronic aseptic meningitis and severe neurological and skeletal signs in NOMID/CINCA [1, 3]
Key genetics	Autosomal dominant or de novo GOF mutation in *NLRP3* gene, with de novo mutations more likely in more severe phenotypes [3]
Tumour necrosis factor receptor-associated periodic syndrome, or protein folding disorder [2]	
Presentation	Persistent or recurrent ≥ 7-d fevers, painful, erythematous, migratory rash, periorbital oedema and other ocular symptoms, pain (abdominal, neurological and/or musculoskeletal), ± family history [3]; amyloidosis is often a preceding diagnosis [4]
Key genetics	Autosomal dominant or de novo GOF mutation in *TNFRSF1A* gene [3]
Mevalonic kinase deficiency	
Subgroups	Mild hyperimmunoglobulinaemia D and periodic fever syndrome, and the most severe form of mevalonic aciduria
Presentation	Episodic fevers lasting 4–6 d, severe abdominal pain, diarrhoea and vomiting, usually maculopapular rash, onset in first year of life
	May be triggered by vaccination or other stimuli, and include lymphadenopathy, stomatitis/pharyngitis, arthralgia, arthritis, and, in mevalonic aciduria, severe cognitive impairment and dysmorphic features [3]
Key genetics	Autosomal recessive LOF mutations in *MVK* gene, with large deletions possible [3]
Deficiency of the IL-1 receptor antagonist	
Presentation	Early-onset pustular rash, non-bacterial osteomyelitis, periostitis and nail changes, but rarely flare-associated fever [3]
Key genetics	Autosomal recessive LOF mutations, which may differ between parents, in *IL1RN* gene, with large deletions possible [3]
	Analysis must exclude genes associated with differential diagnoses (e.g. pustular psoriasis or pyrin-associated conditions) [3]

GOF gain-of-function, *IL* interleukin, *LOF* loss-of-function, *MWS* Muckle-Wells syndrome, *NOMID/CINCA* neonatal onset multisystem inflammatory disease/chronic infantile neurologic cutaneous and articular syndrome, *SAID* systemic autoinflammatory disease,

perform genetic testing where warranted (Table 1) [1, 3]. Initial next-generation sequencing is preferred, but Sanger sequencing is an alternative, especially in patients with a family history and/or a presentation very suggestive of these SAIDs [1].

Treat fast and forever to limit lifelong damage

In the absence of a cure, the goals of IL-1-mediated SAIDs therapy (Table 2) are to control disease activity as quickly as possible, limit irreversible organ damage and achieve the best possible quality of life [3]. Treatment should suppress systemic and organ inflammation, be titrated to age-appropriate effect and aim ultimately at remission [3]. Therapy prior to a genetically proven diagnosis may be warranted if there is a strong clinical likelihood of an IL-1-mediated SAID [1].

The current standard of care is a subcutaneous biologic targeting IL-1 (Table 2) [1–3]. Disease severity (or mildness) may determine dosage levels and intervals [3]. Given the rarity and severity of the four conditions, data from randomized controlled trials is limited (Table 2) [1, 2].

In some cases, anakinra (which requires daily injections), then rilonacept (which has a somewhat longer half-life) are preferred, as they block both IL-1α and IL-1β. [1]. Canakinumab, while often still effective [2], blocks only the latter and may not control bone or central nervous system (CNS) disease [11] or be effective in DIRA [1]. Anakinra is potentially advantageous in neurological disease, due to its good CNS penetration [1, 3]. However, in the absence of these specific concerns, canakinumab's monthly or bi-monthly administration is an advantage [3].

Other than these biologics, treatment options for IL-1-mediated SAIDs are limited, although other agents targeting the *CAPS* gene (Table 1), inflammasome activity or the IL-1 receptor are in development [1]. In these SAIDs, disease-modifying antirheumatic drugs are less effective than IL-1 blockers [3]. Non-steroidal anti-inflammatory drugs or short-term glucocorticoid therapy may effectively treat mild disease or brief MKD or TRAPS flares [1, 2].

Table 2 First-line pharmacological options for interleukin-1-mediated systemic autoinflammatory diseases, as reviewed by Cetin Gedik et al. [1] and Romano et al. [3]

Therapy[a,b]	Comments
CAPS	
Canakinumab	In an open-label study, all 19 recipients with moderate-to-severe CAPS responded completely by wk 48 and ≈ 58% of pts had no disease activity at study end (median 109 wks) [5]
	Was effective in 17 children aged ≤ 5 y with CAPS [6], and no ↓ in non-live vaccine efficacy in nine children [1]
	ADEs: infection in all 19 recipients, five of which were severe events [5]; safe in pts aged ≤ 5 y with CAPS [6]
Rilonacept	In an RCT in 47 adults with FCAS or MWS, more rilonacept recipients experienced improved symptoms than PL recipients; serum amyloid A was ↓ [7]
	ADEs: ISRs and URTIs in occurred in > 25% of pts; cough, diarrhoea, hypoaesthesia, nausea, sinusitis, stomach pain and urinary tract infection in 4–9% of pts [7]
	Two severe infections (bronchitis and fatal bacterial meningitis) in rilonacept recipients in RCT and open-label extension [7]
Anakinra	In an open-label study in 43 pts with NOMID aged 0.7–46 y who received anakinra for ≤ 5 y, ↓ were seen in symptoms and inflammatory markers [8]
	Test of anakinra withdrawal led to worsening of symptoms and inflammatory markers, which reversed on anakinra resumption [8]
	Long-term NOMID therapy improved inner ear, eye and CNS symptoms and preserved hearing and visual acuity [9]
	ADEs: arthralgia, fever, headache, ISRs, nasopharyngitis and vomiting in 10–20% of pts in the first 6 mo, plus rash and URTI later [8]
	Well tolerated and safe for ≤ 5 y of therapy in severe CAPS, with serious infections the most common severe event [1]
Tumour necrosis factor receptor-associated periodic syndrome	
Canakinumab	In an RCT including 46 pts aged ≥ 2 y, 45% of canakinumab recipients (vs 8% of PL recipients) responded by wk 16, with improvement sustained in 53% of pts during gradual withdrawal period [2, 10]
	ADEs: most commonly abdominal pain, headache, ISRs and infections; none serious [2, 10]
Mevalonic kinase deficiency	
Canakinumab	In an RCT including 13 pts aged ≥ 2 y with mevalonic kinase deficiency, 35% of canakinumab recipients (vs 6% of PL recipients) responded by wk 16, with improvement sustained in 23% of pts during gradual withdrawal period [2, 10]
	ADEs: most commonly abdominal pain, headache, ISRs and infections; seven events were serious [2, 10]
Deficiency of the IL-1 receptor antagonist	
Anakinra	In a natural history study, all nine pts who received anakinra for ≤ 10 y from age 1 mo to 9 y achieved inflammatory remission during treatment [8]
	ADEs: fever, gastroenteritis, influenza-like illness, rash and URTIs were common, with serious infections in two pts [8]
Rilonacept	In an open-label study in six pts aged 3–6 y, all achieved remission after 6 mo of therapy, which was sustained throughout the 2 y study period [7]
	ADEs: similar to CAPS effects, with URTIs in six children and otitis media, pharyngitis and rhinorrhoea each in three pts [7]

ADEs adverse drug events, *CAPS* cryopyrin-associated periodic syndromes, *FCAS* familial cold autoinflammatory syndrome, *IL* interleukin, *ISRs* injection-site reactions, *mo* month(s), *MWS* Muckle-Wells syndrome, *NOMID* neonatal onset multisystem inflammatory disease, *PL* placebo, *pts* patients, *RCT* randomized controlled trial, *URTI* upper respiratory tract infection, *wk(s)* week(s), *y* year(s), ↓ decrease(s/d)

[a]All administered via subcutaneous injection

[b]Pneumococcal vaccine should be administered before anti-IL-1 targeted therapy

Case series support the use of the TNF-inhibitor etanercept in patients with MKD who cannot access or do not respond to IL-1 blockers, and an open-label study suggests it may also be effective in TRAPS [2]. TNF-inhibitors should be considered whenever IL-1 blockers are unavailable [3]. Anti-IL-6 agents such as tocilizumab are another option, particularly for MKD or TRAPS [1, 2].

Monitor and manage throughout lifetime

IL-1-mediated SAIDs require chronic therapy throughout childhood, adolescence and adult life, ideally through a multidisciplinary team, with transitions carefully managed, especially in adolescence [3]. Aside from monitoring inflammatory markers and hearing and vision loss, clinicians should be alert to signs of other serious organ damage, such as kidney failure from AA amyloidosis, CNS disease or

bone deformities. This is especially relevant for adults with longstanding disease who have not benefited from early IL-1 targeted therapy [3].

The benefits of vaccinations outweigh the risks of MKD or other flares, and they should be administered as normal [3]. Therapy should be continued in the event of a viral illness, to avoid rebound inflammation [3].

Take home messages

- Effective genetic diagnosis of and therapy for very rare IL-1-mediated SAIDs are now available
- Consider these syndromes (CAPS, TRAPs, MVD and DIRA) in the differential diagnosis of children with regular or chronic unexplained fevers and symptoms of aseptic inflammation
- First-line therapy includes three biologics targeting IL-1: anakinra, canakinumab and rilonacept
- Therapy is lifelong, and monitor patients for uncontrolled inflammation and consequent renal, CNS, ocular, auditory and other organ damage

Declarations

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