Recommendations for the management of autoinflammatory diseases

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ABSTRACT

Autoinflammatory diseases are characterised by fever and systemic inflammation, with potentially serious complications. Owing to the rarity of these diseases, evidence-based guidelines are lacking. In 2012, the European project Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) was launched to optimise and disseminate regimens for the management of children and young adults with rheumatic diseases, facilitating the clinical practice of paediatricians and (paediatric) rheumatologists. One of the aims of SHARE was to provide evidence-based recommendations for the management of the autoinflammatory diseases cryopyrin-associated periodic syndromes (CAPS), tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD). These recommendations were developed using the European League Against Rheumatism standard operating procedure. An expert committee of paediatric and adult rheumatologists was convened. Recommendations derived from the systematic literature review were evaluated by an online survey and subsequently discussed at a consensus meeting using Nominal Group Technique. Recommendations were accepted if more than 80% agreement was reached. In total, four overarching principles, 20 recommendations on therapy and 14 recommendations on monitoring were accepted with ≥80% agreement among the experts. Topics included (but were not limited to) validated disease activity scores, therapy and items to assess in monitoring of a patient. By developing these recommendations, we aim to optimise the management of patients with CAPS, TRAPS and MKD.

INTRODUCTION

Autoinflammatory diseases (AID) are rare disorders that affect multiple organ systems and lead to significant morbidity and mortality. Due to the low patient numbers, evidence-based guidelines for treatment are lacking and management is mostly based on physician's experience. As new effective therapeutic options are now available, early diagnosis and treatment might prevent significant organ damage. Reliable recommendations can thus help paediatricians and (paediatric) rheumatologist in the care of patients with these rare diseases.

In 2012, a European initiative called SHARE *(Single Hub and Access point for paediatric Rheumatology in Europe)* was launched to optimise and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases.[1] One of the aims of SHARE was to provide evidence-based recommendations for the management of paediatric rheumatic diseases.

In this paper, we propose recommendations for the management of three of the main monogenic AID:

1. Cryopyrin-associated periodic syndromes (CAPS), caused by gain-of-function mutations in *NLRP3*, is a spectrum of diseases that includes the relatively mild familial cold autoinflammatory syndrome (FCAS), the intermediate Muckle-Wells syndrome (MWS) and the severe neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurological, cutaneous and articular syndrome (CINCA) and their overlaps (FCAS-MWS and MWS-CINCA).[2] CAPS is characterised by fever, urticarial rash, conjunctivitis and articular involvement (typically triggered by cold exposure in FCAS); more severely affected patients with CAPS may also have hearing loss, visual loss, chronic meningitis and amyloidosis.[3 4]
2. Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominant inherited disease. Mutations in *TNFRSF1A* lead to recurrent fever episodes lasting, on average, 10 days, accompanied by varying symptoms including arthralgia, myalgia and abdominal pain.[5]
3. Mevalonate kinase deficiency (MKD), including hyperimmunoglobulin D syndrome and the more severe mevalonic aciduria (MA), is an autosomal recessive metabolic inflammatory disease caused by mutations in *MVK*, affecting the mevalonate pathway.[6] Fever episodes usually last 3–7 days, with lymphadenopathy, abdominal symptoms, arthralgia and a maculopapular skin rash.[7] In addition to the systemic inflammation, patients with MA have a severe metabolic phenotype, including growth retardation, ataxia and cognitive impairment.[8]

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METHODS

An international panel consisting of 22 experts in paediatric or adult rheumatology, internal medicine or nephrology was established to develop evidence-based recommendations for the management and treatment of CAPS, TRAPS and MKD using the European League Against Rheumatism (EULAR) standard operating procedures for developing best practice.[9 10] Eleven of 22 experts were part of the SHARE consortium; 11 additional experts were asked to join the panel based upon their clinical and research expertise in AID.

