Development of the Autoinflammatory Disease Damage Index (ADDI)

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ABSTRACT

Objectives
Autoinflammatory diseases cause systemic inflammation that can result in damage to multiple organs. A validated instrument is essential to quantify damage in individual patients, and to compare disease outcomes in clinical studies. Curently, there is no such tool. Our objective was to develop a common autoinflammatory disease damage index (ADDI) for Familial Mediterranean Fever (FMF), Cryopyrin Associated Periodic Syndromes (CAPS), Tumour Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) and Mevalonate Kinase Deficiency (MKD).

Methods
We developed the ADDI by consensus building. The top 40 enrollers of patients in the Eurofever registry and nine experts from the Americas participated in multiple rounds of online surveys to select items and definitions. Further, 22 (parents of) patients rated damage items, and suggested new items. A consensus meeting was held to refine the items and definitions, which were then formally weighted in a scoring system derived using decision-making software, known as 1000minds.

Results
More than 80% of the experts and patients completed the online surveys. The preliminary ADDI contains eighteen items, categorized in the following eight organ systems: reproductive, renal/amyloidosis, developmental, serosal, neurological, ears, ocular and musculoskeletal damage The categories renal/amyloidosis and neurological damage were assigned the highest number of points, serosal damage the lowest number of points. The involvement of (parents of) patients resulted in the inclusion of e.g. chronic musculoskeletal pain.

Conclusions
An instrument to measure damage caused by autoinflammatory diseases is developed based on consensus building. Patients fulfilled a significant role in this process.

INTRODUCTION

Autoinflammatory diseases (AID) cover a spectrum of diseases, which lead to chronic or recurrent inflammation caused by activation of the innate immune system, typically in the absence of high-titre autoantibodies.[1] Over recent decades a number of autoinflammatory diseases has been recognized, genetic defects identified and the pathogenic mechanisms elucidated.[2]
The four most common monogenic AID are Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF), Mevalonate Kinase Deficiency (MKD) and Tumour necrosis factor Receptor-Associated Periodic fever Syndrome (TRAPS). In these hereditary AID chronic and recurrent inflammation can lead to both acute disease, and chronic irreversible damage.[3]

Targeted therapy for many AID has become available with blocking interleukin-1 beta (IL-1β) signalling and/or tumour necrosis factor (TNF) signalling, and for many patients, control of active inflammation can be achieved. However, organ damage may have accrued in the pre-diagnostic or pre-therapeutic phase of the illness, particularly for those with delayed diagnosis; and the control of disease activity may not be complete in every patient.[4] Therefore many patients may still develop chronic damage from AID. This is especially true for patients for whom effective therapy is unaffordable or unavailable, since many of these biological treatments are very expensive. To-date there is no validated means of assessing the long-term burden of AID available.

Currently, there is a patient-reported validated tool to quantify acute inflammatory activity in inherited periodic fevers (the autoinflammatory disease activity index, AIDAI); and there is a disease severity index for FMF, but by definition these do not assess long-term damage such as hearing loss, blindness, and renal failure.[5-8] Damage indices for other rheumatic diseases such as vasculitis,

systemic lupus erythematosus, dermatomyositis and juvenile idiopathic arthritis have already been developed and validated.[9-13]

When devising new damage assessment tools therapeutic toxicity must also be considered, for example chronic glucocorticoid toxicity which can lead to cataract, growth failure and other damaging side-effects. Thus, a comprehensive damage outcome measurement tool for AID must capture chronic and potentially irreversible disorders of structure and function that have risen in patients as a result of their autoinflammatory disease and/or its treatment. The creation of such an index was a stated aim of the European Union ERANET-PRIOMEDCHILD RaDiCEA Project No. 40-41800-98-007.

