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The 2021 EULAR/American College of Rheumatology Points to Consider for Diagnosis, Management and Monitoring of the Interleukin 1 Mediated Autoinflammatory Diseases: Cryopyrin-Associated Periodic Syndromes, Tumour Necrosis Factor Receptor-Associated Periodic Syndrome, Mevalonate Kinase Deficiency, and Deficiency of the Intereukin-1 Receptor Antagonist

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All authors contributed to the formulation of the points to consider. In details, the steering committee of the task force (ED, RGM, MG, JBK, HMH, SO, JF, AAD) defined the research questions for the SLR. A systematic literature review was conducted by MR, ZSA, DP with support from a librarian (DH) under supervision of a senior methodologist (ED). MR, ZSA, DP extracted the data. ED, RGM, MG, JBK, HMH, SO, JF and AAD synthesized the results from SLR and the Delphi questionnaires and generated draft statements. The manuscript was drafted by MR, ZSA and DP and revised in detail by the-steering group members and received a final review by the convenors. DA oversaw the proceedings and provided advice of this points to consider project as EULAR methodologist. All other authors participated in the taskforce meetings, in 2 pre-meeting Delphi questionnaires, and suggested and agreed upon the research questions. All members read the final statements prior to the drafting of the manuscript, discussed results and made contributions to the text. All authors approved the final version of the manuscript.

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Abstract

Objective: The Interleukin-1 (IL-1) mediated systemic autoinflammatory diseases (SAIDs), including the cryopyrin-associated periodic syndromes (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), and deficiency of the IL-1 receptor antagonist (DIRA) belong to a group of rare immunodysregulatory diseases that primarily present in early childhood with variable multiorgan involvement. When untreated, patients with severe clinical phenotypes have a poor prognosis, and diagnosis and management of these patients can be challenging. However, approved treatments targeting the pro-inflammatory cytokine IL-1 have been life-changing and have significantly improved patient outcomes. We aimed to establish evidence-based recommendations on diagnosis, treatment, and monitoring to standardize the management of these patients.

Methods: A multinational, multidisciplinary task force consisting of physician experts including rheumatologists, patients or caregivers, and allied health care professionals was established. Evidence synthesis including systematic literature review and expert consensus (Delphi) via surveys were conducted. Consensus methodology was utilized to formulate and vote on statements to guide optimal patient care.

Results: The task force devised five overarching principles, 14 statements related to diagnosis, 10 on therapy, and 9 focused on long-term monitoring that were evidence and/or consensus-based for patients with IL-1 mediated diseases. An outline was developed for disease-specific monitoring of inflammation-induced organ damage progression and reported therapies of CAPS, TRAPS, MKD, and DIRA.

Conclusion: The 2021 EULAR/ACR points to consider represent state-of-the-art knowledge based on published data and expert opinion to guide diagnostic evaluation, treatment, and monitoring of patients with CAPS, TRAPS, MKD and DIRA, and to standardise and improve care, quality of life and disease outcomes.

Keywords

IL-1 mediated autoinflammatory diseases; CAPS; NOMID; MWS; FCAS; TRAPS; MKD; DIRA

INTRODUCTION

Systemic autoinflammatory diseases (SAIDs) are a group of multisystem immunodysregulatory disorders caused primarily by the dysfunction of the innate immune system[1]. Currently, SAIDs are comprised of a wide range of disorders with systemic and organ-specific inflammation in the absence of infections or autoimmunity[2–6]. In a subset of genetically defined SAIDs, the pathogenesis is driven by increased release or signaling of the pro-inflammatory cytokine interleukin-1 (IL-1)[2,7, 8].

The conditions addressed by this task force include the IL-1 mediated SAIDs (monogenic forms) that are most frequently evaluated by rheumatologists, and which have FDA/EMA approval for IL-1 targeted therapies. Cryopyrin-associated periodic syndromes (CAPS[9,10]) or NLRP3-associated autoinflammatory diseases (NLRP3-AIDs[11]) are the spectrum of rare autosomal dominant autoinflammatory diseases caused by gain-of-function mutations in *NLRP3*[9,12–16] ranging from Familial Cold Autoinflammatory Syndrome (FCAS) (mild NLRP3-AID phenotype), Muckle-Wells Syndrome (MWS) (moderate NLRP3-AID phenotype) to Neonatal onset multisystem inflammatory disease (NOMID)/ Chronic Infantile Neurological Cutaneous and Articular (CINCA) (severe NLRP3-AID phenotype). The other IL-1 mediated SAIDs included are, Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), an autosomal-dominant disease caused by mutations in *TNFRSF1A*[17, 18] encoding the Tumour Necrosis Factor Receptor Type 1, Mevalonate kinase deficiency (MKD) caused by autosomal recessive loss-of-function mutations in the mevalonate kinase gene (*MVK)* resulting in a deficiency of mevalonate kinase enzyme[19–22]. Lastly, deficiency of IL-1 receptor antagonist (DIRA) caused by biallelic deleterious loss-of-function mutations in *IL1RN* gene encoding the IL-1 receptor antagonist (IL-1Ra) was addressed by the task force[2]. The most common IL-1 mediated autoinflammatory disease, familial Mediterranean fever (FMF) is not addressed, as EULAR-endorsed recommendations have recently been published for this disease[23].

IL-1 mediated SAIDs are caused by chronic systemic and organ-specific inflammation leading to progressive organ damage and dysfunction[24–27]. Acute disease flares can be life-threatening and contribute to the high morbidity and mortality in untreated patients[17,28, 29]. In this rapidly evolving group of rare diseases, there is a need to harmonize care that reflects our current knowledge of genetics, diagnosis, treatment, and monitoring for all patients globally.

The natural history of untreated patients with pathogenic mutations causing CAPS[10,30,31], TRAPS[18], MKD[32] and DIRA[2] has been characterized in the literature and forms the basis for the guidance on monitoring disease progression and organ damage. Disease severity is dependent on the level of systemic and organ-specific inflammation. Risk factors associated with adverse outcomes include specific mutations, clinically severe phenotypes, frequent and severe inflammatory episodes, and organ damage at the time of initial presentation[17,33–36]. The life-changing positive impact of therapies targeting IL-1 has been documented in patients with CAPS, TRAPS, MKD, and DIRA. There is also mounting evidence for the benefits of maintenance treatment to prevent the progression of organ damage, thus pointing to the importance of early diagnosis and initiating treatment early in life[33,34,37,38].

An early and accurate genetic diagnosis allows for referral for genetic counseling, directs appropriate screening for potential complications, informs prognosis, and improves our ability to define individual treatment goals and to tailor treatment decisions[33,34–37]. Most patients with CAPS, TRAPS, MKD and DIRA are managed by pediatricians and pediatric specialists, and with effective treatments, adolescents and young adults are now reaching adulthood with expectations of a normal life span. They now face new challenges with transitioning care to adult rheumatologists comfortable with the management of these patients. Furthermore, pregnancy and other subspecialty needs (i.e., surgery) are often not addressed adequately in the context of IL-1 mediated SAIDs. For some patients, the diagnosis may be delayed for decades, resulting in inadequate treatment and the development of permanent disabilities that may translate into special care needs.