Systematic literature search

A systematic literature search was performed in Pubmed, Embase and Cochrane databases on 20 June 2013. All synonyms of CAPS, TRAPS and MKD were searched in MeSH/Emtree terms, title and abstract. Further, we searched on 'autoinflammatory diseases' and synonyms, and manually checked references of relevant original studies and reviews for missing articles. For more details on the literature search, refer to online supplementary figures S1, S2 and S3. Fellows (NMtH, MO, JJ) and experts (JBK-D, SMB, MG, JF) selected the relevant papers for validity assessment. Complete reference lists of full-text screened papers can be found in the online supplement.

Validity assessment

A panel of experts (two per paper) independently graded the selected papers on methodological quality and extracted data using predefined scoring forms for diagnostic studies,[11] therapeutic studies[12] and studies describing prognosis and complications.[13] Discrepancies were resolved by discussion between the two experts, or by the opinion of a third expert in select instances. Adapted classification tables for diagnostic,[14] therapeutic[9] and epidemiological studies[15] were used to determine the level of evidence and the strength of each recommendation.

Recommendation development

Recommendations were derived from the available literature and distributed to all experts in an online survey. The drafted recommendations were revised according to comments from the survey and proposed at a face-to-face consensus meeting, where they were discussed by the use of Nominal Group Technique,[16] supervised by an expert (BMF) in consensus building. Recommendations were accepted when ≥80% of the experts agreed.

RESULTS

Literature review

The literature search yielded 1698 unique papers for CAPS, 523 for TRAPS and 618 for MKD. After title/abstract and subsequently full-text screening, 25 CAPS papers, 22 TRAPS papers and 28 MKD papers were assessed for validity and level of evidence, of which 17/25, 17/22 and 17/28 respectively were considered valid and used for recommendation synthesis. For more details, refer to online supplementary figures S1, S2 and S3.

Recommendations

In the following section, we describe each recommendation with the corresponding supporting literature and discuss issues regarding practical implementation. Tables 1–3 summarise the recommendations, their levels of evidence, the recommendation strength and percentage of expert agreement for each. Four additional recommendations, specifically on diagnosis of TRAPS and MKD can be found in online supplementary table S1. Recommendations that did not meet ≥80% agreement are listed in online supplementary table S2.

Overarching principles

AID affect multiple organ systems with potentially severe complications;[4 5 7 8 17–26] hence, management of these patients is complex and warrants a multidisciplinary approach: this could involve physiotherapists, paediatricians, rheumatologists and other specialists when specific organs are involved, for example, ENT specialists, ophthalmologists or nephrologists. Furthermore, access to genetic expertise is important because interpretation of genetic results and genetic counselling for family members may be challenging.[27] For MA, expertise in metabolic diseases is also required.

Given the lifelong duration of AID and impact on patients' and families' life, care should be patient-centred and family-centred, as is the case for most (chronic) diseases.[28] Patients with CAPS, TRAPS and MKD have an impaired quality of life compared with healthy controls, in both physical and psychosocial domains, and could encounter limitations in education and daily activities.[7 25 29] It is therefore important to offer psychosocial support as appropriate.

Treatment goals should include control of the disease activity and prevention of organ damage, since effective therapy might prevent or stabilise organ damage.[21 30 31] Effective treatment can also improve participation in daily activities and quality of life; this is thus an important additional goal of therapy.[31–33]

Table 1 Overarching principles for CAPS, TRAPS and MKD

Overarching principles	L	S	Agree (%)
Management of patients with AID should ideally be guided by a multidisciplinary team in a tertiary centre with expertise in AID, with access to genetic counselling	4	D	100
The care of patients with AID should include shared patient-centred and family-centred decision-making with the multidisciplinary team	4	D	100
Aims of the treatment of AID include: ▶ Early and rapid control of disease activity ▶ Prevention of disease and treatment-related damage ▶ Enabling participation in daily activities ▶ Improvement of health-related quality of life	4	D	100
In patients with AID, psychosocial support is recommended as appropriate	4	D	100