The main intended purpose of the autoinflammatory disease damage index (ADDI) is to analyse the outcome of patient groups, for example to capture and record damage in clinical trials. In addition, it may serve as an aid to physicians in assessing the needs of their patients, for example when trying to secure funding for biologic therapies. The proposed ADDI will be designed for use in the four more commonly encountered monogenic AID: FMF, CAPS, TRAPS and MKD. The ADDI will ideally be used as one of a set of measures to capture the disease burden for affected patients, in addition to validated measures of disease activity, disease severity and quality of life.

METHODS

This study was approved by The Medical Ethical Committee of the University Medical Centre Utrecht. We developed the ADDI by consensus building, with online surveys based on the Delphi method followed by a face-to-face consensus meeting. The Delphi method is a widely accepted and commonly used method to structurally reach consensus in a group of experts.[14]

Selection of experts and patients

The top 40 enrollers to the Eurofever Registry, a European research database for patients with AID,[15] were invited to participate as experts; another nine experts who had not participated in the European-based Eurofever Registry were recruited from the Americas. Members of this expert group participated in multiple online surveys, and were invited for the face-to-face consensus meeting. In close collaboration with the Autoinflammatory Alliance.[16] We also invited 22 patients and parents of patients with FMF, CAPS, TRAPS or MKD to participate in an online survey, and an additional three patients to participate in the weighting of items, using the 1000minds decision-making software (see below, step 4). Inclusion criteria for selection were: 1. English speaking patients of 18 years and older or parents of a paediatric patient with FMF, MKD, CAPS or TRAPS; and 2. Provision of fully informed signed consent to participate in this exercise, separately for both online surveys and interviews.

Step 1: Search for possible damage items

First, a systematic literature search was performed to establish possible damage items for FMF, MKD, CAPS and TRAPS. Inclusion of articles to be considered was based on: 1. all studies and case series describing symptoms and complications of more than three patients with FMF, MKD, CAPS and/or TRAPS; 2. published in English; and 3. case reports (with three or fewer patients) were included if they described significant new damage items. All data on the prevalence of the sequelae were extracted. We included all sequelae described in studies with patients with FMF, CAPS, TRAPS and MKD which were likely to be caused by chronic inflammation or its treatment, and which persisted after resolution of inflammatory episodes.

Secondly, we screened all items scored in the Eurofever Registry to identify new damage items not identified from the literature review. Thirdly, we asked patients in the first online survey to propose relevant new damage items. We interviewed the patients who gave informed consent for the interviews, to try to identify other relevant damage items: we asked them specifically which complications/symptoms they most fear, and which symptoms/complications create the greatest

limitation of daily life. Finally, we asked experts in the first online survey for relevant new damage items (see step 2).

Step 2: Multiple rounds of online surveys with experts
Four rounds of online surveys were performed as a preparation for the consensus meeting. Experts scored all potential damage items for inclusion in the index, as well as the definitions and grading of items. Experts also suggested new items, combinations of items and new options for definitions/grading. If ≥80% of the experts endorsed an item, it was included in the index. If an item reached <50% consensus, the item was excluded. In cases were 50 to 80% of the experts favoured inclusion, it was reconsidered in the next round. These thresholds were also used for the definitions and grading of the items.

Step 3: Face-to-face Consensus meeting
The 43 experts who completed one or more of the online surveys, as well as the director of the Autoinflammatory Alliance as a patient/parent representative, were invited to the consensus meeting. The first day, the definition of damage and the inclusion/definitions of the items that did not reach consensus in the online surveys were discussed. On day two, all items that reached consensus in the online surveys were refined. The results of the online surveys with experts and the patient/parent surveys and interviews were presented per item, followed by a maximum of three voting rounds and discussion. Items and definitions with 80% consensus or more were included in the ADDI. Items with no consensus after three voting rounds were excluded. After the consensus meeting we sent a final online survey to all participants, to ask whether they agreed with the items including the definitions as proposed at the consensus meeting.