The above considerations led to the convening of a task force that was charged with developing standardized guidance for diagnosis, treatment, and long-term monitoring of patients with CAPS, TRAPS, MKD and DIRA that target pediatricians, internists, and subspecialists, (particularly rheumatologists). The statements were developed as a resource for physicians to facilitate management, for policymakers who have a role in authorizing patients' access to diagnostic tools and treatment options, as well as for patients and caregivers to provide knowledge and allow for setting appropriate expectations. Finally, these guidelines aim to standardize the level of care with a goal of improving quality of life and disease outcomes worldwide.

METHODS

With approval granted by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) executive committees, the IL-1 mediated autoinflammatory diseases task force was convened to develop guidance on diagnosis, therapy, and monitoring of four different IL-1 mediated SAIDs, including CAPS, TRAPS, MKD and DIRA. The task force was led by two conveners (ED and RGM) and consisted of 19 pediatric and four adult rheumatologists, that were selected based on expertise in the treatment and care of these patients. In addition, the task force included two health care professionals, three fellows, one patient representative from the Autoinflammatory Alliance and two methodologists. The 31 task force members were from 17 centers in seven different countries from across Europe, the United States and Canada. EULAR[39] and the ACR standardized operating procedures (SOPs) were followed during the project (see online supplementary methods). The first meeting was convened in August 2019 in Bethesda, Maryland, United States, to define the focus of the task force which identified four IL-1 mediated SAIDs to be included in this points to consider project. In line with the EULAR SOPs, the target audience was defined as healthcare professionals, policy makers, health insurance companies, patients and their caregivers. The group worked to determine the PICO (Population, Intervention, Comparison, Outcome) questions related to diagnosis, monitoring and management of these diseases. Using the PICO questions defined during the first meeting, a systemic literature review (SLR) was performed by three research fellows (MR, ZSA, DP) with support from a librarian (DH) and the senior methodologists (ED, DA) to identify relevant publications using PubMed, Embase and the Cochrane Library through August 2020.

Before the first consensus meeting, two surveys that included statements or items pertaining to diagnosis, treatment and long-term monitoring were distributed to all task force members via RedCap. The task force members were asked to indicate their agreement with each statement or item with yes or no. A free text option was provided to capture every member's comments or suggestions for modification; and a request was made to add items to be addressed, edited or altered. Consensus was achieved using the Delphi technique. Draft statements with 80% or higher agreement were retained. Comments and suggestions provided in the questionnaires were used to modify the draft statements and to add additional items. The revised and amended statements were then sent through a second round of questionnaires. After the two rounds, the draft statements were revised to incorporate all suggestions and reviewed by the steering committee members. These draft statements were then included for discussion at the consensus meetings.

Due to the COVID-19 pandemic, three consensus meetings were held online between September and November 2020. At the consensus meetings, statements that did not reach a greater than 80% consensus were discussed in a round robin discussion, re-worded, amended and refined and were then voted on again. If a statement, did not achieve ≥80% agreement after discussion, refinement and revoting, the statetment was excluded. All statements that achieved >80% agreement were considered a final statement for inclusion in the final version of the points to consider. For each statement, the Oxford Levels of Evidence (LoE) and the grade of the recommendation (GoR) were assigned based on the SLR by the fellows under the supervision of the methodologist[40]. The final statements annotated with the LoE and GoR were sent through an online survey to all task force members again; and each member was asked to provide their level of agreement (LoA) on a scale of 0 (absolutely disagree) to 10 (absolutely agree). The mean and standard deviation (SD) of the LoA with each statement were calculated. The manuscript was reviewed and approved by all task force members and the EULAR/ACR Executive Committees prior to submission to the journal.

RESULTS

Systematic literature review

The details for the literature search strategy and summary of results are described in the online supplementary material. Briefly, randomised controlled trials (RCT), cohort studies, cross-sectional studies, case-control studies and case reports including more than three cases were included. Review articles, conference abstracts, book chapters, single case reports and articles written in a language other than English were excluded. For CAPS, of 2041 references identified, 72 studies were selected for inclusion. For TRAPS, of 1161 references identified, 47 studies were selected for inclusion. For MKD, of 1806 references identified, 51 studies were selected for inclusion. For DIRA, of 557 references identified, two studies were selected for inclusion. In total, from the 5565 references identified, 172 were included. After a group discussion that included the results of the SLR, the consensus process was initiated.

OVERARCHING PRINCIPLES

During the consensus meeting, 7 overarching principles and 55 candidate statements were discussed and voted on. The task force decided to merge two overarching principles. Due to lack of agreement, the task force eliminated 22 statements (12 referring to CAPS, 6 to TRAPS, 2 to MKD, and 6 to DIRA). The task force agreed on a final set of five overarching principles (Table 1) and 33 points to consider (Tables 2, 3, 5).

CAPS, TRAPS, MKD and DIRA typically present with complex clinical features and phenotypes in the neonatal or early childhood period; these include features of systemic and organ-specific inflammation[2,17,28,29,36] presenting with early-onset of fever, abdominal pain, rash, musculoskeletal symptoms, neurologic manifestations, and elevated biomarkers of systemic inflammation[17,35,41–45]. The specific biomarkers of systemic inflammation included in this document are referred to as acute phase reactants and include: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A protein (SAA)[46] and S100 proteins, that in most patients correlate with disease activity[41,47,48]. The first goal (overarching Principle A) is to recognize patients with potential monogenic IL-1 mediated SAIDs and to establish a multidisciplinary team for diagnosis, therapy and long-term management. Delay in treatment initiation can result in rapidly progressive organ damage[24–27], morbidity, and increased mortality[34,49,50]. Overarching Principle B outlines the need to initiate a clinical workup that assesses the extent of the inflammatory organ involvement and screens for treatment-related comorbidities, a process that often requires a multidisciplinary team of subspecialists[24,25,47]. The third goal (overarching Principle C) highlights the need for an accurate genetic diagnosis which in many countries may be required to access the IL-1 blocking biologics that prevent life-threatening complications[47,51,52], and facilitate access to supportive care[24,25,47].

The goals of therapy (overarching Principle D) are to rapidly control disease activity by suppressing systemic and organ inflammation. IL-1 blockade has been FDA[53–55] and EMA[56,57] approved for CAPS, TRAPS, MKD and DIRA.[49,58] Rapid disease control using these agents is critical in preventing the development of irreversible early inflammation-related organ damage, and minimizing side effects from the use of other drugs that are ineffective and/or carry substantial toxicities.

There are currently no cures for these lifelong diseases. Overarching Principle E outlines long-term monitoring goals that focus on evaluating disease activity, assessing and monitoring signs and symptoms of disease-specific organ inflammation, growth and development, and adjusting therapeutic doses according to growth, or control of symptoms and inflammation. Monitoring should be developmentally appropriate, include adjustments for adolescence[59], be tailored to accommodate cognitive (i.e. learning and behavioral disorders) and physical disabilities (i.e. bone deformities, hearing and vision loss)[29,60] and prepare patients for transitioning to adult specialists. This transition can be challenging and lengthy and may put patients at risk of unfavorable outcomes. Therefore, the task force emphasized the need to include goals that foster self-management skills and medical decision-making (i.e. including reproductive health) throughout the life of the patient[59,61].