L, level of evidence; 4, expert opinion; S, strength of recommendation; D, based on level 4 evidence.[9] Agree, percentage of experts who agreed on the recommendation during the final voting round of the consensus meeting.
AID, autoinflammatory diseases; CAPS, cryopyrin-associated periodic syndromes; MKD, mevalonate kinase deficiency; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

Table 2 Recommendations for the treatment of CAPS, TRAPS and MKD

	L	S	Agree (%)
Treatment CAPS			
IL-1 inhibition is indicated for the whole spectrum of CAPS, at any age	1B–2A*	A–B	94.4
To prevent organ damage, long-term IL-1 inhibition should be started as early as possible in patients with active disease	2B	B	100
There is no evidence for the efficacy of DMARDs or biological therapy other than IL-1 blockade in CAPS	4	D	94.4
For symptomatic adjunctive therapy, short courses of NSAIDs and corticosteroids may be used,# but they should not be used for primary maintenance therapy##	#3 ##4	#C ##D	100
In patients with CAPS, adjunctive therapy (eg, physiotherapy, orthotic devices, hearing aids) is recommended as appropriate	4	D	100
Treatment TRAPS			
NSAIDs may provide symptom relief during inflammatory attacks	3	D	100
Short-term glucocorticoids, with or without NSAIDs, are effective for terminating inflammatory attacks	3	C	100
The beneficial effect of corticosteroids can decline over time so that increasing doses are required to achieve an equivalent response	3	C	100
IL-1 blockade is beneficial in the majority of patients with TRAPS.	2B	B	100
Etanercept can be effective in some patients, but the effect might decline over time	2B	C	93.8
With frequent attacks and/or subclinical inflammation between attacks, maintenance therapy with IL-1 blockade or etanercept is recommended and may limit corticosteroid exposure	2B–3*	C	100
If one IL-1 blocking agent at adequate dose is ineffective or intolerable, a switch to etanercept or another IL-1 blocking agent should be considered Likewise, if etanercept is ineffective or intolerable, a switch to an IL-1 blocking agent should be considered	4	D	100
Although a beneficial effect is reported in a few cases, the use of anti-TNF monoclonal antibodies is not advised, due to the possible detrimental effect	3	C	100
Treatment MKD			
NSAIDs may provide symptom relief during inflammatory attacks	3	C	100
Short-term glucocorticoids, with or without NSAIDs, may be effective for alleviating inflammatory attacks	3	C	100
Colchicine or statins are not efficacious; therefore we do not recommend their use	3	C	100
Short-term IL-1 blockade may be effective for terminating inflammatory attacks and should be considered to limit or prevent steroid side effects	2B	C	100
With frequent attacks and/or subclinical inflammation between attacks, maintenance therapy with IL-1 blockade or etanercept is recommended, and may limit corticosteroid exposure	2B–3*	C	93.3
If one IL-1 blocking agent at adequate dose is ineffective or intolerable, a switch to another IL-1 blocking agent or another biological agent (including TNF-α blockade or IL-6 blockade) should be considered. Likewise, if TNF-α blockade is ineffective or intolerable, a switch to another biological agent (including an IL-1 or IL-6 blocking agent) should be considered	4	D	100
In selected cases with severe refractory disease with poor quality of life, referral to a specialist centre for consideration of allogeneic haematopoietic stem cell transplantation is recommended.	3	D	93.3

L, level of evidence; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4, expert opinion; S, strength of recommendation; A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 evidence.[9] Agree, percentage of experts who agreed on the recommendation during the final voting round of the consensus meeting.
*See table 4 for detailed information on evidence and approval of IL-1 blocking and TNF-blocking agents.
CAPS, cryopyrin-associated periodic syndromes; DMARDs, disease-modifying antirheumatic drugs; IL, interleukin; MKD, mevalonate kinase deficiency; NSAIDs, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

Diagnosis

Early diagnosis is crucial to enable treatment initiation before damage occurs. Although diagnostic delay has decreased in the last decades, the median time between onset of symptoms and diagnosis is still 1–2 years.[34] The diagnostic score for molecular analysis of patients with recurrent fever[35] and the recently published clinical classification criteria for the diagnosis of monogenic AID[36] can facilitate the diagnostic process and decrease this delay. We refer to these papers for more details. For CAPS, diagnostic criteria are currently being developed.