Step 4: Development of a scoring system.
To assign an appropriate weight to each damage item, we used the 1000minds software in order to develop the scoring system of the ADDI.[17] 1000minds is a decision-making program that compares two items in order to grade the alternatives using the Potentially All Pairwise RanKings of all possible Alternatives (PAPRIKA) method.[18] Briefly, this method provides repeated comparisons between two items; the expert or patient chooses which of the two items constitutes the greater burden for patients. Each item receives a 'preference value' according to the PAPRIKA method, this reflects the importance of this item compared to all the other items. Hence, items with the greatest burden got the highest preference value and thus received most points in the ADDI.

All experts and the patients were asked to complete 1000minds. We compared the means of the patient survey and the expert survey. Differences between the overall mean and the expert mean, as well as maximizing the amount of points per category were discussed in a web conference with a small group of experts. These experts were from different continents and included both paediatric rheumatologists and rheumatologists for adults.

RESULTS

Identification of damage items from literature search and Eurofever registry
In the literature searches we found 1712 articles for CAPS, 632 for MKD, 2602 for FMF and 486 for TRAPS, after screening for title and abstract 150 articles for CAPS, 87 for MKD, 251 for FMF and 55 for TRAPS remained. After screening for full text we included 36 articles for CAPS, 9 for MKD, 54 for FMF and 8 for TRAPS; in total 49 separate damage items were extracted from these articles (Figure 1). Eight additional items extracted from the Eurofever Registry were arterial and venous thrombosis, arterial aneurysm, large vessel vasculopathy, pulmonary fibrosis, lymphatic dysplasia, camptodactyly and kyphoscoliosis. All these items were included in the online surveys with experts and patients. No new items were selected from the case reports.

Patient/parent online survey and interviews

Twenty-two patients/parents of patients provided informed consent to participate in the online surveys. Twenty-one patients (95%) completed the online survey and nine of them gave informed consent for an interview. For patient characteristics, see Table 1. Patients/parents suggested eighteen new damage items, including sexual dysfunction, chronic fatigue and chronic musculoskeletal pain (Table 2). The five most important damage items according to patients were AA amyloidosis, joint damage, vision loss, neurological damage and renal failure. All these items were included in the preliminary ADDI.

Table 1: Patient characteristics

	First online survey	Interviews	1000minds survey
Total no. of participants, n	21	9	14
Type of participant, n (%)			
Patients	12 (57)	3 (33)	8 (57)
Parents	9 (43)	6 (67)	6 (43)
Age, median in years (range)	28 (2-74)	15 (6-68)	29 (6-74)
Disease, n (%)			
MKD	6 (29)	1 (11)	3 (21)
TRAPS	5 (24)	3 (33)	3 (21)
CAPS	9 (43)	4 (44)	6 (43)
FMF	1 (5)	1 (11)	2 (14)
Country of residence, n (%)			
Australia	2 (10)	7 (78)	1 (7)
Canada	1 (5)	2 (22)	0 (0)
Switzerland	1 (5)	0 (0)	0 (0)
Netherlands	2 (10)	0 (0)	2 (14)
United States of America	15 (71)	0 (0)	10 (71)
United Kingdom	0 (0)	0 (0)	1 (7)

Expert online surveys

Forty-nine experts were invited for the online surveys. The median number (range) of included patients in the Eurofever registry for the 40 Eurofever experts was 49 (19-194) patients per expert. All rounds were completed by more than 80% of the experts. Experts suggested sixteen new damage items, including persistent haematuria, chronic fatigue and corneal opacities (Table 2). Eight items reached consensus for inclusion in the online surveys. Forty-two items were excluded as <50% of the experts voted in favour of the item. Examples were lymphatic dysplasia, sexual dysfunction and glomerulonephritis. Sexual dysfunction was excluded, because experts concluded that it would be difficult to prove a causal relation with the disease (i.e. whether it can be seen as disease-associated damage), moreover it might reflect disease activity rather than damage. Seven items were discussed in the consensus meeting as between 50% and 80% of the experts wanted to include the item. Six of the fifteen definitions required further discussion in the consensus meeting.