Focus on the diagnosis of IL-1 mediated SAIDs, including recognizing clinical diagnostic and damage- related features of the respective diseases, genetic testing, disease-specific clinical and laboratory workup and initiation of early treatment: Points to consider 1–14—Disease-specific clinical features of untreated CAPS, TRAPS, MKD and DIRA and the resulting organ damage have been characterized in clinical descriptions of patient cohorts before anti-IL-1 treatment was used[2,17,36,62]. These signs and symptoms form the basis of evidence-based classification criteria for CAPS[48], TRAPS and MKD[41] and are listed in Table 2, recommendations 8 (CAPS), 10 (TRAPS), 11 (MKD) and 13 (DIRA), respectively. In combination with the molecular analyses, these features help physicians recognize disease-specific characteristics and differentiate these conditions from clinically complex diseases that can present with overlapping inflammatory manifestations, including systemic juvenile idiopathic arthritis (JIA), adult-onset Still's disease, neoplasms, infections, and autoimmune disorders[63,64].

Genetic workup: Points to consider 2–6—Suggestive clinical features should trigger a genetic investigation, as genetic testing is a crucial component of an accurate diagnosis of CAPS, TRAPS, MKD and DIRA[41,65]. Next-generation sequencing (NGS) platforms are now widely used and are replacing the Sanger sequencing “gene by gene” approach[51,52,66–68]. NGS is therefore generally recommended.[52, 63,66,69,70]. In certain conditions, Sanger sequencing of a single gene may be cost-effective, such as in patients with a known familial disease or classic disease features. In some countries, Sanger sequencing may be the only modality of genetic testing available[52,71–73].

CAPS and TRAPS are autosomal dominant diseases caused by gain-of-function mutations in *NLRP3* and *TNFRSF1A*[18] genes, respectively, and can be familial[63,74] or caused by *de novo* mutations. In CAPS, *de novo* mutations are most frequently found in patients with severe phenotypes[7]. Somatic mutations in these patients may be undetected by standard coverage of NGS and may require deep sequencing, though this analysis may not be available to all providers[51,74–77]. In contrast, MKD and DIRA are caused by recessive loss-of-function mutations in *MVK*[78,79] and *IL1RN*[2] genes, respectively. In patients with clinical symptoms suggestive of MKD or DIRA, Sanger sequencing, whole exome sequencing, and whole genome sequencing may not detect large deletions[2]. If appropriate, chromosomal microarray analysis by comparative genomic hybridization array or by single nucleotide polymorphism array should be performed[2]. For the genetic diagnosis of DIRA, PCR and sequencing using specific deletion breakpoint primers to screen reported *IL1RN* large deletions may aid the genetic evaluation in selected ethnic backgrounds (i.e., Puerto Rico, Brazil, India)[2,80,81]. If a genetic diagnosis cannot be made following routine genetic workup, patients should be referred to a research centre of excellence with expertise in the molecular diagnosis of SAIDs.

One significant challenge is the interpretation of genetic results that have not been classified or validated as pathogenic mutations, including variants of uncertain significance (VUS), variants that have not been described previously or studied functionally, or likely benign variants that may be present in the general population at a relatively high frequency and could be low-penetrance mutations with inconsistent clinical significance. Patients with these genetic findings may display distinct clinical and biologic phenotypes, and can include IL-1β and non-IL-1β-mediated inflammatory pathway activation, which may have implications for their management, further emphasizing the need for specialty care.

Clinical workup: Points to consider 7–14—In IL-1-mediated SAIDs patients, systemic inflammation typically accompanies clinical signs and symptoms which can be episodic/periodic or chronic/persisting [36,82]. MKD, TRAPS, and the mildest form of CAPS, known as FCAS, may in rare cases, present with intermittent episodes (flares of symptoms) separated by periods of perceived improvement [17,41,65,83–85]. However, most patients except for patients with milder disease (i.e. some FCAS and TRAPS patients) have evidence of chronic subclinical inflammation between episodes. Patients with more severe forms of CAPS such as MWS or NOMID/CINCA, or those with severe MKD with almost complete absence of the enzymatic activity of mevalonate kinase, or with DIRA, all present with chronic systemic inflammation that rarely spontaneously remits. In general, markers of systemic inflammation correlate with disease symptoms and risk of organ damage[75,86–88]. Historically, CRP, ESR, and, if available, SAA[46] have been used to assess systemic inflammation. Additionally, S100 proteins[89] have been used by some investigators as sensitive markers in research settings. How to best use S100 protein markers for patient care, given increased clinical availability, remains under investigation. The diagnostic workup across all four diseases is broadly similar and can be synchronized. Typical signs and symptoms of active disease (i.e. hepatosplenomegaly), organ inflammation and damage should prompt a diagnostic workup (Tables 2 and 6).

The clinical presentation of the CAPS disease spectrum includes systemic inflammation and an urticaria-like rash with histologic features of a neutrophilic dermatosis involving eccrine glands, which is present in almost all patients[24,43,75,86,88,90–92]. Cold-induced flares often last less than 24 hours and are most often observed in patients at the mild end of the disease spectrum (FCAS)[14,42]. A negative localized cold challenge (ice cube test) differentiates FCAS from patients with cold urticaria[42]. Progressive sensorineural hearing loss is often seen in moderately (MWS) and severely (NOMID/CINCA) affected patients[24,29,60,75], while neurologic findings (chronic aseptic meningitis, increased intracranial pressure, cognitive impairment)[87,93] and skeletal abnormalities (distal femur overgrowth, frontal bossing) are typically seen in NOMID/CINCA[75,86]. Ophthalmologic involvement can vary and most typically includes conjunctivitis, but keratitis, episcleritis, anterior and/or posterior uveitis have also been described. Increased intracranial pressure may cause papilledema and subsequent optic disc atrophy. Therefore, a slit lamp exam and retinal evaluation should be performed in all CAPS patients at baseline[25,43,88]. In patients with suspected neurologic involvement, brain imaging[28,94,95] and lumbar puncture may be needed to evaluate for elevated intracranial pressure or aseptic meningitis, while a specialized brain MRI can detect cochlear enhancement, cerebral atrophy and ventriculomegaly[87,96]. Epiphyseal bony overgrowth, commonly found around the knees, may be assessed by bone MRI or radiograph[25 26 92].

TRAPS is characterized by episodes of fever lasting more than 7 days, abdominal pain that can mimic an acute abdomen, variable chest pain and, rarely, testicular pain[17,41,70]. Especially in adults, a sub-chronic disease course might be observed, with fatigue, diffuse limb pain and persistent elevation of acute phase reactants[17]. Periorbital edema and myalgias might herald the onset of an attack. Typical findings of a flare include painful, migratory skin plaques with hazy edges that are erythematous, swollen, and warm[3] and predominantly affect the limbs. Suspected fasciitis may be imaged on MRI[97]. There is now consensus that population frequent variants of uncertain significance, such as R121Q (previously referred to as R92Q) should not be considered as pathogenic [17,45,98–103]. Therefore, the interpretation of these variants should occur in the context of the inflammatory phenotype by an expert in the field if available.