Interpretation of genetic tests can also be challenging, especially with low-penetrance *TNFRSF1A* mutations or *NLRP3* mutation-negative CAPS patients. Recently published guidelines for genetic diagnosis of AID can guide physicians and geneticists.[27] We support the use of these guidelines in the diagnostic process. Specific recommendations on diagnosis, for example, the use of serum immunoglobulin D and urinary mevalonic acid excretion in the diagnostic process of MKD, can be found in supplementary table S1.

Therapy

Cryopyrin-associated periodic syndromes

Three interleukin (IL)-1 blocking agents are currently used for CAPS. For a summary of the evidence and the authorisation of the European Medicines Agency (EMA) and Food and Drug Administration (FDA), refer to table 4 and the websites of both organisations.[37 38]

Anakinra was effective in observational studies of patients with CINCA/NOMID (aged 9 months–42 years),[31 39 40] MWS (3–75 years)[40–42] and adult patients with FCAS.[40 43] Starting dose of anakinra varied between 0.5 and 2 mg/kg/day (children) or 100 mg (adults) subcutaneously, but some patients, especially young children, required dose escalation up to 5 or 8 mg/kg/day to achieve sustained remission.[31 42] A study on pharmacokinetics of anakinra supports this finding: in order to reach the same effective steady-state concentration, young children need higher doses of anakinra.[44]

Canakinumab was effective in two randomised controlled trials (RCTs) of patients with CAPS (MWS and CINCA/MWS-overlap, aged 9–74 years),[32 45] and in four observational studies of all disease phenotypes and age categories.[40 42 46 47] Canakinumab was administered subcutaneously at a dose of 2 mg/kg (children) or 150 mg (adults) once per 8 weeks, but one study mentions that 24% of 166 patients required dose escalation up to 8 mg/kg or 600 mg; this was especially the case for paediatric patients or patients with more severe phenotypes.[47]

The efficacy of rilonacept (2.2 mg/kg or 160 mg weekly) was demonstrated in one RCT including adult patients with MWS