Table 2: Items suggested by patients and experts, as an addition to the literature.

Category	Patient suggestions	Expert suggestions
Developmental	Learning difficulties Speech developmental delay	Learning disabilities
Reproductive	Amenorrhoea Sexual dysfunction	Amenorrhoea
Neurological	Memory problems Delayed motor skill development Hand coordination problems	Hemiplegia/quadriplegia Mobility impairment
Gastrointestinal	Irritable bowel syndrome Portal hypertension	Malabsorption Portal hypertension Liver steatosis
Musculoskeletal	Craniofacial deformities	Facial deformities Muscle wasting
Ocular	Corneal haze Retinitis pigmentosa	Corneal opacity Retinitis pigmentosa
Renal		Persistent haematuria
Other	Social problems Loss of future perspective Chronic fatigue Surgeries Autonomic dysregulation Chronic pain	Weight gain Somatic growth Chronic fatigue Dysphonia

Consensus meeting

On the first day, 31 of the 43 invited participants were able to attend the meeting. The participants discussed the items and definitions that did not reach consensus in the online survey. The participants excluded neuropathy, muscle weakness and mood disorders. Consensus was reached about all definitions that needed reconsideration. On the second day, 29 experts were present and refined all items that already reached consensus, including the definitions of these items. In the online survey following the consensus meeting, 35 experts agreed with almost all adaptions made in the consensus meeting. Only fatigue was finally excluded following this survey.

Most important discussions in the consensus meeting

Inclusion of infertility and amenorrhea did not reach consensus in the online surveys, but in the consensus meeting adult rheumatologists emphasized the great burden for patients caused by infertility. After discussion, >80% of the participants agreed on including these items.
Cognitive impairment was included as an addition to developmental delay in the consensus meeting. As there is a variety of rare but severe central nervous system (CNS) complications, the participants decided to group all in one item, CNS involvement.

The group decided to replace the item abdominal adhesions with serosal scarring in order to include all potential serosal damage, e.g. retroperitoneal fibrosis. Destructive arthritis and joint contractures were combined into one inclusive item, joint restriction, as movement limitation was considered the most important functional impact of both items.

Chronic headache was excluded, because this item had a significant overlap with elevated intracranial pressure. Chronic musculoskeletal pain and fatigue were initially included in the consensus meeting because of the important burden for patients, albeit with a lot of discussion. Fatigue was later excluded in the final online survey, because the experts agreed that although

fatigue can hugely impact a patient's life, it is difficult to assess due to its subjective nature and variable relationship with disease activity.

Development of the scoring system

Thirty-seven experts and fourteen patients completed the 1000minds survey. The means of preference values (experts and patients) ranged from 1.5 to 7.5, in which 1.5 reflected the lowest and 7.5 the highest burden for patients. Experts and patients generally scored similar on the preference values (Figure 2). A preliminary scoring system based on these preference values was presented to a panel of seven representative experts and discussed in a conference call. All items with a mean preference value of <3.5 received one point, 3.5 to 5.5 received two points (with the exception of serosal scarring which received one point) and of >5.5 three points. Serosal scarring received one point; the experts agreed in the conference call that the consequences are less severe in comparison to other items receiving two points. Further, a maximum of points per category was defined in order to prevent double scoring of identical items. Renal/amyloidosis received a maximum amount of six points, as amyloidosis often leads to renal damage. Also the neurological and musculoskeletal categories received a decreased maximum of points because of the overlap of the items.

Preliminary ADDI

Table 3: preliminary ADDI including glossary of terms.

Preliminary ADDI

Definition of damage: Damage is defined as persistent or irreversible change in structure or function, which is present for at least 6 months. Damage items should not be scored if they are attributed to ongoing disease activity. Damage may be the result of prior disease activity, complications of therapy or co-morbid conditions that developed after the onset of autoinflammatory disease signs and symptoms. If damage has been present for longer than 6 months, but later resolves, it should still be scored in order to capture the damage that was present in the individual for that time period.