Patients with MKD usually present in the first year of life[5,104] with recurrent episodes of fever lasting 4 to 6 days[104], gastrointestinal symptoms (severe abdominal pain with vomiting and diarrhea), cervical lymphadenopathy, aphthous stomatitis and/or skin rash (urticarial or maculopapular)[32,64,84,105–110]. The most severe form of MKD, namely mevalonic aciduria presents with severe cognitive impairment, and patients can present with hyperinflammation leading to macrophage activation syndrome (MAS)[36] along with the clinical features described above[84,110,111]. Febrile attacks triggered by vaccinations suggest a diagnosis of MKD[36,85,112–115].

High levels of circulating immunoglobulin D that were described formerly and led to the name Hyper IgD syndrome have low diagnostic sensitivity and specificity[82,105,116,117]. However, elevated urine mevalonate levels during disease flares, due to reduced MVK enzyme activity and accumulation of mevalonic acid, are more specific for MKD[118,119] and can be used to aid in diagnosis.

Patients with DIRA present with early-onset pustular rashes that can be triggered by mechanical stress (pathergy), with sterile osteomyelitis, and nail changes (onychomadesis)[2,120]. Although the inflammatory markers are typically highly elevated, fever may be absent. Vertebral involvement can include odontoid osteomyelitis resulting in destruction and neck instability, vertebral block formation and gibbus-like spinal changes that need to be screened for by MRI or CT[2,120]. In contrast to patients with CAPS, TRAPS and MKD, patients with DIRA rarely present with flare-associated fever. In patients with presumed DIRA, a diagnostic workup includes assessing peripheral neutrophilia and elevated inflammatory markers, determining bone involvement (i.e. x-ray or bone MRI) and genetic testing[2,120]. The differential diagnosis for DIRA includes chronic recurrent multifocal osteomyelitis (CRMO)[121,122], synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO)[123] syndrome and pustular psoriasis[124]. Genetic testing for monogenic defects with overlapping clinical features should include *LPIN2, FGR, FBLIM1* for CRMO[125,126], *CARD14* for CARD14-Mediated Psoriasis (CAMPS)[127,128], *IL36RN* for Deficiency of IL-36 Receptor Antagonist (DITRA)[127,128], *AP1S3*[128] for other pustular psoriasis and *MEFV* for Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis (PAAND)[129].

Focus on the therapy of IL-1 mediated diseases: Points to consider 15–24 —Disease management involves a shared decision-making approach and a combination of pharmacologic and non-pharmacologic interventions. The current standard of care for patients with CAPS, TRAPS, MKD, and DIRA is subcutaneous IL-1 targeted biologic therapy when available[28,49,130–132]. While the specific pharmacologic mechanisms, pharmacokinetics, disease indications and costs differ for each of the three available drugs, anakinra (Kineret[R]), rilonacept (Arcalyst[R]) and canakinumab (Ilaris[R]), each blocks the effect of IL-1β on the IL-1 receptor and downstream signaling resulting in improved symptom control, as well as reduced systemic and tissue/organ inflammation. Anakinra is a recombinant IL-1 receptor antagonist with a short half-life that binds to the IL-1 receptor and blocks both IL-1α and IL-1β signaling[95,133–135]. Rilonacept is a recombinant fusion protein with a relatively longer half-life that binds to both IL-1α and IL-1β[130,136,137]. Canakinumab is a human monoclonal antibody to IL-1β with a long half-life[49,131,138,139]. As expected for treatment of rare disorders, case reports and small patient series have demonstrated the success of IL-1 blockade across the spectrum of disease. The highest level of evidence, however, stems from pivotal studies including randomized studies in CAPS[137,140,141] (MWS and FCAS), in TRAPS and MKD[142] which have confirmed that rilanocept was effective in CAPS,[137] and that canakinumab was efficacious in controlling and preventing flares in patients with CAPS[140] and with MKD and TRAPS,[142] respectively (Table 3). The availability of these drugs varies significantly in different countries.

Aims of therapy are early control of disease activity, prevention of disease and treatment related damage, and optimal health-related quality of life[58 142]. The ultimate goal of a treat-to-target approach is complete remission[37]. In the absence of a consensus definition of remission or minimal disease activity for these diseases, remission has been defined for clinical studies and clinical monitoring as an absence of clinical symptoms and normal inflammatory markers. The instruments used to measure disease activity include daily symptom diary scores[28,95] or Autoinflammatory disease activity index (AIDAI)[143], and a Physician global assessment (PGA) and Patient-parent global assessment (PPGA). The most commonly used inflammatory marker is CRP (also known as high sensitivity or cardio CRP in some countries) with levels of less than 5mg/L or 10mg/L indicating adequate control of inflammation[95,120,142]. Minimal disease activity has been suggested as an alternative target if remission cannot be achieved. Definitions of remission and minimal disease activity and their validations are on the research agenda for autoinflammatory diseases[142,143].

Treat-to-target strategies aiming for low disease activity assessed by clinical symptoms and normalization of serum markers of systemic inflammation, are effective and used in the treatment of patients with IL-1 mediated SAIDs to find individualized and optimal dosing regimens for each patient and disease[37]. IL-1 blocking therapies control inflammation in the absence of corticosteroids[134,142,144]. Treatment can delay or prevent development or progression of organ damage in patients with moderate or even severe disease activity[60,95,145]. Management by a multidisciplinary team that includes subspecialists results in better disease control in patients with CAPS[37]. To achieve and maintain optimal disease control, IL-1 targeted therapies need to be administered continuously in most patients, and the dose and/or frequency of administration should be adjusted for control of disease activity, normalization of markers of systemic inflammation, and for weight gain and appropriate development in the growing patient.

Medication dose adjustments for weight gain and growth and higher mg/kg doses to optimize treatment responses should be individualized for each patient[37,95]. Some CAPS patients may require more frequent or higher dosing of these medicines than that approved by FDA or EMA (Table 4), such as dosing of canakinumab more often than the approved frequency of every 8 weeks, if they have not achieved remission[34,37,141]. On-demand regimens may be used in selected patients with MKD, TRAPS and FCAS who have very mild disease and/or episodic disease manifestations and who maintain normal inflammatory markers in between episodes[146,147]. Patients with severe disease manifestations, such as those with NOMID/CINCA, may require frequent adjustments and higher doses than patients with less severe diseases (Table 4)[37,95,141]. There is a potential clinical advantage of using anakinra for patients with severe CAPS, especially for those with neurologic disease[156,157]. Patients with *NLRP3* variants that have not been validated as pathogenic (i.e. V198M, R488K, Q703K) may respond to IL-1 blockade and specific recommendations have previously been published[148,149]. To improve symptom control, NSAIDs may be efficacious when used together with IL-1 targeted therapy. Ongoing efficacy and a beneficial long-term safety profile have been demonstrated for the long-term use of all three IL-1 blockers (anakinra, rilonacept, and canakinumab) in CAPS, although direct comparative studies are lacking[44,49,130,134,136–139,150–155].

A large body of evidence suggests that IL-1 inhibitors should be considered as the treatment of choice for TRAPS[100]. Although anakinra was the first IL-1 blocker successfully used in TRAPS patients in small series and observational registries[100,131,145,158], the long-acting anti-IL-1β monoclonal antibody, canakinumab is currently the only IL-1 blocker that the FDA and EMA have approved for the treatment of patients with TRAPS[54,57](Table 4). Individual patients with TRAPS may respond to treatment with short-term glucocorticoids or etanercept, however responses often wane and patients should be monitored for increased disease activity[45,100,159]. Patients with *TNFRSF1A* variants that are not classified as pathogenic (i.e. D41E, I57S, P75L, R121Q, N145S (previously referred to as: D12E, I28E, P46L, R92Q, N116S, respectively)) do not have TRAPS, however they may still have signs of clinical autoinflammation requiring treatment with colchicine or biologic therapies[100].

