

## Recommendations for the management of autoinflammatory diseases

This is the peer reviewed version of the following article:

*Original:*

Ter Haar, N.M., Oswald, M., Jeyaratnam, J., Anton, J., Barron, K.S., Brogan, P.A., et al. (2015). Recommendations for the management of autoinflammatory diseases. ANNALS OF THE RHEUMATIC DISEASES, 74(9), 1636-1644 [10.1136/annrheumdis-2015-207546].

*Availability:*

This version is available <http://hdl.handle.net/11365/980241> since 2016-01-15T12:06:12Z

*Published:*

DOI:10.1136/annrheumdis-2015-207546

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## RECOMMENDATIONS FOR THE MANAGEMENT OF AUTOINFLAMMATORY DISEASES

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### **Key words**

Hereditary Autoinflammatory Diseases

Cryopyrin-Associated Periodic Syndromes

Tumor necrosis factor receptor-associated periodic syndrome

Mevalonate Kinase Deficiency

Guidelines

Word count: 3275

Abstract: 216

### **Contributor statement**

NW and [SBV](#) designed the SHARE initiative. NH, MO and JJ performed the systematic literature review, supervised by JF, JKD, SB and MG. Validity assessment of selected papers was done by MH, IKP, LC, MG and JKD (CAPS), MG, HL, PB, GG (TRAPS) and JF, AS, JA, CG (MKD). Recommendations were formulated by NH, MO, JF, JKD, SB and MG. The expert committee consisted of JA, KB, PB, LC, CG, GG, VH, MH, TK, IKP, HL, HO, SO, RR, AS, YU, CW, [SBV](#), JF, MG and JKD; they completed the online surveys and/or participated in the subsequent consensus meeting. BF assisted in the preparation of the live consensus meeting and led the consensus procedure using nominal group technique. NH wrote the manuscript, with contribution and approval of all co-authors.

## **Abstract**

### **Background**

*Autoinflammatory diseases are characterized by fever and systemic inflammation, with potentially serious complications. Due to the rarity of these diseases, evidence-based guidelines are lacking. In 2012, the European project SHARE was launched to optimize 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), Tumor necrosis factor (TNF) Receptor Associated Periodic Syndrome (TRAPS) and Mevalonate Kinase Deficiency (MKD).*

### **Patients and methods**

*Evidence-based recommendations were developed using the European League Against Rheumatism (EULAR) 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.*

### **Results**

*In total, four overarching principles, twenty recommendations on therapy and fourteen recommendations on monitoring were accepted with  $\geq 80\%$  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.*

### **Conclusion**

*The SHARE initiative provides recommendations for the management of the autoinflammatory diseases 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 optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases.<sup>1</sup> 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 autoinflammatory diseases:

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 Neurologic, Cutaneous and Articular Syndrome (CINCA) and their overlaps (FCAS-MWS and MWS-CINCA).<sup>2</sup> CAPS is characterized by fever, urticarial rash, conjunctivitis and articular involvement (typically triggered by cold exposure in FCAS); more severely affected CAPS patients can also suffer from hearing loss, visual loss, chronic meningitis and amyloidosis.<sup>3,4</sup>

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.<sup>5</sup>

3. Mevalonate Kinase Deficiency (MKD), including Hyper-IgD Syndrome (HIDS), and the more severe Mevalonic Aciduria (MA), is an autosomal recessive metabolic inflammatory disease caused by mutations in *MVK*, affecting the mevalonate pathway.<sup>6</sup> Fever episodes usually last 3-7 days, with lymphadenopathy, abdominal symptoms, arthralgia and a maculopapular skin rash.<sup>7</sup> In addition to the systemic inflammation, MA patients have a severe metabolic phenotype, including growth retardation, ataxia and cognitive impairment.<sup>8</sup>

## 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 EULAR standard operating procedures for developing best practice.<sup>9, 10</sup> Eleven of 22 experts were part of the SHARE consortium; eleven additional experts were asked to join the panel based upon their clinical and research expertise in autoinflammatory diseases.

### **Systematic literature search**

A systematic literature search was performed in Pubmed, Embase and Cochrane databases on 20th 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. The reader is referred to supplementary figures S1, S2 and S3 for more details on the literature search. Fellows (NtH, MO, JJ) and experts (JKD, SB, 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,<sup>11</sup> therapeutic studies<sup>12</sup> and studies describing prognosis and complications.<sup>13</sup> 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,<sup>14</sup> therapeutic<sup>9</sup> and epidemiological studies<sup>15</sup> 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,<sup>16</sup> supervised by an expert (BF) in consensus building. Recommendations were accepted when  $\geq 80\%$  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, we refer to 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 summarize 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 supplementary table S1. Recommendations that did not meet  $\geq 80\%$  agreement are listed in supplementary table S2.