Damage item	**Grading**	**Points**
Reproductive		***Max. 3***
Sub/infertility		2
Amenorrhea		1
Renal/amyloidosis		***Max. 6***
Amyloidosis	Limited amyloidosis	2
	Extensive amyloidosis	3
Proteinuria		1
Renal insufficiency	Moderate renal insufficiency	2
	Severe renal insufficiency	3
Developmental		***Max. 3***
Growth failure		2
Puberty delay		1
Serosal		***Max. 1***
Serosal scarring		1
Neurological		***Max. 6***
Developmental delay [1]		2
Cognitive impairment		3
Elevated intracranial pressure		2
Central nervous system involvement.		3
Ears		***Max. 2***
Hearing loss	Moderate hearing loss of better ear	1
	Severe hearing loss of better ear	2
Ocular		***Max. 3***

Ocular involvement	Mild ocular involvement of better eye Moderate ocular involvement of better eye Severe moderate ocular involvement of better eye	1 2 3
Musculoskeletal		***Max. 4***
Joint restriction		2
Bone deformity		2
Osteoporosis		1
Musculoskeletal pain		1

Glossary of terms

Infertility: A disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, not due to known disorders in the unaffected partner.

Amenorrhea: Primary amenorrhea: absence of menarche at the age of 16 years or absence of menarche 5 years after thelarche in a female. Secondary amenorrhea: absence of the menses for six consecutive months or more, in a female who previously had menstrual cycles.

Limited amyloidosis*:* Symptomatic amyloidosis affecting one organ and confirmed by examination of tissue sections by Congo red dye or SAP scintigraphy.

Extensive amyloidosis*:* Symptomatic amyloidosis affecting more than one organ and confirmed by examination of tissue sections by Congo red dye or SAP scintigraphy.

Proteinuria: Persistent urinary protein to creatinine ratio of >20mg/mmol in the first morning void; and/or a daily protein excretion of > 0.3 g/24 hours, or urine albumin to creatinine ratio of > 15 mg/mmol.

Moderate renal insufficiency*:* Glomerular filtration rate *(*GFR) between 15-60 ml/min/1,73m^2.

Severe renal insufficiency: GFR <15 ml/min/1,73m^2, dialysis or transplantation.

Growth failure: defined as the presence of at least <u>two</u> of the three features:
- lower than the 3rd percentile height for age
- growth velocity over 6 months lower than the 3rd percentile for age
- crossing at least 2 centiles (5%, 10%, 25%, 50%, 75%, 90%, 95%) on growth chart

For patients older than 18 years: Pathological short stature (e.g. below 3rd percentile for normal ethnic population)

Puberty delay: A Tanner stage below minus two standard deviations for age.

Serosal scarring: Adhesions or fibrosis affecting pericardium, pleura, peritoneum and/or retroperitoneum, supported by imaging techniques, endoscopy or surgery.

Developmental delay: Failure to reach age-appropriate developmental milestones, including language/speech, motor, social/emotional, and cognitive milestones. As soon as there is any delay in one of the development categories, this item has to be scored.[1]

Cognitive impairment: Requirement of special education because of cognitive impairment or IQ below 70 as defined by neuropsychological assessment (e.g. WISC) or other age-appropriate equivalents.

Elevated intracranial pressure: Signs and/or symptoms of elevated intracranial pressure supported by appropriate techniques. [2]

Central nervous system involvement: Focal deficits (gross and/or fine sensorimotor), diffuse deficits (e.g. memory, behaviour), seizures, and spinal cord symptoms.

Moderate hearing loss: Sensorineural hearing impairment confirmed by audiometry or another age appropriate technique without requirement of hearing aids or a cochlear implant

Severe hearing loss: Sensorineural hearing impairment confirmed by audiometry or another age appropriate technique requiring hearing aids or a cochlear implant.