Anakinra and canakinumab have been used in children with MKD with success, but only canakinumab has been evaluated in a randomized study and approved by the FDA and EMA[54,57,142,146]. Some patients with MKD with milder disease phenotypes, characterized by occasional attacks separated by symptom-free periods, can be managed with on-demand treatment[146]. Glucocorticoids may also be beneficial during flares, but their extended use is limited by adverse effects[146]. The panel suggested the use of IL-1 blockade, but noted that treatment could be switched to anti-TNF agents, if IL-1 blockade is not available or is ineffective[146].

Anakinra and rilonacept both block IL-1α and IL-1β and should be used for DIRA patients[2,80,81,120]. The FDA recently approved both anakinra and rilonacept for treatment of DIRA[53,55]. Blocking IL-1α may be necessary to completely block bone inflammation, as observed in a patient who developed osteitis during therapy with canakinumab, which only blocks IL-1β[121]. While anakinra has been used initially in all patients with DIRA to achieve disease control, rilonacept can be used to maintain remission[120]. Doses of IL-1 blocking therapies required for disease control in patients with DIRA have typically been lower than those required in patients with severe CAPS-NOMID/CINCA. Long-term sustained and complete remission is an achievable goal of treatment for patients with DIRA.

For all IL-1 mediated SAIDs, individualized dose adjustments of IL-1 blocking agents may be necessary in young patients or in those with severe disease. In infants and preschool-aged children, twice daily dosing of anakinra may be required for control of disease activity. This is likely due to the higher liver blood flow, which increases the hepatic clearance of drugs owing to the larger ratio of liver to total body mass in children compared to adults[160]. Some older patients with severe and difficult to control disease, including CNS disease, may also achieve improved disease control on twice daily dosing. While canakinumab is approved by the EMA for CAPS-NOMID/CINCA at a frequency of every 8 weeks, supporting evidence suggests that this may be inadequate, so the consensus of experts recommends more frequent dosing up to every 4 weeks for these severely affected patients based on clinical experience and numerous reports[34,37,141]. This is consistent with dose frequency for other SAIDs, and with EMA provided consumer medical information for patients with inadequate responses[57].

Focus on monitoring of IL-1 mediated SAIDs: CAPS, TRAPS, MKD and DIRA: Points to consider 25–33—Ongoing management includes adjustment of pharmacologic therapy, monitoring of disease activity, development of disease-related complications and recognition of drug toxicity. Additionally, individual focus on the needs of the growing child, adolescent, adult or even elderly should include age-, and developmentally appropriate measures that foster self-management skills, encourage shared medical decision-making, address reproductive health issues, and facilitate timely and effective transition to adult medical care[47,162,163] (Table 5).

Appropriate management of patients with IL-1 mediated SAIDs necessitates a multidisciplinary team of local primary care givers working together with experienced physicians, rheumatologists and other specialists on a case-by-case basis that can include, but is not limited to immunologists, ophthalmologists, otolaryngologists, nephrologists, neurologists and genetic counselors, as well as physiotherapists, occupational therapists and psychosocial specialists[47,162,164]. The management of patients, particularly those with cognitive (i.e. learning and behavioral disorders) and those with physical disabilities (i.e. bone deformities, hearing and vision loss)[29,60] is complex. The physical, mental, psychosocial health, and social functioning of entire families should be considered. Individualized support services, including but not limited to psychosocial support, genetic counseling, cognitive and learning support, school accommodations, and occupational and physiotherapy may be needed to address and manage these challenges[110,162,164,165]. Some adult patients may have increased difficulties due to their disease and chronic organ involvement that may require accommodations for work, or other aspects of their daily life.

Long-term monitoring requires age appropriate dose adjustment of IL-1 blocking treatment to maintain control of systemic and organ-specific inflammatory manifestations, and of laboratory markers[49,130,134,135,139,155]. Systemic inflammation should be monitored by following inflammatory markers, that include peripheral neutrophilia[166], CRP and ESR. SAA and S100 protein may be used as inflammatory markers where available[45,131].

Chronic systemic inflammation can have significant effects on growth and development and ongoing inflammation may predispose to AA amyloidosis[27]. Patients with IL-1 mediated SAIDs need continuous and developmentally appropriate care during and beyond adolescence. However, up to half of adolescent patients are not appropriately transferred to adult specialist care due to general lack of transition readiness, inadequately robust quality indicators, and insufficient understanding of the needs of adolescents. This population is therefore at particular risk of unfavorable outcomes[59,61]. Relevant for this group are complications related to amyloidosis, hearing loss, and vision loss. Although AA amyloidosis has become less frequent with the early initiation of early anti-IL-1 targeted treatment, adults who have had long-standing uncontrolled disease should be closely monitored[49,100,140]. The task force recommended that proteinuria should be evaluated every six months in all patients with IL-1 mediated SAIDs, particularly in patients with a positive family history of amyloidosis as they may have other factors including genetic variants contributing to the development of amyloidosis (i.e. *SAA1* variants).

Disease-specific monitoring plans that take into account the different disease manifestations in CAPS, TRAPS, MKD and DIRA are outlined in Table 5. Hearing loss, CNS disease, bone deformities, renal failure due to amyloidosis and visual loss are the most severe organ manifestations in CAPS patients[62]. In patients with TRAPS the disease may progress from longer-lasting episodes of fever, migratory and painful rash, to a more chronic disease course with persistent inflammation in the absence of the typical fever episodes which may still represent an important risk factor for the development of AA amyloidosis[27], and are an indication for long-term treatment with biological DMARDs[131,145]. Rare MKD-associated manifestations include retinitis pigmentosa and hearing loss. Therefore, ophthalmologic evaluations and audiograms should be included as clinically indicated[32,35,36,118]. Secondary hemophagocytosis in the context of infections has been reported and should be considered in the context of severe disease flares in MKD[35,36,82]. For all IL-1-mediated SAIDs, appropriate monitoring aims to limit or prevent complications of inflammation and disease-associated damage through ongoing individualized therapy, while encouraging the best possible quality of life for patients and families[162].

Beyond objective laboratory measurements, patient-reported outcomes and disease assessment tools can be helpful in the monitoring of disease symptoms. Patient or physician reported outcomes[110,167,168] can include measures of health-related quality of life[47,169,170] (HRQoL), disease activity[143] (i.e. Auto-inflammatory Diseases Activity Index (AIDAI for CAPS, TRAPS and MKD[100,143,152,167,170,171]), global assessment scales for physicians and patients/parents[142] (PGA, PPGA) and assessment of disease-related organ damage[168] (i.e. Auto-inflammatory Diseases Damage Index (ADDI)) that are listed in Table 6. Questions regarding performance at school and workplace and recording missing school/work days help assess the burden of disease and guide revisions to the therapy plan[164].