Table 3 Recommendations for monitoring of CAPS, TRAPS and MKD

	L	S	Agree (%)
Monitoring—overarching principles			
Monitoring of disease activity and damage is important in patients with AID and should be done regularly	4	D	93.8
Monitoring frequency should depend on disease severity and activity	4	D	93.8
The Autoinflammatory Diseases Activity Index (AIDAI) is a validated tool to assess disease activity and should be used in clinical studies of patients with TRAPS and MKD	2B	B	100
Physicians should consider other potential causes (eg, infections) when patients experience inflammatory episodes that are atypical of their disease	4	D	100
Prior to therapy with biological agents, consideration should be made to give live and killed vaccines as appropriate. There are currently insufficient safety data to recommend live vaccines during therapy with biological agents.	4	D	100
Monitoring CAPS			
Monitoring in all patients with CAPS should include: ▶ General physical examination, emphasising musculoskeletal and neurological examination, and growth and development of children ▶ Blood count and inflammatory parameters, such as C-reactive protein (CRP) and serum amyloid A (SAA), if available ▶ Disease activity, using a validated tool ▶ Hearing (audiograms) and ophthalmological examination ▶ Testing for proteinuria ▶ Impact of disease on well-being, functioning and social participation	4	D	100
For monitoring the disease course of patients with more severe phenotypes, consider including the following tests: ▶ Cognitive testing ▶ Lumbar puncture (pressure, cells, protein level) ▶ Bone MRI and skeletal X-ray ▶ Brain MRI (including imaging of the inner ear)	4	D	100
Monitoring TRAPS			
Monitoring in all patients with TRAPS should include: ▶ General physical examination and growth and development of children. ▶ Full blood count and inflammatory parameters, such as CRP and SAA, if available ▶ Disease activity, using a validated tool ▶ Testing for proteinuria ▶ Impact of disease on well-being, functioning and social participation	4	D	100
Interpretation of the significance of the R92Q and P46L sequence variants can be difficult. These occur at a high frequency in healthy controls, and their pathogenic significance remains contentious. Some individuals develop a clinical phenotype of TRAPS, although sometimes with shorter and/or more frequent fever episodes.	2B	B	100
Generally, patients carrying R92Q or P46L have milder disease and a better prognosis (improvement over time; and low risk of AA amyloidosis) compared with structural *TNFRSF1A* mutations.	1B	B	89.5
Patients with chronic, persistent disease activity have a higher risk of developing AA amyloidosis.	2B	B	100
Monitoring MKD			
Monitoring in all patients with MKD should include: ▶ General physical examination; and growth and development of children ▶ Full blood count and inflammatory parameters, such as CRP and SAA, if available ▶ Disease activity, using a validated tool ▶ Analysis for proteinuria and haematuria ▶ Impact of disease on well-being, functioning and social participation ▶ Ophthalmological examination	4	D	87.5
For monitoring the disease course of patients with more severe phenotypes, consider including the following examinations: ▶ Cognitive testing ▶ Muscle and liver enzymes ▶ Specific neurological examination	4	D	100
Besides infections, physicians should also be alert to the possibility of macrophage activation syndrome in patients with MKD.	3	C	100

L, level of evidence; 1B, prospective cohort study with good follow-up; 2B, retrospective cohort study, or prospective with poor follow-up; 3, non-consecutive or limited cohort study; 4, case series or expert opinion. S, strength of recommendation; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 evidence.[15] Agree, percentage of experts who agreed on the recommendation during the final voting round of the consensus meeting.
AID, autoinflammatory diseases; CAPS, cryopyrin-associated periodic syndromes; MKD, mevalonate kinase deficiency; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

and FCAS[48] and two observational studies including patients with MWS and FCAS aged 12–80 years.[40 49]

In CAPS, there is no evidence for the efficacy of disease-modifying antirheumatic drugs or biological therapy other than IL-1 blockade.[50] Some patients benefit from non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, mostly as on-demand symptom relief next to IL-1 blocking agents.[39 50] Because of the lack of valid literature on efficacy and prevention of organ damage if used solely, we do not recommend the use of NSAIDs and corticosteroids without IL-1 inhibition.

Organ damage such as hearing loss, neurological damage and joint deformity causes considerable morbidity in patients with CAPS and can partly be stabilised or improved with IL-1 inhibition.[21 30 31 51] Therefore, it is important to start IL-1 inhibition early, before severe damage occurs. When patients develop irreversible damage, they may need adjunctive therapy such as physiotherapy, orthotic devices and hearing aids.

TNF receptor-associated periodic syndrome

Evidence for therapy of patients with TRAPS relies on retrospective cohorts or small prospective studies at best. In one retrospective cohort, NSAIDs provided symptom relief in approximately 75% of patients with TRAPS, but were rarely completely effective in terminating inflammatory episodes.[50] Efficacy of corticosteroids has only been assessed in

Table 4 Summary of evidence and regulatory authorisations for IL-1 blockade and TNF-blockade