Mild ocular involvement*:* Ocular damage (e.g. optic nerve atrophy, elevated intraocular pressure or cataract) documented by an ophthalmologist, without visual impairment.

Moderate ocular involvement: Ocular damage (e.g. optic nerve atrophy, elevated intraocular pressure or cataract) documented by an ophthalmologist, resulting in visual impairment.

Severe ocular involvement: Ocular damage (e.g. optic nerve atrophy, elevated intraocular pressure or cataract) documented by an ophthalmologist, resulting in legal blindness.

Joint restriction: Fixed limitation in the normal range of motion of joints, with or without destructive arthropathy or avascular necrosis.

Bone deformity: Bone deformation or overgrowth on clinical examination and/or imaging studies.

Osteoporosis: Reduced bone mineral density with vertebral collapse and/or pathological fractures

confirmed with imaging, which may include bone densitometry. Requires both evidence of decreased bone density and fracture, 'low bone density' by itself is insufficient
***Musculoskeletal pain**:* Non-inflammatory musculoskeletal pain impairing activities of daily living.

[1] Only for paediatric patients. [2] Such as fundoscopy, neuroimaging or lumbar CSF pressure measurement.

DISCUSSION

We developed a damage index for AID. The proposed ADDI contains eighteen items. The damage items are categorized by organ system. All damage items are clearly defined and easy to score. Completing the ADDI should take approximately five minutes. The ADDI will make it possible to analyse outcomes in patient groups and compare the results of different studies, but also to systematically measure damage in a single patient.

The first key strength in the development of the ADDI is the number of worldwide experts that participated. Forty European/Middle Eastern and nine American experts were invited, with the aim of making the ADDI a global instrument. We made the selection of experts based on their clinical experience, which guarantees the capability of these experts to judge the importance of damage caused by AID. Furthermore, all online surveys were completed by more than eighty percent of the experts, which is important for both validity and acceptability of consensus statements. A high proportion of the experts attended the consensus meeting.

The second key strength is the participation of patients and parents of patients in all the steps that led to the development of the ADDI. This is important to make it a widely relevant damage index that can represent the burden for patients.

The third key strength is the methodology used to select the possible damage items. We screened for possible damage items in three ways. It was evident from the literature search that studies of long-term damage using a large sample size are extremely scarce in autoinflammatory diseases. The screening of items in the Eurofever registry, and suggestions of patients and experts were consequently valuable in developing a comprehensive set of items to asses in the online surveys.

Although many new damage items were suggested by patients and parents of patients, it might be possible that the participating patients have not suggested all possible damage items and they may not reflect the opinion of the whole patient population. Nevertheless, their contribution strengthens the process and resulted in consideration of previously neglected damage items that had not been described in the literature nor mentioned by experts, for example chronic pain and chronic fatigue.
FMF patients were underrepresented in this study, despite attempts to recruit more patients for the 1000minds survey. Overall the amount of patients that signed informed consent as well as the response rate to surveys was lower than expected. Possible reasons might be the inclusion criterium for patients to be English speaking, the difficulty and length of the questionnaires and the informed consent procedure.

We chose to develop a general damage index limited to the four most prevalent monogenetic AID: FMF, CAPS, TRAPS and MKD. Based on the literature the affected organ systems might differ in prevalence between these diseases, nevertheless the ADDI will be a good tool to structurally score damage and covers all the important damage items for these four diseases. It would be challenging to develop the ADDI to capture damage in all AID, due to the expanding number of new ultra-rare autoinflammatory diseases, and their varied clinical features. An example of a recently discovered AID is the chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. While CANDLE does share some damage items with other AID, lipodystrophy is

characteristic for CANDLE[121], but is uncommon in FMF, CAPS, TRAPS and MKD, illustrating the difficulty in developing a damage index applicable to all existing and yet to be discovered AID.