The safety profile for IL-1 blocking treatment has generally been favorable. However, monitoring for infection, particularly respiratory tract infections with *Streptococcus pneumoniae* and skin infections due to *Staphylococcus,* is recommended[142]. Even though in some conditions, such as MKD, vaccination may lead to a disease flare, patients should be vaccinated in accordance with regional recommendations[172]. This includes pneumococcal vaccines, including the polysaccharide vaccine (Pneumovax^{R}) in patient with CAPS, as benefits generally outweigh the potential risks of local and systemic reactions[49,173]. Patients who are receiving, or planning to initiate, anti-IL-1 targeted therapy should receive pneumococcal vaccinations. While it is preferable to administer vaccines before starting treatment, it is also acceptable to do so during therapy[49]. Preliminary data suggests that an adequate antibody response to vaccines occurs in patients on canakinumab[49]. Whether vaccines against COVID-19 have the potential to provoke disease flares is unknown, theoretical concerns about disease flare in IL-1 mediated SAIDs caused by RNA vaccines exist. However, there are currently insufficient data to make recommendations regarding COVID vaccines.

Data on IL-1 treatment in pregnancy is limited[100,163,174]. In women with IL-1 mediated SAIDs who require biological treatment and are considering pregnancy, a benefit-risk discussion should be held before conception including the risk of untreated disease to mother and fetus compared to the risk of continuing biologics. At present, regulatory advice and clinical case series reports support the use of anakinra rather than any other anti -IL-1 agent in pregnancy[100].

CONCLUSION

In recent years, we have learned more about the phenotypic breadth and pathogenesis of IL-1 mediated SAIDs which has led to a more efficient diagnosis and better therapy and monitoring of these diseases. An improved understanding of the pathogenesis and presentation of patients with IL-1 mediated SAIDs, along with the development of effective therapies, has dramatically improved our ability to diagnose and treat patients. As formalized training in the diagnosis and management of IL-1 mediated SAIDs is variable, many physicians, including rheumatologists, lack the knowledge to optimally manage these patients. The task force aims to raise awareness and assist both specialists and primary health care providers in managing patients with IL-1 mediated SAIDs. The panel has also highlighted the distinguishing clinical features of CAPS, TRAPS, MKD and DIRA in the suggested recommendations. These points to consider attempt to address the unmet needs for guidance based on an EULAR and ACR consensus process for diagnosing, managing and treating CAPS, TRAPS, MKD and DIRA.

The task force included specialists with broad expertise in managing patients with IL-1 mediated autoinflammatory diseases, representing different countries, disease interests, and practice environments. Due to the rarity of these disorders, statements have been developed based on low level of evidence and on expert opinion, which will likely require revisions as new knowledge is generated. Multi-center collaborative efforts, prospective registries and randomized trials will help define optimal treatment strategies to relieve patient symptoms and to further improve long-term clinical outcomes. The panel also suggests areas for future research:

Research Agenda
• To create transition clinics for patients with these rare disorders and optimize treatment during this vulnerable period
• To evaluate best treatment options during pregnancy and their effect on the fetus and newborn
• To establish biobanks for biomarker studies to validate the markers that best correlate with disease activity and severity
• To evaluate the effect of vaccination in triggering or exacerbating disease activity in patients with IL-1 mediated SAIDs while on or off treatment with biologic DMARDs and/or glucocorticoids.
• To identify novel therapeutic targets and treatments
• To establish multicenter collaborative efforts to address: ◦ Development of prospectively enrolling registries ◦ Better characterization of phenotype-genotype correlations ◦ Pathophysiology of organ damage in IL-1 mediated disorders ◦ Validation of remission criteria for each disease, including patient-reported outcome measures ◦ Development of minimal disease activity criteria, response criteria ◦ Understanding of additional factors (epigenetics, environment) defining the disease course
• Continuation of: defining long-term outcomes, assessing long-term safety of biologics in IL-1 mediated disorders, updating and refining disease-specific outcome instruments for measuring disease activity and severity

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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This project is part of a series of “points to consider” consensus efforts to standardize the diagnosis and care of patients with the 3 major groups of known autoinflammatory diseases including 1. the IL-1 mediated diseases CAPS, TRAPS, MKD and DIRA, 2. the autoinflammatory interferonopathies chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), STING-associated vasculopathy with onset in infancy (SAVI) and Aicardi-Goutieres syndrome (AGS) and 3. the early diagnosis and management of inflammatory conditions with the potential progression to hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).

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Competing Interest

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Data availability statement:

All data relevant to the study are included in the article or uploaded as supplementary information

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Table 1

Overarching principles for the diagnosis, therapy and monitoring of CAPS, TRAPS, MKD and DIRA

	Overarching principles	LoE	GoR	LoA (0–10) mean ± SD
A	Patients with the IL-1 mediated diseases CAPS, TRAPS, MKD and DIRA present with chronic or intermittent flares of systemic and organ inflammation, that if untreated results in progressive organ damage, morbidity and increased mortality. A multidisciplinary team is required to diagnostically evaluate and manage patients with CAPS, TRAPS, MKD and DIRA, which includes evaluation of systemic inflammation, disease-associated complications and long-term treatment and management.	5	D	9.5±0.7
B	Patients presenting with chronic or episodic flares of unexplained systemic inflammation (including elevations of CRP and ESR) and clinical features suggestive of CAPS, TRAPS, MKD and DIRA should receive a prompt diagnostic work up comprising: • genetic testing • clinical workup focusing on the extent of inflammatory organ involvement • screening for disease and treatment-related comorbidities	5	D	9.8±0.6
C	A genetic diagnosis for CAPS, TRAPS, MKD and DIRA is required which facilitates initiation of targeted treatments, genetic counselling, and informs prognosis. Genetic testing using a next-generation sequencing (NGS) platform should be used to diagnose CAPS, TRAPS, MKD and DIRA.	4	C	8.9±1.6
D	The goal of therapy is to control clinical signs and symptoms and normalize laboratory biomarkers of systemic inflammation using a treat-to-target approach.	5	D	9.6±0.8
E	Long-term monitoring goals should focus on: • adequate treatment adjusted to the needs of the growing child and prevention of systemic and organ-specific inflammatory manifestations, • fostering of self-management skills and medical decision-making, • initiating a transition program to adult specialist care in adolescent patients.	5	D	9.6±0.9

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; Level of evidence (LoE): 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'; Grade of recommendation (GoR): A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; level of agreement (LoA); CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2