**Table 1. Overarching principles for CAPS, TRAPS and MKD.**

Overarching principles	L	S	Agree
Management of AID patients should ideally be guided by a multidisciplinary team in a tertiary center with expertise in autoinflammatory diseases, with access to genetic counseling.	4	D	100%
The care of AID patients should include shared patient and family-centered decision making with the multidisciplinary team.	4	D	100%
Aims of the treatment of AID include: <ul style="list-style-type: none"> <li>• Early and rapid control of disease activity</li> <li>• Prevention of disease and treatment-related damage</li> <li>• Enabling participation in daily activities</li> <li>• Improvement of health-related quality of life</li> </ul>	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.<sup>9</sup>  
**Agree**, percentage of experts that agreed on the recommendation during the final voting round of the consensus meeting. AID, autoinflammatory diseases.

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

Treatment CAPS	L	S	Agree
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 <sup>1</sup> , but they should not be used for primary maintenance therapy. <sup>2</sup>	<sup>1</sup> 3 <sup>2</sup> 4	<sup>1</sup> C <sup>2</sup> D	100%
In patients with CAPS, adjunctive therapy (for example physiotherapy, orthotic devices, hearing aids) is recommended as appropriate.	4	D	100%
Treatment TRAPS	L	S	Agree
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 TRAPS patients.	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	L	S	Agree
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 biologic agent (including TNF- $\alpha$ blockade or IL-6 blockade) should be considered. Likewise, if TNF- $\alpha$ blockade is ineffective or intolerable, a switch to another biologic 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; 1A, meta-analysis of randomised controlled trial; 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<sup>9</sup> \* see table 4 for detailed information on evidence and approval of IL-1 blocking and TNF-blocking agents. **Agree**, percentage of experts that agreed on the recommendation during the final voting round of the consensus meeting. DMARDs, disease-modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs.

**Table 3. Recommendations for monitoring of CAPS, TRAPS and MKD**

<b>Monitoring – overarching principles</b>	<b>L</b>	<b>S</b>	<b>Agree</b>
Monitoring of disease activity and damage is important in AID patients 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 with TRAPS and MKD patients.	2A	B	100%
Physicians should consider other potential causes (e.g. infections) when patients experience inflammatory episodes which are atypical of their disease.	4	D	100%
Prior to therapy with biologic 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 biologic agents.	4	D	100%
<b>Monitoring CAPS</b>	<b>L</b>	<b>S</b>	<b>Agree</b>
Monitoring in all CAPS patients should include: <ul style="list-style-type: none"> <li>• General physical examination, emphasizing musculoskeletal and neurological examination, and growth and development for children</li> <li>• Blood count and inflammatory parameters, such as CRP and SAA if available</li> <li>• Disease activity, using a validated tool</li> <li>• Hearing (audiograms), and ophthalmological examination</li> <li>• Testing for proteinuria</li> <li>• Impact of disease on wellbeing, functioning and social</li> </ul>	4	D	100%

participation			
For monitoring the disease course of patients with more severe phenotypes, consider including the following tests: <ul style="list-style-type: none"> <li>• Cognitive testing</li> <li>• Lumbar puncture (pressure, cells, protein level)</li> <li>• Bone MRI and skeletal X-ray</li> <li>• Brain MRI (including imaging of the inner ear)</li> </ul>	4	D	100%
<b>Monitoring TRAPS</b>	<b>L</b>	<b>S</b>	<b>Agree</b>
Monitoring in all TRAPS patients should include: <ul style="list-style-type: none"> <li>• General physical examination and growth and development for children.</li> <li>• Full blood count and inflammatory parameters, such as C-reactive protein (CRP)</li> <li>• and serum amyloid A (SAA) if available</li> <li>• Disease activity, using a validated tool</li> <li>• Testing for proteinuria</li> <li>• Impact of disease on well-being, functioning and social participation</li> </ul>	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, albeit 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 to structural <i>TNFRSF1A</i> mutations.	1B	B	89.5%
Patients with chronic, persistent disease activity have a higher risk of developing AA amyloidosis.	2B	B	100%
<b>Monitoring MKD</b>	<b>L</b>	<b>S</b>	<b>Agree</b>
Monitoring in all MKD patients should include: <ul style="list-style-type: none"> <li>• General physical examination; and growth and development for children.</li> <li>• Full blood count and inflammatory parameters, such as CRP and SAA if available</li> <li>• Disease activity, using a validated tool</li> <li>• Analysis for proteinuria and haematuria</li> <li>• Impact of disease on well-being, functioning and social participation</li> <li>• Ophthalmologic examination</li> </ul>	4	D	87.5%
For monitoring the disease course of patients with more severe phenotypes, consider including the following examinations: <ul style="list-style-type: none"> <li>• Cognitive testing</li> <li>• Muscle and liver enzymes</li> <li>• Specific neurological examination</li> </ul>	4	D	100%
Besides infections, physicians should also be alert to the possibility of macrophage activation syndrome (MAS) in patients with MKD.	3	C	100%

**L**, level of evidence; 1A, meta-analysis of prospective cohort studies; 1B, prospective cohort study with good follow-up; 2A, meta-analysis of 2B studies; 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; 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.<sup>15</sup> **Agree**, percentage of experts that agreed on the recommendation during the final voting round of the consensus meeting.

## Overarching principles

AID affect multiple organ systems with potentially severe complications,<sup>4, 5, 7, 8, 17-26</sup> 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, e.g. ENT specialists, ophthalmologists or nephrologists. Furthermore, access to genetic expertise is important because interpretation of genetic results and genetic counseling for family members may be challenging.<sup>27</sup> For mevalonic aciduria, expertise in metabolic diseases is also required.

Given the lifelong duration of AID and impact on patients' and families' life, care should be patient- and family-centered, as is the case for most (chronic) diseases.<sup>28</sup> CAPS, TRAPS and MKD patients have an impaired quality of life compared to healthy controls, in both physical and psychosocial domains, and could encounter limitations in education and daily activities.<sup>7, 25, 29</sup> 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 stabilize organ damage.<sup>21, 30, 31</sup> Effective treatment can also improve participation in daily activities and quality of life; this is thus an important additional goal of therapy.<sup>31-33</sup>

## 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.<sup>34</sup> The diagnostic score for molecular analysis of patients with recurrent fever<sup>35</sup> and the recently published clinical classification criteria for the diagnosis of monogenic AID<sup>36</sup> 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.<sup>27</sup> We support the use of these guidelines in the diagnostic process. Specific recommendations on diagnosis, for example the use of serum IgD and urinary mevalonic acid excretion in the diagnostic process of MKD, can be found in supplementary table S1.

## Therapy

### CAPS

Three IL-1 blocking agents are currently used for CAPS. For a summary of the evidence and the authorization of the European Medicines Agency (EMA) and Food and Drug Administration (FDA), we refer to table 4 and the websites of both organizations.<sup>37, 38</sup>

Anakinra was effective in observational studies with CINCA/NOMID patients (aged 9 months-42 years),<sup>31, 39, 40</sup> MWS patients (3-75 years)<sup>40-42</sup> and adult FCAS patients.<sup>40, 43</sup> Starting dose of anakinra varied between 0.5 to 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.<sup>31, 42</sup> 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.<sup>44</sup>

Canakinumab was effective in two randomized controlled trials (RCTs) of CAPS patients (MWS and CINCA/MWS-overlap, aged 9-74 years),<sup>32, 45</sup> ADDIN EN.CITE and in four observational studies with all disease phenotypes and age categories.<sup>40, 42, 46, 47</sup> 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.<sup>47</sup>

The efficacy of rilonacept (2.2 mg/kg or 160 mg weekly) was demonstrated in one RCT including adult MWS and FCAS patients,<sup>48</sup> and two observational studies including MWS and FCAS patients aged 12-80 years.<sup>40, 49</sup>

In CAPS, there is no evidence for the efficacy of disease-modifying anti-rheumatic drugs (DMARDs) or biological therapy other than IL-1 blockade.<sup>50</sup> Some patients benefit from non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, mostly as on-demand symptom relief next to IL-1 blocking agents.<sup>39, 50</sup> 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 CAPS patients, and can partly be stabilized or improved with IL-1 inhibition.<sup>21, 30, 31, 51</sup> 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.

## **TRAPS**

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

studies, in which most patients reported a beneficial effect.<sup>23, 50, 52-54</sup> Unfortunately, this initial favourable response often declines with time.<sup>53</sup>

A summary of the evidence and authorization 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.<sup>55-57</sup> 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.<sup>50, 58</sup> Anakinra was effective as on-demand as well as maintenance therapy in a small prospective study.<sup>59</sup> Retrospective studies confirm this finding; a complete response was reported in two-thirds of the patients.<sup>50, 58</sup> However, anakinra-failure was also observed.<sup>50, 60</sup>

Because long-term disease activity can cause AA amyloidosis<sup>5</sup> and long-term use of corticosteroids can induce significant side-effects,<sup>61-63</sup> 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.<sup>50</sup> However, as prospective randomized 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 biologic agent to another is restricted to one study that showed efficacy of anakinra after patients experienced loss of efficacy to etanercept.<sup>55</sup> Studies in other diseases also suggest that switching could be beneficial, and should be considered when the initial treatment choice is ineffective or intolerable.<sup>42, 64</sup> For IL-1 blockade, dose adjustments might be necessary to achieve complete response, as has been shown in CAPS patients.<sup>31, 42, 44, 47</sup>

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.<sup>50, 56, 57</sup>

## **MKD**

Treatment efficacy in MKD is mostly described in retrospective cohorts. Most patients benefited from the use of NSAIDs, mainly given during inflammatory attacks.<sup>7, 8, 50</sup> 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.<sup>7, 8, 50</sup> Colchicine and statins are ineffective; moreover statins induced a severe attack in a mevalonic aciduria patient.<sup>7, 8, 26, 50</sup>

A small prospective study showed that anakinra on demand significantly reduced all features of the fever episode compared to attacks not treated with anakinra.<sup>65</sup> When patients suffer from 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.<sup>7, 26, 50, 66</sup> 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 biologic agents in MKD when initial treatment fails, based on the success of this approach in other diseases,<sup>42, 64</sup> 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.<sup>67-69</sup> 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.

**Table 4. Summary of evidence, and regulatory authorizations for IL-1 blockade and TNF-blockade.**

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

**L:** level of evidence as assessed in a systematic review up to June 2013. 1A, meta-analysis of randomised controlled trial; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4 expert opinion.<sup>9</sup> **Approval** as published on websites of EMA (European Medicines Agency) and FDA (U.S. Food and Drug

Administration) up to ~~February–June 2015~~.<sup>37, 38</sup> \*Severe FCAS is defined by EMA as FCAS presenting with signs and symptoms beyond cold-induced urticarial skin rash.

## Monitoring

### *General*

Since disease 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.<sup>39, 47</sup> 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 standardized monitoring of AID patients. The Auto-Inflammatory Diseases Activity Index (AIDAI) is the only validated disease activity index for TRAPS and MKD, and one of the validated scores for CAPS.<sup>70, 71</sup> An other validated disease activity score for CAPS patients is the MWS-DAS.<sup>72</sup> To increase standardized outcome measurements and thus improve comparisons between studies, we recommend that a validated score should be used in clinical studies with AID patients: the AIDAI for TRAPS and MKD; and either the AIDAI, or MWS-DAS for CAPS.

During monitoring, patients can experience inflammatory episodes which 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 AID patients due to their disease and/or immunosuppressive medication.<sup>26, 31, 39, 41-43, 45, 47, 49, 73</sup> When initiating therapy with biologic 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 biologic agents.<sup>74, 75</sup> 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.<sup>76-78</sup> Evidence on safety of vaccinations during IL-1 blocking agents is limited to one randomized study with healthy subjects<sup>79</sup> and a note that 25 CAPS patients on canakinumab received vaccinations without abnormal immune responses or pathogen-related infections.<sup>47</sup> However, data on live-attenuated vaccines is still scarce; hence we concluded that there are currently insufficient safety data to recommend live vaccines during therapy with biologic agents, especially during IL-1 blockade.

### *CAPS*

Experts created a list of items that should be included in the monitoring of all CAPS patients (table 3), based on all relevant symptoms and complications described in CAPS

patients as well as the impact of disease on daily life.<sup>17, 18, 20, 21, 30, 32, 72, 80-83</sup> 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.

### *TRAPS*

Most TRAPS symptoms can be assessed by history taking and physical examination.<sup>5, 22-25</sup> Amyloidosis is described in about 10% of the TRAPS patients and occurs more often in patients with long disease duration.<sup>5, 22, 23, 84</sup> Hence, inflammatory parameters and proteinuria should be checked regularly.<sup>5, 22, 23</sup> A list of particularly relevant items to check when monitoring a TRAPS patient 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.<sup>22, 84</sup> Patients with R92Q or P46L variants who do experience symptoms compatible with TRAPS, have a similar phenotype as patients with other *TNFRSF1A* mutations, albeit sometimes with shorter and/or more frequent fever episodes.<sup>5, 23, 25</sup> 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 to patients with structural *TNFRSF1A* mutations.<sup>5, 22, 23, 25</sup>

### *MKD*

Most of the mild MKD symptoms can be assessed by history taking and physical examination, and routine laboratory measures such as full blood count, CRP and SAA to assess systemic inflammation.<sup>7, 26</sup> Urine analysis should be performed for renal complications such as AA amyloidosis, glomerulonephritis and renal angiomyolipoma<sup>7, 26</sup> as well as ophthalmologic examination for retinitis pigmentosa and cataracts.<sup>26, 85</sup>

Patients with more severe MKD phenotypes suffer from neurologic complications such as ataxia, hypotonia, and psychomotor retardation; thus cognitive testing and full neurologic examination should be considered.<sup>8, 26</sup> 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 MKD patients, especially in the assessment of atypical fever episodes. MAS is a life-threatening complication of some rheumatic diseases (e.g. systemic juvenile idiopathic arthritis), characterized by high fever,



pancytopenia and liver damage.<sup>86</sup> In one cohort of MKD patients, the frequency of MAS was surprisingly high (6/50, 12%).<sup>26</sup>

## 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 AID patients; this is especially true for CAPS patients 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).<sup>87</sup> 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 recognized, however, that some young patients with severe CAPS may require treatment earlier in life than currently recommended by the authorities~~EMA or FDA~~. Studies on the safety of canakinumab in the very young are soon-to-be published.

Close monitoring of patients' symptoms, damage and wellbeing is an important requirement for 'treat to target' strategies. Structured long-term follow-up studies of patients with autoinflammatory diseases 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, but also 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 biologic 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 ~~the~~ diagnosis, treatment and monitoring of CAPS, TRAPS and MKD, aiming to optimize the management of these rare ~~patients with CAPS, TRAPS or MKD~~.

## **DECLARATION OF FINANCIAL SUPPORT OR CONFLICT OF INTEREST**

J. Anton Grant / Research Support from Abbvie, Novartis, Pfizer, Consultant for Novartis, Speaker Bureau of Abbvie, Novartis, Pfizer, Roche, SOBI; P. Brogan Grant / Research Support from Novartis, Roche, and SOBI, Consultant for Roche and SOBI; L. Cantarini Grant / Research Support from Novartis, SOBI, Consultant for Novartis, SOBI; C. Galeotti Grant / Research Support from Novartis; V. Hentgen Consultant for Novartis; M. Hofer Consultant for Novartis; T. Kallinich Grant / Research Support from Novartis, Speaker Bureau of Novartis, SOBI; I. Kone-Paut Grant / Research Support from Chugai, Novartis, SOBI, Consultant for Abbvie, Chugai, Novartis, Pfizer, SOBI, Speaker Bureau of Novartis, Pfizer; H. Lachmann Research Support and speaker Bureau from Novartis; S. Ozen Consultant for Novartis, Speaker Bureau of SOBI; A. Simon Consultant for Novartis, Xoma and SOBI; Y. Uziel Grant / Research Support from Novartis, Consultant for Novartis, Speaker Bureau of Abbvie, Neopharm, Novartis, Roche; B. Feldman Consultant for Novartis, Pfizer, BMS; [BS.J.](#)-Vastert Consultant for Novartis; N. Wulffraat Grant / Research Support from EAHC, Abbvie, GSK, Roche, Consultant for Genzyme, Novartis, Pfizer, Roche; J. Frenkel Grant / Research Support from Takeda, Consultant for Novartis, Speaker Bureau of SOBI; M. Gattorno Grant / Research Support and speaker Bureau from Novartis and SOBI; J. B. Kuemmerle-Deschner Grant / Research Support from Novartis, Speaker Bureau of SOBI. All other authors (NH, MO, JJ, KB, GG, HO, RR, CW) declared no conflicts of interests.

## **FUNDING**

This project is supported by a grant from European Agency for Health and Consumers (EAHC), grant number 2011 1202.

## **ACKNOWLEDGEMENTS**

This SHARE initiative has been endorsed by the executive committee of the Paediatric Rheumatology European Society (PReS) and the International Society of Systemic Auto-Inflammatory Diseases (ISSAID).

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