Common nonspecific symptoms like chronic headache, fatigue and chronic musculoskeletal pain gave rise to intense discussions. Ultimately, only chronic musculoskeletal pain is included in the preliminary ADDI. Although patients considered these items as important in the surveys and interviews, experts thought that these items were difficult to assess objectively in daily clinical practice, and found it hard to define whether these items actually reflected disease damage, rather than on-going disease activity. Nonetheless experts acknowledged that these items have a considerable impact on the quality of life. In the future these items might be better included in a different tool, e.g. with specific items to measure quality of life.

Another difficulty in the development of the ADDI was the influence of comorbidities on the damage in AID patients. This is a common issue for all damage indices. For example neurological impairment can be caused by the AID or by an unrelated stroke. It is very hard to distinguish whether it is caused by independent comorbidities or the disease itself, even though we only include damage items that arose after the onset of symptoms of the AID.

In the near future, the preliminary ADDI will be validated using patient cases of FMF, CAPS, TRAPS and MKD. By this effort, we will be able to assess the validity of the ADDI in total, and for the individual diseases. Furthermore, we will analyse the specificity of the ADDI items (e.g. whether the damage items are not influenced by disease activity) and the grading system. Prospective validation in longitudinal cohorts will then be needed to investigate responsiveness to change over time and correlation with the burden of disease-associated damage to daily life.

In conclusion, we developed the ADDI, a universal instrument to measure persisting damage caused by chronic inflammation in the autoinflammatory diseases FMF, CAPS, TRAPS and MKD. This ADDI is based on consensus building with experts from around the world; patients and parents of patients fulfilled a significant role in this process.

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COMPETING INTERESTS

Novartis Pharma AG financially supported the final consensus meeting. They did not have any influence on the selection of participants or on the content of the ADDI / consensus meeting or the reporting of the findings.

Competing interests of the co-authors

FdB: Novartis, Novimmune, Hoffmann-La Roche, SOBI, AbbVie. LC: speaker's fee for Novartis and SOBI. MC: consultancy fees for Novartis, SOBI and Abbvie. KLD: Consultancy work for SOBI and Novartis, donations, honorariums and unrestricted grants have been received by the Autoinflammatory Alliance from SOBI, Novartis, and Regeneron. RG: consultant for Abbvie. RGM: Study support from SOBI, Novartis, Regeneron. VH: Honorariums and educational grants from Novartis, honorariums from SOBI. MH: consultant for Novartis. HMH: Consultant for Novartis and SOBI, and speaker for Novartis. TK: Research grant by Novartis, Speakers bureau by Roche, BMS, Novartis and SOBI. JKD: consultant/speaker for Novartis and SOBI and has received grant support from SOBI and Novartis. RML: Ad Board and consultant for Abbvie and Novartis. PQ: Investigator, consultant and speaker bureau for Novartis and SOBI. MG: Consultant for and unrestricted grants to Eurofever and speaker's fee from SOBI and Novartis. YU: Y. Uziel Grant/Research Support from Novartis, Consultant for Novartis, Speaker Bureau of Abbvie, Neopharm, Novartis, Roche. JF: Consultant for Novartis.
All others declared no competing interests.

AUTHOR CONTRIBUTION

NMtH, KVA and JF designed the study and wrote the manuscript. ODCA was principle investigator of RADICEA. KLD contacted patients for patient recruitment. The consensus meeting was prepared with and led by AR. KLD, JF and all other authors contributed to the online surveys and/or the consensus meeting, and attributed to and approved the manuscript.

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LEGENDS OF FIGURES

Figure 1: damage items extracted from literature for FMF[3 19-71], CAPS[3 72-106], TRAPS[3 107-113], and MKD[3 114-120].

Figure 2. Scoring of the preference values from experts (black) and patients (grey), derived from the 1000minds decision making software. A higher preference value means a higher burden for patients. The preference values range from 1.5 to 7.5, all items with a weighted mean preference value of <3.5 received one point in the ADDI, and of >5.5 three points.