Points to consider for the diagnosis of CAPS, TRAPS, MKD and DIRA

		LoE	GoR	LoA (0–10) mean ± SD
1	Patients with clinical symptoms of CAPS, TRAPS, MKD and DIRA who do not carry any of the disease-causing mutations described here should be referred to specialty/research centers to guide further workup and treatment.	5	D	9.4±1
Genetic Workup				
2	Genetic testing using an NGS platform, if available, should be used to make a genetic diagnosis. • Sanger sequencing of targeted genes known to cause CAPS (NLRP3), TRAPS (TNFRSF1A), MKD (MVK) and DIRA (IL1RN) can be used if the clinical suspicion is strong or to validate NGS.	4	D	9.4±1.1
3	Deep sequencing in patients with CAPS and TRAPS may be needed to detect some somatic mutations that may not be identified by standard NGS or Sanger sequencing.	5	D	9.5±1.1
CAPS specific				
4	Patients with low penetrance variants in *NLRP3* may present with clinical manifestations different from CAPS; their treatment response and prognosis may differ from “canonical” CAPS.	2	B	9.4±1.2
TRAPS specific				
5	Patients with low penetrance variants in *TNFRSF1A* (i.e., R121Q (previously referred to: R92Q)) may present with clinical manifestations different from TRAPS and their treatment response and prognosis may differ from “canonical” TRAPS.	2	B	9.5±1.2
DIRA specific				
6	In patients with DIRA, Sanger sequencing, WES, or WGS may not detect large deletions in *IL1RN,* thus complicating a genetic diagnosis. • In cases with a high clinical suspicion of DIRA and negative Sanger Sequencing or WES/WGS, chromosomal microarray analysis (CMA) is recommended to detect large deletions. • The use of deletion-specific primers in countries with founder variants that include large deletions, is recommended.	3	B	9.3±1.2
Clinical Workup				
7	The clinical workup of systemic inflammation should include CRP, ESR and CBC with differential; if available SAA and S100 proteins may be assessed. • Patients with long-standing untreated systemic inflammation need to be screened for the presence of amyloidosis.	5	D	9.7±0.6
CAPS Specific				
8	The following clinical features in the presence or absence of autosomal dominant inheritance should prompt consideration of a diagnostic workup of CAPS: • urticaria-like rash, • cold/stress-triggered episodes, • sensorineural hearing loss, • chronic aseptic meningitis, • skeletal abnormalities	2	B	9.8±0.5
9	The initial diagnostic workup should include an audiogram and an ophthalmologic exam. Lumbar puncture and a head MRI should be performed if clinically indicated.	5	D	9.8±0.5
TRAPS Specific				
10	The following clinical features should prompt consideration of a diagnostic workup of TRAPS: • long-lasting fever episodes, • migratory rash,	2	B	9.8±0.5

		LoE	GoR	LoA (0–10) mean ± SD
	• periorbital edema, • myalgia, • a positive family history			
MKD Specific				
11	The following clinical features should prompt consideration of a diagnostic workup of MKD: • age at onset < 1 year, • gastrointestinal symptoms, • painful lymph nodes, • aphthous stomatitis, • a history of triggers of the periodic fever attack (i.e., post-vaccination), and • a maculopapular rash	2	B	9.8±0.5
12	In patients with unexplained/undifferentiated inflammatory diseases, the presence of mevalonate acid in urine should prompt further diagnostic work up for MKD	4	C	9.5±0.7
DIRA Specific				
13	The following clinical features particularly if occurring sporadically, should prompt consideration of a diagnostic workup of DIRA: • pustular-psoriasis like rashes, • osteomyelitis (i.e., CRMO-like disease, rib flaring and cloaking of the femoral head, odontoid lesions/osteomyelitis • absence of bacterial osteomyelitis, • nail changes (i.e. onychomadesis)	5	D	9.6±0.8
14	For patients with suspected DIRA, X-rays of the chest and upper and lower limbs and/or MRI/CT to assess the spine, including odontoid, should be included in the diagnostic workup to assess the extent of the inflammatory bone involvement. A dermatology consult and skin biopsy should be considered as the presence of neutrophilic dermatosis with exocytosis of neutrophils and subcorneal pustules is highly suggestive of DIRA.	5	D	9.7±0.8

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; CRMO, chronic recurrent multifocal osteomyelitis; Level of evidence (LoE): 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or ‘first principles’; Grade of recommendation (GoR): A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; Level of agreement (LoA); CNS, central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NGS, next-generation sequencing; WES, whole exome sequencing; WGS, whole genome sequencing NA, not applicable;

Table 3

Points to consider for the therapy of CAPS, TRAPS, MKD and DIRA

		LoE	GoR	LoA (0–10) mean ± SD
15	IL-1 blocking therapy has become the treatment of choice and a therapeutic trial with IL-1 blocking treatment may be started when a strong clinical suspicion of a diagnosis of CAPS, TRAPS, MKD or DIRA is entertained.	4	C	9.5±0.9
16	In the context of viral infections, including COVID-19, IL-1 blocking therapy should not be altered, as stopping treatment may lead to rebound inflammation.	4	C	9.5±0.8
CAPS Specific				
17	Treatment with IL-1 blockers is recommended standard of care and currently includes anakinra[1], canakinumab[2] and rilonacept[3].	[1]2 [2]1 [3]1	A B B	9.9±0.3
18	Anakinra may be the most effective anti-IL-1 treatment for CNS disease.	2	B	9.6±0.8
19	Higher and more frequent dosing with IL-1 blockers may be required to control disease activity in more severe cases and/or younger children to prevent complications. Less frequent dosing may be appropriate for patients with milder disease.	1	B	9.8±0.5
TRAPS Specific				
20	Anti-IL-1 drugs are more effective than traditional disease-modifying antirheumatic drugs (DMARDS) and other biologic DMARDS in achieving disease remission and preventing long-term complications.	4	C	9.6±0.9
MKD Specific				
21	In children with MKD, IL-1 blocking therapy is generally required. In patients without chronic systemic inflammation, on-demand IL-1 blockade should be attempted at the onset of flares.	4	C	9.4±1.0
22	If anti-IL1 is not effective or available, then anti-TNF agents should be considered.	3	B	9.3±0.9
23	Glucocorticoids on demand may be effective in treating acute flares, however frequent or long-term use is limited by side effects.	2	B	9.3±1.0
DIRA Specific				
24	In patients with DIRA, treatment with agents that block both IL-1α and IL-1β is recommended and includes anakinra and rilonacept. Both have shown benefit in controlling disease flares and in preventing long-term complications.	4	C	9.6±0.8

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumor necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; Level of evidence (LoE): 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'; Grade of recommendation (GoR): A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; Level of agreement(LoA); CNS, central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NA, not applicable.

Table 4.

Treatments based on FDA, EMA* or expert panel consensus

Disease	Treatment	Recommended dosing based on FDA, EMA or task force consensus	FDA	EMA	LoE
CAPS (NLRP3-AID)					
FCAS	Canakinumab	PD:2–8 mg/kg/q8w AD: >40kg, 150–600 mg/q8w	+	+	**1B**
	Rilonacept	PD: LD 4.4 and (MD) 2.2 mg/kg/q1w AD: LD 320mg/q1w and MD 160mg/q1w	+	-	**1B**
	Anakinra	1–2 mg/kg/day	-	+	**4C**
MWS	Canakinumab **	PD: 2–8 mg/kg/ q8w ** AD: >40kg, 150–600 mg/q8w	+	+	**1B**
	Rilonacept	PD: LD 4.4 and (MD) 2.2 mg/kg/q1w AD: LD 320 mg/q1w and MD 160 mg/q1w	+	-	**1B**
	Anakinra	1–8 mg/kg/day	-	+	**2B**
NOMID/CINCA	Anakinra	1–8mg/kg/day	+	+	**2A**
	Canakinumab ***	PD: 2–8 mg/kg/4w *** AD: >40kg, 150–600 mg/q4w	-	+	**4C**
TRAPS	Canakinumab	PD: 2–4 mg/kg/q4w AD: >40kg, 150–300 mg/q4w	+	+	**1B**
MKD	Canakinumab	PD: 2–4 mg/kg/q4w AD: >40kg, 150–300 mg/q4w	+	+	**1B**
DIRA	Anakinra	1–8 mg/kg/day	+	-	**4C**
	Rilonacept	PD: 4.4 mg/kg/q1w AD: LD 320 mg/q1w and MD 320 mg/q1w	+	-	**4C**

* Drug approvals, dosages may vary between different countries and local regulations should be followed in the respective countries[53–57].