	L	EMA approval	FDA approval
CAPS			
Canakinumab	1B	Approved for patients with CINCA/NOMID, MWS and 'severe FCAS'* ≥2 years and ≥7.5 kg body weight	Approved for patients with FCAS and MWS ≥4 years
Rilonacept	1B	–	Approved for patients with FCAS and MWS ≥12 years
Anakinra	2A	Approved for all patients with CAPS ≥8 months and ≥10 kg body weight	Approved for patients with CINCA/NOMID (all ages)
TRAPS			
Canakinumab	3	Orphan designation	–
Anakinra	2B	–	–
Etanercept	2B	–	–
MKD			
Canakinumab	3	–	–
Anakinra	2B	–	–
Etanercept	3	–	–
Adalimumab	3	–	–

L, level of evidence as assessed in a systematic review up to June 2013. 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study.[9] Approval as published on websites of EMA (European Medicines Agency) and FDA (US Food and Drug Administration) up to June 2015.[37 38]
*Severe FCAS is defined by EMA as FCAS presenting with signs and symptoms beyond cold-induced urticarial skin rash.
CAPS, cryopyrin-associated periodic syndromes; CINCA, chronic, infantile, neurological, cutaneous and articular syndrome; FCAS, familial cold autoinflammatory syndrome; IL, interleukin; MKD, mevalonate kinase deficiency; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; TNF, tumour necrosis factor; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

retrospective studies, in which most patients reported a beneficial effect.[23 50 52–54] Unfortunately, this initial favourable response often declines with time.[53]

A summary of the evidence and authorisation details for IL-1 blocking and TNF-blocking agents is provided in table 4. Etanercept efficacy was assessed in two small prospective studies; these demonstrated significant improvement in symptoms and inflammatory parameters in most patients but also highlighted declining efficacy over time. This latter finding was the reason for discontinuing etanercept in 11/13 patients in one study.[55–57] Loss of etanercept efficacy was also reported in larger retrospective studies describing transient responses, and a complete remission rate of less than one-third of patients.[50 58] Anakinra was effective as on-demand as well as maintenance therapy in a small prospective study.[59] Retrospective studies confirm this finding; a complete response was reported in two-thirds of the patients.[50 58] However, anakinra-failure was also observed.[50 60]

Because long-term disease activity can cause AA amyloidosis[5] and long-term use of corticosteroids can induce significant side-effects,[61–63] we recommend maintenance therapy with IL-1 blockade or etanercept in patients with frequent attacks and/or ongoing (subclinical) inflammation. In retrospective studies, IL-1 blockade seems to be superior to etanercept.[50] However, as prospective randomised trials comparing efficacy between these drugs are lacking, insufficient evidence is available to clearly recommend one specific agent as first-line.

Evidence in TRAPS for switching from one biological agent to another is restricted to one study that showed efficacy of anakinra after patients experienced loss of efficacy to etanercept.[55] Studies in other diseases also suggest that switching could be beneficial and should be considered when the initial treatment choice is ineffective or intolerable.[42 64] For IL-1 blockade, dose adjustments might be necessary to achieve complete response, as has been shown in patients with CAPS.[31 42 44 47]

The use of adalimumab and infliximab induces variable results in case reports, including failure and even worsening of TRAPS symptoms; these drugs are thus not recommended.[50 56 57]

Mevalonate kinase deficiency

Treatment efficacy in MKD is mostly described in retrospective cohorts. Most patients benefited from the use of NSAIDs, mainly given during inflammatory attacks.[7 8 50] However, NSAIDs are not effective for terminating inflammatory attacks. Similarly, the efficacy of glucocorticoids has only been assessed retrospectively, and most patients derive some therapeutic benefit.[7 8 50] Colchicine and statins are ineffective; moreover, statins induced a severe attack in a patient with MA.[7 8 26 50]

A small prospective study showed that anakinra on demand significantly reduced all features of the fever episode compared with attacks not treated with anakinra.[65] When patients have frequent attacks and/or subclinical inflammation between attacks, maintenance therapy with IL-1 blockade or etanercept is recommended. Continuous IL-1 blockade with anakinra or canakinumab, or TNF-blockade with etanercept or adalimumab, was beneficial in approximately two-thirds of reported patients.[7 26 50 66] Because head-to-head comparisons are lacking, it is not possible to recommend any one of these agents as first-line biological therapy. Table 4 summarises the evidence relating to IL-1 and TNF-blocking agents in MKD. Although there is currently no evidence to support switching biological agents in MKD when initial treatment fails, based on the success of this approach in other diseases,[42 64] this should be considered. Again, for IL-1 blockade, dose adjustments might be tried first, as the initial dose might be insufficient.

In selected cases with severe refractory disease and poor quality of life, allogeneic haematopoietic stem cell transplantation (HSCT) could be a valuable option. Four cases of successful allogeneic HSCT have been reported: all experienced a remission of systemic inflammation and an improvement of neurological symptoms.[67–69] Nonetheless, because of the inherent risks associated with HSCT, this should only be considered in severely affected patients resistant to (or intolerant of) all the other aforementioned therapeutic agents.

Monitoring

General

Since disease-related and treatment-related morbidity is common, and dose adjustment of IL-1 blocking agents to achieve complete

remission may be required, regular monitoring is crucial.[39 47] Disease severity varies widely among patients, and thus we recommend that the specific monitoring frequency should be tailored to suit individual patient requirements.

The use of a validated disease activity score is crucial for standardised monitoring of patients with AID. The Autoinflammatory Diseases Activity Index (AIDAI) is the only validated disease activity index for TRAPS and MKD, and one of the validated scores for CAPS.[70 71] Another validated disease activity score for patients with CAPS is the MWS Disease Activity Score (MWS-DAS).[72] To increase standardised outcome measurements and thus improve comparisons between studies, we recommend that a validated score should be used in clinical studies of patients with AID: the AIDAI for TRAPS and MKD, and either the AIDAI or MWS-DAS for CAPS.

During monitoring, patients may experience inflammatory episodes that are atypical of their disease; it is important to be aware of other causes of these atypical episodes. Infections are common, especially in children, and might be more common or more dangerous in patients with AID due to their disease and/or immunosuppressive medication.[26 31 39 41–43 45 47 49 73] When initiating therapy with biological agents, consideration should be made to give live-attenuated and non-live vaccines as appropriate. According to EULAR recommendations for vaccination in patients with rheumatic diseases, physicians should withhold live-attenuated vaccines when a patient is treated with biological agents.[74 75] Some studies suggest that live-attenuated booster vaccination against measles-mumps-rubella and yellow fever can be safely used in patients using TNF-blocking agents.[76–78] Evidence on safety of vaccinations during IL-1 blocking agents is limited to one randomised study of healthy subjects[79] and a note that 25 patients with CAPS on canakinumab received vaccinations without abnormal immune responses or pathogen-related infections.[47] However, data on live-attenuated vaccines are still scarce; hence we concluded that there are currently insufficient safety data to recommend live vaccines during therapy with biological agents, especially during IL-1 blockade.

Cryopyrin-associated periodic syndromes

Experts created a list of items that should be included in the monitoring of all patients with CAPS (table 3), based on all relevant symptoms and complications described in patients with CAPS as well as the impact of disease on daily life.[17 18 20 21 30 32 72 80–83] For the more severe CAPS phenotypes, additional tests such as imaging of bone and brain, including inner ear should be considered, as well as cognitive testing and lumbar puncture to assess chronic meningitis. Because bone overgrowth mainly involves the lower limbs, we recommend performing imaging (including skeletal X-ray and MRI) of the femurs, patellae and tibiae.

TNF receptor-associated periodic syndrome

Most TRAPS symptoms can be assessed by history taking and physical examination.[5 22–25] Amyloidosis is described in about 10% of the patients with TRAPS and occurs more often in patients with long disease duration.[5 22 23 84] Hence, inflammatory parameters and proteinuria should be checked regularly.[5 22 23] A list of particularly relevant items to check when monitoring a patient with TRAPS can be found in table 3.

Interpretation of the low-penetrance variants R92Q and P46L can be difficult, as 1%–2% of asymptomatic controls also harbour these variants.[22 84] Patients with R92Q or P46L variants who experience symptoms compatible with TRAPS have a similar phenotype as patients with other *TNFRSF1A* mutations, although sometimes with shorter and/or more frequent fever episodes.[5 23 25] These patients are also more likely to have a milder disease course (resolution or decrease in fever episodes) and a decreased risk of developing AA amyloidosis compared with patients with structural *TNFRSF1A* mutations.[5 22 23 25]

Mevalonate kinase deficiency

Most of the mild MKD symptoms can be assessed by history taking and physical examination and routine laboratory measures such as full blood count, C-reactive protein (CRP) and serum amyloid A (SAA) to assess systemic inflammation.[7 26] Urine analysis should be performed for renal complications such as AA amyloidosis, glomerulonephritis and renal angiomyolipoma[7 26] as well as ophthalmological examination for retinitis pigmentosa and cataracts.[26 85]

Patients with more severe MKD phenotypes have neurological complications such as ataxia, hypotonia and psychomotor retardation; thus cognitive testing and full neurological examination should be considered.[8 26] Since hepatitis and myopathy are also reported in these patients, testing muscle and liver enzymes may be relevant. A list of items particularly relevant for monitoring MKD is provided in table 3.

In addition to an increased infection risk, physicians should also be aware of a higher risk of macrophage activation syndrome (MAS) in patients with MKD, especially in the assessment of atypical fever episodes. MAS is a life-threatening complication of some rheumatic diseases (eg, systemic juvenile idiopathic arthritis), characterised by high fever, pancytopenia and liver damage.[86] In one cohort of patients with MKD, the frequency of MAS was surprisingly high (6/50, 12%).[26]

DISCUSSION

The SHARE taskforce formulated a total of 42 recommendations for the management of patients with the autoinflammatory diseases CAPS, TRAPS and MKD, based on a systematic literature review and consensus procedure.

Biological therapies have dramatically improved the outcome of patients with AID; this is especially true for patients with CAPS on IL-1 blockade. However, evidence supporting the use of biologicals is still very limited in TRAPS and MKD. Prospective studies and head-to-head comparisons are needed to draw solid conclusions on the efficacy of biologicals and to enable EMA/FDA approval. At the time of writing, prospective clinical trials are ongoing: two Phase 2 studies on canakinumab for MKD (NCT01303380) and TRAPS (NCT01242813) and a Phase 3 study on canakinumab for hereditary periodic fevers (NCT02059291).[87] Regarding the use of IL-1 blockade in very young children with CAPS, the current regulatory approvals by FDA and EMA are provided in table 4. It is recognised, however, that some young patients with severe CAPS may require treatment earlier in life than currently recommended by the authorities. Studies on the safety of canakinumab in the very young are soon-to-be published.

Close monitoring of patients' symptoms, damage and well-being is an important requirement for 'treat to target' strategies. Structured long-term follow-up studies of patients with AID are warranted to clarify complication risks. Given the rarity of these diseases, international collaboration is crucial to recruit sufficient patient numbers. Validated scores for disease activity and damage are essential in order to perform a structured assessment of outcome, especially to determine long-term therapeutic efficacy and therapy-associated morbidity. Disease activity scores have now been developed, however, disease damage scores are still lacking.

A significant limitation of these recommendations is the lack of high-quality evidence. Other than the use of IL-1 blockade in CAPS, most topics are not thoroughly studied. Thus, most of our recommendations have a strength C or D and depend mainly on expert opinion. Therefore, further research on complications, monitoring and the use of biological agents in TRAPS and MKD is necessary to enable better evidence-based recommendations. To conclude, based on the best available evidence and expert opinion, this SHARE initiative provides recommendations on diagnosis, treatment and monitoring of CAPS, TRAPS and MKD, aiming to optimise the management of these rare patients.

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