** Canakinumab is approved by the FDA and EMA for the treatment of CAPS at the same dosing regimens for FCAS and MWS, however, some patients with MWS may require more frequent dosing according to the expert panel.

*** Although canakinumab was approved by the EMA for the treatment of CAPS at the same dosing regimens for all 3 disease severity phenotypes (which also includes patients with NOMID/CINCA), the study submitted for approval only included 5 NOMID/CINCA patients and a subanalysis in NOMID/CINCA patients was not performed. The dosing frequency required for NOMID patients is typically every 4 weeks. We therefore added the panel's recommendation as 4C in the dosing table[151,157,161].

FDA, US Food and Drug Administration; EMA, European Medicines Agency, Level of evidence (LoE): 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

CAPS, cryopyrin-associated periodic syndromes; FCAS, familial cold autoinflammatory syndrome; PD, pediatric dosage; AD, adult dosage; LD, loading dose; MD, maintenance dosing; MWS, Muckle-Wells syndrome; NOMID, neonatal onset multisystem inflammatory disease; CINCA, chronic infantile neurologic cutaneous articular syndrome; TRAPS, tumor necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist;

Table 5

Points to consider for the monitoring of CAPS, TRAPS, MKD and DIRA

		LoE	GoR	LoA (%)
25	Disease activity and burden of disease should be monitored regularly depending on disease activity and severity, often requiring a multidisciplinary team. • Symptom control can be monitored with validated tools that asses disease-specific symptoms, with patient-reported outcome and quality of life assessments and by recording missing school or workdays. • The frequency of the follow-up evaluations should be tailored to disease severity and clinical needs.	5	D	9.7±0.6
26	Growth and development of children should be monitored at each visit	5	D	9.9±0.3
27	Systemic inflammation should be monitored by following inflammatory markers, including peripheral neutrophilia, CRP and ESR. SAA and S100 protein may be used as inflammatory markers where available.	5	D	9.8±0.5
28	Systemic inflammation may predispose to the development of amyloidosis, and patients should be monitored for the development of amyloidosis by monitoring proteinuria and microalbuminuria.	5	D	9.8±0.5
29	Physicians should be aware of the increased risk of infections in patients with IL-1 targeted therapy, including respiratory tract infections with *Streptococcus pneumoniae* and skin infections due to *Staphylococci*.	1	B	9.8±0.4
30	Patients should receive immunizations, in particular live-attenuated vaccines, in accordance with their regional policy, prior to beginning anti-IL-1 targeted therapy when possible.	5	D	9.2±1.4
CAPS Specific				
31	Monitoring of organ damage should be established based on disease manifestations and can include monitoring of hearing loss, eye disease, aseptic meningitis, CNS disease and bone disease.	5	D	9.7±0.6
32	Patients with CNS and/or bone involvement should be assessed for developmental delay, the development of bone deformities and limb-length discrepancies	5	D	9.7±0.6
DIRA Specific				
33	Normalization of acute phase reactants and absence of inflammatory skin and bone findings is required to determine the adequate dose of IL-1 blocking treatment, and to monitor disease activity long-term.	5	D	9.5±0.8

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumor necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; LoE: 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles';GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level; LoA: level of agreement; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; NA, not applicable

Table 6.

Disease-specific monitoring of the IL-1 mediated AID, CAPS, TRAPS, MKD and DIRA

Monitoring Table		
For all diseases systemic inflammation needs to be monitored		
A. Monitoring of systemic inflammation in all diseases		**Frequency**
	ESR, CRP, CBC+Differential (granulocytosis), S100 proteins and SAA where available, hepatosplenomegaly, lymphadenopathy, fatigue	each visit
	Urinalysis to monitor proteinuria (AA amyloidosis)	Every 6–12 months
	Monitor growth, BMD, sexual development	each visit as indicated
B. Monitoring of disease-specific symptoms * and patient-related outcomes		**each visit**
CAPS	Fever, rash (urticaria-like), progressive hearing loss, headaches, early morning nausea and vomiting, musculoskeletal symptoms, conjunctivitis, cognitive development (severe disease)	each visit
TRAPS	Fever, rash (migratory), periorbital edema, pain (abdomen, chest, testicular), myalgia	each visit
MKD	Periodic fever attacks (including triggered post-vaccination), rash (urticarial or maculopapular), gastrointestinal symptoms (abdominal pain, diarrhea, vomiting), cervical lymphadenopathy, aphthous stomatitis, cognitive impairment in severe cases	each visit
DIRA	Pustular-psoriasis like rashes (pathergy), musculoskeletal (bone) pain (caused by osteomyelitis), nail changes	
Patient-related outcomes for all 4 diseases	QoL, PGA, PPGA, missing school/workdays	each visit
C. Monitoring of organ manifestations/damage		
CAPS		
Amyloidosis	Urinalysis	each visit
Hearing loss (S)	Audiogram	3–6 months till stable then every 6–12 months
Eye disease (S)	Ophthalmologic exam (vision, retina evaluation and slit lamp exam)	6–12 months
CNS disease (S)	Lumbar puncture, head MRI (with special evaluation of cochlea, cerebral atrophy and ventriculomegaly)	12–36 months depending on symptoms
Bone deformity (S)	Bone MRI, scanogram to monitor limb length, epiphyseal overgrowth	12–36 months depending on symptoms
TRAPS		
Amyloidosis	Urinalysis	each visit
Bone deformity (S)	Bone MRI, X-Ray	12–36 months depending on symptoms
MKD		
Amyloidosis	Urinalysis	each visit
Eye disease (S)	Ophthalmologic exam	as needed

Monitoring Table		
Neurologic involvement (S)	Neuropsychological testing	as needed
DIRA		
Spinal and bone deformities (S)	Neck, spine MRI (vertebral osteomyelitis), bone x-ray/MRI, corrective surgery or spinal fusion	as needed
D. Monitoring of treatment-related complications (IL-1 blocking treatments)		
Infections	Clinical history, skin infections, other infections	each visit
Laboratory work	CBC+Diff, LFTs, urinalysis, renal function, Lipid profile	each visit

*The following instruments can be used for symptom monitoring: auto-inflammatory diseases activity index (AIDAI), for damage assessment the autoinflammatory disease damage index (ADDI), for quality of life (QoL), physician global assessment (PGA), Patient's/Parent's Global Assessment (PPGA) (S) may require subspecialty care

CAPS, cryopyrin-associated periodic syndromes; TRAPS, tumour necrosis factor receptor associated periodic syndrome; MKD, mevalonate kinase deficiency; DIRA, deficiency of the IL-1 receptor antagonist; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CBC, complete blood count; SAA, serum amyloid A; LFT, liver function test; BMD, bone mineral density; CNS, central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging;