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The 2021 EULAR and ACR points to consider for diagnosis and management of autoinflammatory type I interferonopathies: CANDLE/PRAAS, SAVI and AGS

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ABSTRACT

Objective: Autoinflammatory type I interferonopathies, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature / proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS), stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), and Aicardi-Goutières syndrome (AGS) are rare, and clinically complex immunodysregulatory diseases. With emerging knowledge of genetic causes and targeted treatments, a Task Force was charged with the development of "points to consider" to improve diagnosis, treatment, and long-term monitoring of patients with these rare diseases.

Methods: Members of a Task Force consisting of rheumatologists, neurologists, an immunologist, geneticists, patient advocates, and an allied health care professional, formulated research questions for a systematic literature review. Then, based on literature, Delphi questionnaires, and consensus methodology, "points to consider" to guide patient management were developed.

Results: The Task Force devised consensus and evidence-based guidance of four overarching principles and 17 points to consider regarding the diagnosis, treatment, and long-term monitoring of patients with the autoinflammatory interferonopathies, CANDLE/PRAAS, SAVI, and AGS.

Conclusion: These points to consider represent state-of-the-art knowledge to guide diagnostic evaluation, treatment, and management of patients with CANDLE/PRAAS, SAVI and AGS and aim to standardize and improve care, quality of life, and disease outcomes.

INTRODUCTION

Autoinflammatory type I interferonopathies are genetically defined (monogenic or digenic) immunodysregulatory disorders characterized by the presence of a type I interferon (IFN) signature in peripheral blood, and variable systemic inflammation.[1-3] In this expanding group of

ultra-rare diseases, the most common are chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature / proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS), stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), and Aicardi-Goutières syndrome (AGS) are the most common.

Patients with type I interferonopathies present early in life often within the first week of life; prenatal onset has been reported in AGS patients; however, late-onset cases presenting at ages 14, 18 and 5.6 years with CANDLE/PRAAS, SAVI and AGS respectively have been reported.[4-11] Despite CANDLE/PRAAS, SAVI and AGS having distinct clinical phenotypes of varying disease severity, their individual clinical manifestations of these diseases can overlap, and all are associated with high morbidity and mortality if untreated.[4 12] Recent advances in the genetic description of these disorders permit better characterization of disease-specific clinical manifestations, and provide evidence supporting the pathogenic role of type I IFN signaling.[1 2 12 13] These developments prompted the Task Force lead by the steering committee (two convenors [PB, RGM], a neurologist [AV], two methodologists [BF, ED] and three pediatric rheumatologists/EULAR fellows [KCG, LL, MR] and a rheumatologist [ST]) to review the existing data, and develop consensus statements, with the aim of formulating state-of-the-art guidance on the diagnosis, treatment and long-term monitoring of patients with these rare diseases.

Thus, the objective of this project was to develop points to consider for the diagnosis, treatment, and long-term monitoring of patients with CANDLE/PRAAS, SAVI and AGS.

The Task Force targets their guidance to pediatricians, internists, and subspecialists involved in the care of patients with autoinflammatory type I interferonopathies and to patients and caregivers. These points to consider were developed not only to provide a resource for physicians to facilitate management, but also for policy makers governing who have a role in

authorizing patients' access to various diagnostic tools and treatment options; all with the ultimate goal to harmonize the level of care, and to improve quality of life and disease outcomes in this patient population.

METHODS

The European Alliance of Rheumatology Associations (EULAR)[14] and the American College of Rheumatology (ACR) standardized operating procedures (SOPs) were followed during the project period (see online supplementary methods). With approval from the EULAR and ACR Executive Committees, an international Task Force consisting of worldwide recognized experts from North America, South America, Europe, and Australia convened to develop points to consider for the diagnosis, treatment, and long-term monitoring of three type I interferonopathies: CANDLE/PRAAS, SAVI and AGS. The Task Force members were selected based on expertise in treatment and care of these patients.

A face-to-face meeting in August 2019 defined the goal of the project and the target population. Then, the Task Force developed research questions related to diagnosis, treatment and long-term monitoring of these diseases using the Population, Intervention, Comparison, Outcome (PICO) format. Search terms were derived from PICO questions and a systematic literature review (SLR) was performed by three research fellows (KCG, MR, LL), with support from a librarian and an epidemiologist (DH and DP), and a senior methodologist (ED) to identify relevant literature published before September 2020.

Two rounds of pre-consensus meeting questionnaires, using the Delphi technique,[15] included questions pertaining to diagnosis, treatment and long-term monitoring were sent to all Task Force members to indicate their agreement with each question or statement with yes/no using

the Delphi technique; the Delphi questionnaire was sent to 28 Task Force Members of who 22 were voting members. The Task Force members were asked to indicate their agreement with each statement, and a free text option was provided to capture every member's comment for each statement. Draft statements and items in questions with 80% or higher agreement were retained for voting at the consensus meetings. Statements and items questions that did not reach a greater than 80% consensus were reviewed and re-worded and sent out in a second round of the Delphi questionnaire. The original and the revised/modified draft statements with the previously achieved level of agreement and the participants' comments were included in the second survey. A free text option to capture comments and additional items was again included. Draft statements with 80% or higher agreement were retained for voting at the consensus meetings, and statements, that did not achieve 80% agreement, were marked for further discussion and refinement at the two consensus meetings. Responses were anonymous.

Based on the SLR findings and two pre-consensus meeting Delphi questionnaires, draft statements were refined by the steering group and were sent to the voting members prior to the consensus meetings. These draft statements were reviewed, discussed, revised, and voted on in two consensus meetings, that were held online in October 2020 due to the coronavirus disease 2019 (COVID-19) pandemic, one for CANDLE/PRAAS and SAVI, and one for AGS.

Two conveners (RGM, PB), three methodologists (BF, ED, DA), three fellows, an allied health professional, and three disease experts attended both consensus meetings and, otherwise, participation was based on disease specific expertise. The voting panel included 19 experts, one allied health professional and one patient representative for each disease. The joint statements addressing all three interferonopathies were voted on by the entire voting panel; CANDLE/SAVI specific statements were voted on by 10 experts, one allied health professional, one SAVI and one

CANDLE patient presentative, and AGS specific statements were voted on by 14 experts, one allied health professional and one AGS patient representative. During the meetings, statements that achieved at least 80% agreement were accepted; statements with <80% were discussed a final time in a Nominal Groups round robin discussion (https://www.cdc.gov/healthyyouth/evaluation/pdf/brief7.pdf) and were only accepted if the revised statement reached an 80% agreement.

The Oxford Levels of Evidence (LoE) were applied to each point to consider.[16] The strength of each statement ranged from A (directly based on level I evidence) to D (directly based on level IV evidence or extrapolated recommendations from level I, II or III evidence).[16] Finally, the finalized statements were circulated in a post-consensus meeting Delphi questionnaire to determine level of agreement (LoA). Members of the Task Force were asked to provide their final LoA for each point to consider using a scale of 0 (completely disagree) to 10 (completely agree), which is reported in the tables below.

RESULTS

Systematic literature review

A summary of the literature search strategy and results are provided as supplementary material (online supplementary methods). Based on SLR and consensus conferences, four overarching principles and 17 disease-specific points to consider pertaining to the genetically defined interferonopathies (table 1) with their respective LoE, grade of recommendation (GoR), and LoA were generated.[17]

Table 1 Points to consider for the diagnosis, treatment, and long-term monitoring of patients with type I interferonopathies, CANDLE/PRAAS, SAVI and AGS

		LoE/GoR C/S/AGS	LoA (mean ± SD)
Overarching principles			
A	Patients with autoinflammatory interferonopathies CANDLE/PRAAS, SAVI or AGS present with chronic systemic and organ-specific inflammation; when untreated, chronic inflammation results in progressive organ damage, early morbidity, and increased mortality.	4C/4C/4C	9.8±0.7
B	A confirmed genetic diagnosis is required to make the diagnosis of CANDLE/PRAAS, SAVI and AGS, which facilitates initiation of targeted treatments, genetic counselling, screening for complications, and informs prognosis.	5D/5D/4C	9.5±1.0
C	The goal of treatment of type I interferonopathies is to reduce systemic and organ inflammation to prevent or limit the development of and/or the progression of organ injury and damage, and to improve quality of life.	2B/2B/2B	9.8±0.5
D	In CANDLE/PRAAS, SAVI or AGS, long-term monitoring of disease activity, organ-specific injury/damage and of treatment related complications is required and involves a multi-disciplinary team.	5D/5D/4C	9.9±0.3
Individual points to consider			
I.	**Points to consider for diagnostic evaluation**		
1	Patients presenting with unexplained systemic inflammation (including elevations of CRP, ESR and/or an IFN signature) and clinical features* that include rashes, lipodystrophy, musculoskeletal, neurologic, pulmonary, and metabolic findings should receive a prompt diagnostic work up for CANDLE/PRAAS, SAVI and AGS comprising: • genetic evaluation • clinical evaluation focusing on the extent of inflammatory organ involvement • screening for disease-related comorbidities	4C/4C/4C	9.8±0.7
2	Patients with clinical symptoms of CANDLE/PRAAS, SAVI or AGS who do not carry any of the disease-causing mutations described here should be referred to specialty/research centers that can guide further work up and treatment.	5D/5D/5D	9.8±0.5
Genetic evaluation			
3	Mutations in the following disease-causing genes should be included in the genetic analyses: • CANDLE/PRAAS: *PSMB8, PSMA3, PSMB4, PSMB9, PSMB10, POMP*, and *PSMG2*. • SAVI: *STING1 (*previously *TMEM173).* • AGS: *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, IFIH1, LSM11*** and *RNU7-1***.	4C/4C/4C	9.8±0.6
4	Genetic mimics of CANDLE/PRAAS, SAVI and AGS are recognized and should be included in the diagnostic work up (a non-exhaustive list is below for reference): • for CANDLE-like conditions: Splice variants in *IKBKG*, frameshift mutations in *SAMD9L*, and recessive mutations in *RNASEH2 (A, B, C).* • for SAVI-like conditions: *TREX1, ADA2* and *COPA.* • for AGS-like conditions: *RNASET2.*	4C/4C/4C	9.4±0.9
Clinical evaluation (see also table 3)			

5	In patients with suspected CANDLE/PRAAS, SAVI or AGS, assessment for disease and treatment related comorbidities should include screening for: • *Skin manifestations:* nodular rashes, violaceous annular rashes, panniculitis, lipodystrophy or vasculopathic skin lesions. • *Neurological manifestations*: intracerebral calcifications, leukoencephalopathy, progressive microcephaly, or cerebral atrophy. • *Pulmonary manifestations*: interstitial lung disease/pulmonary hypertension. • *Hepatic manifestations*: hepatic steatosis, hepatitis, hepatosplenomegaly. • *Metabolic manifestations*: hypertension, hyperlipidemia, glucose intolerance (=metabolic syndrome). • *Musculoskeletal manifestations*: arthritis, contractures, and myositis. • *Growth and development*: growth retardation, osteoporosis, bone development delay, pubertal delay. • *Hematologic manifestations:* cytopenias (e.g., more specifically lymphopenia, thrombocytopenia). • *Ophthalmologic manifestations*: Episcleritis, keratitis, retinopathy, glaucoma. • *Cardiac manifestations*: Cardiomyopathy.	4C/4C/4C	9.7±0.6
6	Neuroimaging should be performed in individuals with suspected neurologic symptoms. • MRI best identifies white and grey matter changes. • CT is generally more sensitive for detecting cerebral calcification and can be considered when calcium sensitive modalities on MRI are not available or do not detect calcifications.	4C/4C/4C	9.8±0.4
7	In patients with presumed CANDLE/PRAAS, SAVI or AGS, tissue sampling as appropriate (e.g., CSF if neurologic involvement is suspected, or lesional skin biopsies) may support the diagnosis.	4C/4C/4C	9.4±1.1
8	All patients should undergo a basic immunodeficiency work up that includes a history of infections, lymphocyte subsets and immunoglobulin levels, as a minimum.	4C/4C/4C	9.3±1.5
II.	**Points to consider for treatment**		
9	Treatment of patients with CANDLE/PRAAS, SAVI and AGS should be aimed at achieving disease control or low disease activity to prevent progression of organ damage. For SAVI and CANDLE patients, disease control should be maintained with the lowest possible dose of glucocorticoids).	2B/2B/2B 4C/4C/NA	9.4±1.2
10	Janus Kinase inhibitors (JAKI) are of benefit for improving symptoms*** in CANDLE/PRAAS, SAVI, and AGS.	2B/2B/2B	9.3±0.9
11	In patients with CANDLE/PRAAS, SAVI or AGS on JAKI, screening for treatment-related comorbidities is important. We currently recommend monitoring for BK viral loads in urine and blood to prevent viral organ injury such as nephropathy.	4C/4C/5D	9.3±1.6
12	Glucocorticoids are of benefit for improving symptoms*** in CANDLE/PRAAS or SAVI. Chronic glucocorticoids do not improve the neurological features of AGS although acute courses of glucocorticoids may be useful for the treatment of non-CNS inflammatory conditions.	4C/4C/5D	9.0±1.3
III.	**Points to consider for long-term monitoring and management**		
	Disease related comorbidities and disease progression		

13	A multidisciplinary management team is required for optimal care of patients with CANDLE/PRAAS, SAVI and AGS, that is customized based on patient's disease manifestations.	5D/5D/5D	9.9±0.3
14	Disease activity and burden of disease should be monitored regularly depending on disease activity and severity (see table 3). • Symptom control can be monitored by assessing disease-specific symptoms*** using validated patient reported outcome and quality of life assessments, and by recording missing school or workdays.	5D/5D/5D 5D/5D/5D	9.3±1.8
15	Growth and development of children should be monitored at each visit.	5D/5D/5D	9.8±0.4
Risk of COVID-19			
16	At the time of writing there is no evidence to suggest that risks to patients with CANDLE/PRAAS, SAVI or AGS of COVID-19 are any different from the healthy population. Therefore, treatment for interferonopathy should not be stopped unless a specific contraindication to ongoing treatment arises.	5D/5D/5D	9.5±0.8
Vaccinations			
17	Generally, for CANDLE/PRAAS and SAVI all routine vaccines (live and killed) are indicated when not receiving immunosuppressive treatments or glucocorticoids, although this should be considered on a case-by-case basis.	5D/5D/5D	9.4±0.9

GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level.
LoE: 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case-series (and poor-quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
LoE and GoR are reported separately for each disease.
*Disease-characteristic clinical features are listed in online supplementary table 4.
**These two genes were published after the consensus meeting occurred.
***Clinical symptoms are listed in Table 3 and Supplementary Table 4.
AGS, Aicardi-Goutières Goutières syndrome; CANDLE/PRAAS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; C/S/AGS: CANDLE/PRAAS/SAVI/AGS; CNS, central nervous system; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; ESR, erythrocyte sedimentation rate; GoR, grade of recommendation; IFN, interferon; JAKI, Janus kinase inhibitors; LoA, level of agreement; LoE, level of evidence; MRI, magnetic resonance imaging; NA, not applicable; SAVI, STING-associated vasculopathy with onset in infancy; SD, standard deviation.

Overarching principles guiding the management of patients with CANDLE/PRAAS, SAVI and AGS

The systemic inflammatory multiorgan involvement in patients with CANDLE/PRAAS, SAVI or AGS can ultimately result in progressive organ injury and early mortality.[4] Damage accrues over

time, often manifesting later in life, thus highlighting the importance of early diagnosis and treatment.[1 12]

Autoinflammatory syndromes may present with phenotypic overlap early in life, which poses diagnostic challenges.[12] In addition, mutations in individuals genes may be associated with considerable phenotypic heterogeneity and variable disease severity.[18 19] Genetic confirmation is thus essential for making a precise diagnosis which then facilitates targeted therapy and initiation of genetic counseling with the goal to achieve better clinical outcomes. Patients, their parents, and siblings should have access to formal genetic counselling. Genetic counseling can initiate the risk assessment process depending on the type of inheritance for specific disease-causing mutation and help patients understand their test results, including the medical implications for themselves, their reproductive health concerns, and impact on their relatives. Patients with clinical symptoms of CANDLE/PRAAS, SAVI or AGS who do not harbor any of the disease-causing mutations described here should be referred to specialty/research centers that can guide further work up and treatment. There is no cure for type I interferonopathies. Current treatment options therefore aim to prevent development or progression of end organ damage by controlling systemic and organ inflammation,[20 21] to improve quality of life and to improve disease outcomes.[1] Given the paucity of long-term outcome data on newly available treatments, monitoring of disease activity, and development of organ-specific and treatment-related complications is essential.[1 22 23] A multi-disciplinary team is required to provide optimal care in the context of multiorgan system involvement.[24 25]

Points to consider 1-8: Diagnostic evaluation focuses on raising an early suspicion and on facilitating genetic testing, appropriate clinical and laboratory work up and early treatment

Diagnostic evaluation

The presence of a chronically elevated peripheral blood IFN signature is a common finding in patients with the type I interferonopathies CANDLE/PRAAS, SAVI and AGS. In contrast, traditional inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are typically elevated in CANDLE/PRAAS and SAVI but rarely in patients with AGS.[2 7 12 18 26-30] A peripheral blood IFN signature may be measured using different methodologies, including a 28-gene IFN scoring system using NanoString technology or by quantitative reverse transcriptase (RT) polymerase chain reaction (PCR) methods of gene subsets should be measured repeatedly to establish chronic elevation.[13] Scores may be negative in the diagnostic phase in patients with milder disease; or in response to glucocorticoid treatment. In addition, patients with AGS with *RNASEH2B* mutations may have a negative IFN signature even with active disease.[31] A practical barrier is the limited number of centers with the ability to check an IFN signature. Thus, a chronically elevated peripheral blood IFN signature is not required for diagnosis but can be very useful in raising the suspicion of an interferonopathy. For most IFN signatures, sensitivity and specificity data are not available. However, in a retrospective study, the IFN signature at a set cut-off score was helpful in differentiated patients with an interferonopathy from healthy controls and from patients with a cryopyrin associated periodic syndrome (an interleukin-1 mediated autoinflammatory disease). The IFN signature demonstrated an area under the receiver operator characteristic (ROC) curve of 0.98, with sensitivity and specificity exceeding 0.8.[12] Currently, the IFN signature should be interpreted in the context of normal values of the laboratory that conducts

the test, since no internationally standardized methodologies or reference ranges are currently available.

Genetic evaluation

As there can be significant overlap of clinical features across several autoinflammatory disorders, a confirmed genetic diagnosis is critical to facilitating a precision medicine approach and targeted therapy. Next generation sequencing (e.g., targeted gene panel, whole exome, or whole genome sequencing) to screen for pathogenic variants rather than single gene Sanger sequencing is recommended. Sanger sequencing of individual genes may still be cost effective in patients with known familial disease; and may be the only available option if next generation sequencing is not yet available to the patient. However, this increasingly outdated "gene by gene" approach ultimately may result in diagnostic delay and may not be cost-effective.[32] In addition to the known disease-causing genes[1 2 5 7 12 18 31 33-39] (table 1), screening should be considered for diseases that can mimic one of these disorders; their genetic causes[8 12 40-45] are listed in table 2. Allelic, monogenic or digenic, double heterozygous mutations in genes encoding proteasome or immunoproteasome subunits are the cause for CANDLE/PRAAS with biallelic pathogenic *PSMB8* variants being the most common cause. Digenic disease causing mutations including *PSMB8, PSMA3, PSMB4* and *PSMB9*[1 2 26], compound heterozygous mutations including *PSMB4*, *PSMB8* and *PSMG2*[2 12] and autosomal dominant loss-of-function mutations in *POMP*[2] also cause CANDLE/PRAAS but are rarer. However, novel disease-causing genes are being added as causes for CANDLE/PRAAS. All proteasome genes should be specifically assessed in a patient with a suggestive clinical phenotype. Both parents may need to be tested to confirm digenic inheritance. The inheritance of SAVI is mostly autosomal dominant, and most patients harbor a de novo

heterozygous missense mutations in the *STING1* gene that confers a gain-of-function in activating the IRF3 and *IFNB1* transcription.[7 46] Liu et al. also reported somatic mosaic mutations in one patient (OMIM-615934). So far only additive *STING1* gain-of-function mutations in p.R284W require homozygosity to confer disease.[47] Furthermore, mostly loss-of-function mutations in genes encoding proteins that regulate nucleic acid metabolism or signaling cause AGS.[34] These include biallelic null mutations in *TREX1* an *SAMHD1;* biallelic null mutations in the disease-causing genes, *RNASEH2A*, *RNASEH2B, RNASEH2C* or *ADAR1* have not been reported. Disease-causing *IFIH1* variants are all heterozygous gain-of-function mutations that increase IFN signaling.[34] Recently, biallelic mutations in *LSM11* and *RNU7-1*, which encode components of the replication-dependent histone pre-mRNA–processing complex extend defects in nucleic acid metabolism to histone mRNAs.[48] It is important to notice that large deletions, such as deletions in AGS related genes including *SAMHD1*, may be missed on exome sequencing and need to be reviewed using other testing modalities.[31 49 50] If following routine genetic work up, a molecular diagnosis is not established in a patient with suggestive phenotypic features, referral to a research center of excellence for further evaluation should be considered.

Table 2 List of genetically defined disease and genes that should be considered in the differential diagnosis of CANDLE/PRAAS, SAVI and AGS

Genetically defined diseases*	**Genes**
CANDLE/PRAAS mimics/overlaps	
Differential diagnoses:	
▪ NEMO Deleted exon 5 Autoinflammatory Syndrome (NEMO-NDAS)	*IKBKG* (exon 5 deletion/splice variant)
▪ SAMD9L associated autoinflammatory disease (SAAD)	*SAMD9L* (frame shift mutations)
▪ Other	*RNASEH2B*
SAVI mimics/overlaps	
Differential diagnoses:	
▪ Deficiency of the enzyme adenosine deaminase 2 (DADA2)	*ADA2*
▪ Familial chilblain lupus (CHBL)	*TREX1, SAMHD1*
▪ COPA syndrome	*COPA*
AGS mimics/overlaps	
Differential diagnoses:	
▪ **Other**	*RNASET2*

Other disorders with partially overlapping phenotypes	
Differential diagnoses:	
▪ Spondyloenchondrodysplasia (SPENCD)	*ACP5*
▪ Singleton Merten syndromes	*IFIH1, DDX58*
▪ Retinal vasculopathy with cerebral leukodystrophy (RVCL)	*TREX1*
▪ Trichohepatoenteric syndrome (THES)	*TTC37, SKIV2L*
▪ Lipopolysaccharide responsive and beige-like anchor protein (LRBA) deficiency	*LRBA*
▪ Monogenic early onset lupus	e.g., *C1Q (A, B, C)*, several other

*Based on current evidence, all type I interferonopathies, including but not limited to the genetically defined diseases listed in the table should be considered in the differential diagnosis of CANDLE/PRAAS, SAVI or AGS because of overlapping clinical and laboratory features.
AGS, Aicardi-Goutières syndrome; CANDLE/PRAAS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; SAVI, STING-associated vasculopathy with onset in infancy.

Clinical evaluation

In patients with undifferentiated autoinflammatory diseases or otherwise unexplained systemic inflammation, certain clinical features are suggestive of CANDLE/PRAAS, SAVI or AGS (table 1 and online supplementary table 4). The following clinical features are relevant to the work up of patients with suspected interferonopathies:

Cutaneous manifestations

Inflammatory skin lesions are present in all three diseases; however, the nature of the rash differs. Nodular rashes or violaceous annular rashes should prompt a diagnostic work-up for CANDLE/PRAAS. Another specific cutaneous finding for CANDLE/PRAAS is panniculitis (particularly neutrophilic panniculitis) and panniculitis induced lipodystrophy, which are hallmarks of the disease.[1 2 9 12 18 36 37 51]

The presence of vasculopathic skin lesions (e.g., pernio ("chilblain lesions") or acral ischemia,) is suggestive of SAVI[44] and AGS.[33 52-55] Skin involvement is the most common symptom in patients with SAVI at presentation[1 7 56-59] but some patients can present with severe lung disease and only minimal skin involvement.[8 46 60 61]

In addition to chilblain-like lesions and acrocyanosis, other skin manifestations such as periungual erythema, or necrotic lesions of the toes, fingers, and outer helix, can be seen in AGS patients.[33 52-55] Moreover, some AGS patients can have panniculitis as well.[34] Finally, some AGS patients have recurrent oral ulcers.[50 62]

Lesional skin biopsies in areas that can safely be biopsied can be beneficial in revealing the neutrophilic dermatosis, small vessel vasculitis (from necrotic area), fasciitis,[57] and granulomatous nodular dermatitis[59] thus supporting the diagnosis of SAVI while in AGS specifically, a lesional biopsy can demonstrate deposition of immunoglobulin and complement in the walls of small vessels.[63]

Neurologic manifestations

Although CANDLE/PRAAS affected patients present with headaches and may develop aseptic meningitis,[24] neurologic findings are most common and severe in AGS and include subacute or acute neurologic decline, unexplained developmental delay, progressive microcephaly, dystonia, spasticity, encephalopathy, irritability and focal motor findings. A lumbar puncture typically shows sterile cerebrospinal fluid (CSF) pleocytosis.[11 64 65]

Neuroimaging should be performed in individuals with a suspected diagnosis of an interferonopathy in the presence of neurologic symptoms. The initial work up may include magnetic resonance imaging (MRI) of the brain which identifies best white and grey matter changes.[41] Computerized tomography (CT) head should be considered when calcium sensitive modalities on MRI are not available or not able to detect calcifications, since it is more sensitive for the detection of cerebral calcification.[66] Risks and benefits of sedating a child for MRI brain should be considered.[67] It is useful to have a baseline brain MRI to assess the severity and to

monitor disease associated complications; however, this is not a diagnostic prerequisite, especially for SAVI and CANDLE/PRAAS. Neuroimaging may be particularly helpful in patients with suspected AGS due to the dominant neurologic phenotype which should be differentiated from mimickers of interferonopathies.

Basal ganglia or other intracerebral calcifications are overlapping neuroimaging findings for all three diseases;[68] they are more common, more severe, and typically start earlier in life in patients with AGS compared with CANDLE/PRAAS, while calcifications are rare in SAVI.[8 41 68 69] In addition, the presence of leukoencephalopathy is suggestive of AGS and typically starts early in life in AGS patients with severe disease; it is unusual in CANDLE/PRAAS or SAVI.[11 70 71] Other supportive neuroimaging characteristics for AGS are early and rapid cerebral atrophy with or without calcifications, cerebral white and gray matter changes, and Moyamoya disease.[12 41 69 70 72-74] Intracerebral large vessel vasculitis or Moyamoya can be seen and is associated with *SAMHD1* mutations.[49 74-77]

Additional work up for neurodegenerative diseases in patients with suspected AGS may also be considered. Lumbar punctures are not required to make the diagnosis of AGS but may support the diagnosis[72] and characterize the immunologic features of the CNS inflammation, including the presence of lymphocytosis and raised levels of interferon-alpha (IFN-α), CXCL10, and CCL2 in the CSF.[31 54 69] The CSF studies are most beneficial if a molecular diagnosis of AGS is not confirmed by genetic testing and provide support for additional molecular testing. [72]

Pulmonary manifestations

The presence of early onset interstitial lung disease (ILD) raises suspicion for SAVI, in particular in the context of unexplained systemic inflammation.[1 7 46 56 61] Many patients with SAVI

are reported to have lung involvement, mostly manifested as ILD, ranging from mild ILD with no respiratory symptoms to lung fibrosis. Also, alveolar hemorrhage is reported as the presenting feature in a few cases with SAVI.[47 60] Although ILD is a major concern for patients with SAVI, it is rarely present in patients with CANDLE/PRAAS[1 18 51] and not reported in AGS. Low radiation chest CT and pulmonary function tests (PFTs) are recommended modalities to screen for ILD.[8] Lung biopsies may distinguish infectious from inflammatory disease but are not required to make the diagnosis of SAVI.[7 46 60 61]

Another significant pulmonary manifestation is pulmonary hypertension, which is a potentially life threatening and possibly underdiagnosed complication of CANDLE/PRAAS and AGS.[1 12 78] While CANDLE/PRAAS and AGS are known to affect the vascular system, the full impact of systemic vasculopathy is currently under-characterized. All patients with suspected CANDLE/PRAAS and AGS should undergo regular evaluation for pulmonary hypertension; echocardiography is recommended as a screening and monitoring tool.

Hepatic manifestations

Forty to eighty percent of CANDLE/PRAAS patients develop metabolic syndrome and hepatic steatosis, often in the first decade of life.[1] In addition, patients may develop hepatosplenomegaly which could be due to extensive metabolic disturbance in fat processing.[2 5 9 36 37 39 51] In an open-label trial in CANDLE/PRAAS, it is reported that baricitinib did not significantly improve hepatic steatosis in two patients with hepatic steatosis prior to baricitinib treatment nor prevent it in three patients with hyperlipidemia at baseline pointing to the role of proteasome dysfunction in the etiology of hepatic steatosis.[1]

In AGS, hepatosplenomegaly and/or transaminitis can be an initial presentation in the neonatal period when it resembles congenital viral infection.[31 33 72 79] Later in life, patients can develop autoimmune hepatitis.[34]

Transaminases should be evaluated at presentation and may be monitored as a marker for hepatic disease activity in patients with type I interferonopathies, although it should be noted they can also be elevated in CANDLE/PRAAS and AGS due to myositis.[12]

Information about the clinical features of hepatic involvement in patients with SAVI is limited. However, case reports of patients with SAVI presenting with hepatic disease, such as necrotizing granulomatous hepatitis, cholestatic hepatitis and cholangitis and multiple biliary cysts are presented.[58 80]

Metabolic manifestation

Metabolic abnormalities are significant concerns in patients with CANDLE/PRAAS and patients can develop metabolic syndrome defined by Ford et al. [presence of at least three of the following five criteria: hypertriglyceridemia $\geq$110 mg/dL, low high-density lipoprotein (HDL) cholesterol $\leq$40 mg/dL, abdominal obesity with waist circumference $\geq 90^{th}$ percentile (sex specific), hyperglycemia $\geq$110 mg/dL, systolic or diastolic blood pressure $\geq 90^{th}$ percentile (age, height, sex specific)].[81] In addition, these patients can have increased abdominal girth secondary to intra-abdominal fat deposition.[1 51] The work-up in CANDLE/PRAAS should include screening for metabolic abnormalities.

Patients with AGS may have hypothyroidism, often requiring replacement therapy, and insulin-dependent diabetes mellitus is reported.[34 49 53 54 77 82-84] Other endocrine manifestations include central diabetes insipidus, growth hormone deficiency and adrenal insufficiency.[34 82]

Musculoskeletal manifestations

Myositis is a common feature of patients with CANDLE/PRAAS. It is usually patchy in distribution and can be demonstrated by muscle MRI.[1 39 51] In addition, most CANDLE/PRAAS patients will develop variable degrees of joint contractures in the hands and feet; these can be severely disabling.[1 2 9 37 51] Myopathy is described in individual case reports in AGS.[85] In AGS affected patients, joint involvement can include a lupus like arthritis, or progressive arthropathy with joint contractures.[50 86 87] Articular involvement in SAVI is seen in one third of the patients.[8] Rheumatoid factor (RF) positivity was reported in majority of cases (57%)[8] while anti-cyclic citrullinated peptide (anti-CCP) positivity was not common in patients with SAVI.[7 43] Interestingly, the course of the arthritis in SAVI can be destructive, especially in childhood, when associated with RF and anti-CCP antibodies.[43]

Growth and development

Many children with chronic inflammation, including patients with type I interferonopathies, have lengths/heights and bone mineral density (BMD)s that are below that of age-matched controls. Height and BMD are further decreased in the context of treatment with glucocorticoids. Weight percentiles can increase sharply with high doses of glucocorticoids, and this should be taken into consideration when evaluating weight.[1]

In addition to abnormalities in stature, patients with AGS can have significant developmental delay; after a sub-acute onset most individuals develop profound neurologic regression and present with severe impairment in psychomotor development. [22 23 34] Patients with

AGS and CANDLE/PRAAS may also present with mild developmental delay;[5 22 51] these delays are not reported in patients with SAVI.[8]

Hematologic manifestations

Cytopenias can occur in all three diseases due to temporary bone marrow suppression or homing changes and may correlate with disease activity.[1 12] Cytopenias including autoimmune cytopenias occur more frequently in CANDLE/PRAAS and AGS patients but are also seen in SAVI patients.[1 8 18 33 50 52 54 60 79 82 88] Thrombocytopenia in AGS patients can be present during the neonatal period mimicking congenital infection, but also later during the course of the disease associated with other hematologic abnormalities such as anemia and leukopenia.[19 79] Complete blood count with differential, should be evaluated at presentation and may be monitored as a marker for disease activity in patients with type I interferonopathies.

Ophthalmologic manifestations

Patients with type I interferonopathies can develop different types of ophthalmologic manifestations. While patients with CANDLE/PRAAS can present with keratitis and/or episcleritis,[2 18 51] patients with SAVI and AGS can develop glaucoma.[8 54 76] Retinopathy has been described in AGS and SAVI but it remains unclear whether this occurs in the context of secondary mutations.[89]

Cardiac manifestations

Patients with AGS, especially those with mutations in *TREX1,* are prone to develop infantile-onset hypertrophic cardiomyopathy.[31 34] There is an important risk of cardiac valve calcification in disease related to mutations in *IFIH1* and *ADAR*.[90]

Other considerations

Immunodeficiency work up

Patients with known type I interferonopathies may have some degree of immunodeficiency, either due to chronic disease and cytopenias or due to treatment with immunosuppressants.[91] Early manifestations may overlap with non-type I interferonopathy immunodeficiencies. Therefore, a basic immunologic work-up should be considered even in the context of a confirmed diagnosis. The work up should include a history of infections and assessment of lymphocyte subsets and immunoglobulin levels, as a minimum.[1 12 92]

Infections in patients with CANDLE/PRAAS can be associated with the development of macrophage activation syndrome (MAS). Opportunistic infections in patients with other CANDLE mutations or SAVI and AGS are rare, although pneumocystis infection has been reported in a SAVI patient who was not on any immunosuppressive treatment.[88] Furthermore, defects in maturation of CD8+ cells are identified in CANDLE patients,[2 93] and in some SAVI patients[8 57 88] severe infections are reported in two patients with *POMP* mutations,[93] which may be modified by additional genetic variants.

Points to consider 9-12: Treatment focus on optimizing inflammatory disease control

The goal of treatment is the control of the systemic and organ-specific disease manifestations, and to manage complications of existing organ damage that are consequences of untreated disease.

Pharmacologic treatment with Janus Kinase inhibitors (JAKI), particularly baricitinib, is widely used to treat patients with type I interferonopathies.[1 94-97] The JAKI are reported to be beneficial in controlling inflammatory symptoms and in preventing progression of end organ damage. Specifically, treatment with baricitinib resulted in a significantly lower daily diary score as well as significant reduction in glucocorticoid use in patients with type I interferonopathies in different open label trials.[1 94] In the study by Sanchez et al., none of the patients had achieved remission before initiating baricitinib treatment, and 50% of the CANDLE/PRAAS patients achieved lasting remission with no clinical symptoms, normalization of inflammatory markers on baricitinib, all discontinued glucocorticoids. In addition, patients with CANDLE had improvement in myositis and cytopenias (hemoglobin, lymphocyte, and platelets). Moreover, significant clinical improvement, including fewer vasculitis flares, prevention of skin involvement/progression of spontaneous amputations/the development of gangrene, and stabilization of ILD by preserving pulmonary function, was achieved in patients with SAVI.[1] However, to date, no SAVI patient treated with JAKI achieved complete remission. Furthermore, JAKI reduce IFN-α mediated STAT-1 phosphorylation in a dose dependent manner in interferonopathy patients[26 56] thus demonstrating an in vivo effect of the JAKI on type-1 IFN signaling. The JAKI, ruxolitinib and tofacitinib, are also reported as potential treatment options.[44 56 59 97] Population pharmacokinetics and pharmacodynamic analyses in children treated with baricitinib showed a substantially shorter half-life in pediatric than in adult populations requiring more frequent dosing, and led to a proposed weight- and estimated glomerular filtration rate-based dosing regimen to guide dose adjustments

in the growing child.[26,17] Doses of JAKI used to treat these conditions that were published are summarized in supplementary table 5. A beneficial effect of JAKI inflammatory disease manifestations is also observed in patients with AGS, including in an open label trial. The treatment led to decrease in interferon signaling genes (ISG) expression scores and improvement of AGS-related symptoms, including neurologic disability, crying, sleep disturbances, irritability, seizures, fever, and skin inflammation of the trunk, arms, and legs.[94-96] In all instances, pre-existing organ damage is irreparable (i.e., the neurologic manifestations) stressing the need for early treatment. In patients with AGS, treatment with HIV-1 reverse-transcriptase inhibitors reduced IFN scores, however, clinical benefit was not demonstrated[98] and thus it is unclear if these drugs can be recommended.

Viral reactivation including BK viral reactivation have been reported in type I interferonopathy patients treated with JAKI.[1 59] BK polyomavirus reactivation caused by therapeutic immunosuppression a commonly reported complication in renal transplant patients that can result in nephropathy and renal allograft loss. There is no proven treatment for BK nephropathy and management is limited to early detection and to controlling BK viral load by reducing the dose of immunosuppressive medications.[99 100] Monitoring for BK viral load in blood and urine and renal function prior to initiation of JAKI, at baseline, and then routinely at each visit is recommended.

Other viral reactivations, such as herpes, are reported in CANDLE/PRAAS and SAVI;[1] however, there are insufficient data to routinely recommend anti-viral drug prophylaxis for patients with CANDLE/PRAAS and SAVI treated with JAKI. Similarly, in AGS, viral prophylaxis for patients on JAKI is not currently recommended.

Finally, the date from an open label trial indicated that AGS patients who are receiving baricitinib should be monitored closely for thrombocytosis, leukopenia and infection, especially

those with underlying thrombotic risk factors or those who are receiving systemic glucocorticoids or immunosuppressive regimens,[94] while no such events were reported in two other reports.[95 96]

Glucocorticoids are generally considered useful in CANDLE/PRAAS and SAVI patients with systemic inflammation, although their use is limited by toxicity.[1] When used for a prolonged time, glucocorticoids cause serious side effects including growth arrest, truncal obesity, hypertension, glucose intolerance, and osteopenia.[101] Therefore the lowest possible dose of glucocorticoids should be targeted for disease control.

There is generally no role for chronic glucocorticoids in AGS, as glucocorticoids do not improve the long-term neurological features nor outcome of AGS. However, short courses of glucocorticoids to treat acute CNS and non-central nervous system (non-CNS) inflammatory manifestations, such as cytopenias and hepatitis, may be beneficial.

Points to consider 13-17: Long-term monitoring and management focus on assessing inflammatory organ manifestations, minimizing treatment related toxicities, and encouraging general health measures, including vaccines, and fostering of self-management skills and medical decision-making

A multidisciplinary team approach to regular clinical follow-up is recommended, and may include access to medical subspecialists including a rheumatologist, geneticist, neurologist, ophthalmologist, pulmonologist, cardiologist, hepatologist, gastroenterologist, hematologist, immunologist, dermatologist, endocrinologist, nephrologist, and access to supportive services including a physiatrist, wound care specialist, psychologist, bone health specialist, physical therapist, dental/oral surgeon, dietitian, psychiatrist, rehabilitation care, orthopedic care, and social support services. With current treatment strategies the ultimate treatment goal in inflammatory diseases, namely inflammatory remission, can only be achieved in a subset of patients. Remission

is mainly described in patients with CANDLE.[1] The current treatment goal is therefore to reduce systemic and organ inflammation and to prevent or limit the development or progression of organ injury/damage. This requires treatment adjustments and close monitoring of disease progression. Table 3 provides general and disease specific guidance for the monitoring of disease activity and assessment of organ damage. The monitoring should include a. assessment of the level of systemic inflammation, and of growth and sexual development, b. the assessment of general and disease-specific clinical signs and symptoms including the use of validated instruments when available,[1] [22] [23] c. monitoring of disease-specific organ manifestations and d. monitoring of the development of autoimmune features, cytopenias, treatment related complications and infections (immunodeficiencies). Preliminary guidance regarding the monitoring of JAKI treatment (Table 3) are provided but may need to be adjusted as experience with treatment of interferonopathies grows.

Table 3 Evaluation of inflammatory disease manifestations and organ involvement with proposed interval monitoring

		Follow-up frequency*
A. Monitoring of systemic inflammation and development		
	ESR, CRP, CBC with differential (cytopenias), IFN signature when available	At each visit*
	Urinalysis (proteinuria, renal disease) Renal ultrasound	At each visit* To consider at baseline
	Hepatosplenomegaly and lymphadenopathy	At each visit*
	Height and weight DEXA scan** (BMD) Sexual development	At each visit* As clinically indicated As clinically indicated
B. Monitoring of clinical disease signs and symptoms		
CANDLE/PRAAS		
	Fever, rash, progressive lipodystrophy, headache, musculoskeletal symptoms (joint pain, contractures, weakness), shortness of breath, weight changes, developmental assessment, fatigue	At each visit*
SAVI		

	Fever, rash, peripheral acral vasculitis and dystrophic changes, respiratory symptoms (shortness of breath, tachypnea, digital clubbing), fatigue	At each visit*
AGS		
	Developmental assessment, changes in neurologic tone affecting joint integrity, skin findings, musculoskeletal findings, clinical evidence of cytopenias, endocrine disturbance, ocular abnormalities, or cardiomyopathy	At each visit*
C. Monitoring of organ manifestations		
CANDLE/PRAAS		
Skin disease	Skin exam, assessment of lipodystrophy Lesional skin biopsy (neutrophilic panniculitis)	Every 3-6 months till stable then every 6-12 months Baseline only
Musculoskeletal disease	Arthritis, contractures, weakness CK, aldolase, LDH for myositis	Every 6-12 months
Endocrine, metabolic disease**	Metabolic syndrome Lipid profile (dyslipidemia), fasting glucose, Hemoglobin A1C, serum insulin (insulin resistance) BP measurement (systemic hypertension)	Every 12-36 months depending on symptoms. At each visit* At each visit*
Hepatic disease**	ALT, AST, GGT, liver elastography, or screening for hepatic steatosis with the best available method	Every 6-12 months
Pulmonary arterial hypertension**	Echocardiography Cardiology and/or pulmonology referral if signs of PAH	Every 6-12 months, if PAH then as clinically indicated
CNS disease**	Lumbar puncture (if headaches), Brain MRI	Every 12-36 months depending on symptoms
Eye disease**	Scleritis, episcleritis, keratitis	Yearly or based on clinical need
Dental disease	Tooth abnormalities (tooth agenesis, hypodontia), delayed tooth eruption	Yearly or based on clinical need
SAVI		
Skin disease	Wound care (including wound culture as necessary)	As needed
Pulmonary disease**	Low radiation chest CT PFTs Pulmonology referral if signs of ILD	At baseline and then as needed Every 3-6 months As needed
AGS		
Neurologic damage/progression**	Brain MRI (cerebral white and grey matter changes) MRI/MRA in patients with *SAMHD1* associated AGS (intracerebral vasculitis) Electroencephalogram (epilepsy) Muscle MRI or ultrasound (myositis)	At baseline and then as needed Yearly As needed As needed
Hepatic disease**	ALT, AST, GGT, bilirubin total and direct, albumin, and INR (autoimmune hepatitis)	Every 6-12 months
Endocrinopathies	TSH (hypothyroidism) GH testing and glucose tolerance test	Yearly As needed based on symptoms
Renal disease	Urinalysis	Every 6-12 months
Eye disease**	Ophthalmologic evaluation (glaucoma)	Yearly
Cardiorespiratory	Echocardiogram (cardiomyopathy and PAH)	Every 1-2 years
Scoliosis, hip dislocation**	Hip X-rays and spine screening in non-ambulatory patients (hip dislocation)	Every 6-12 months

D. Monitoring of autoimmunity, cytopenias, immunodeficiency, and JAK inhibitor related complications		
Autoimmunity and cytopenias and immunodeficiency	Screening for autoimmunity (autoantibodies as indicated), CBC with differential (screening for anemia, thrombocytopenia, leukopenias) History of infections, lymphocyte subsets, immunoglobulin levels. Consider immunology or hematology referral	Every 6-12 months and when indicated At baseline and then every 3-6 months
Infections	Clinical history, viral reactivation (on JAK inhibitors), opportunistic infections	At each visit
JAK inhibitor monitoring	CBC with differential, LFTs, urinalysis, renal function, creatinine clearance, BK viral loads in urine and blood, urine beta 2 microglobulin	At each visit

*The visit frequency is set according to clinical need and the patient's disease activity. If there is no active disease, then patients should be followed every 3 months to assess disease activity and monitor drug toxicity.
**Requires subspecialty evaluation
AGS, Aicardi-Goutières Syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMD, bone mineral density; BP, blood pressure; CANDLE/PRAAS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; CBC, complete blood count; CK, creatinine kinase; CRP, C-reactive protein; CT, computed tomography; DEXA, dual energy X-ray absorptiometry; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; GH, growth hormone; IFN, interferon; ILD, interstitial lung disease; INR, international normalized ratio; JAK: janus kinase; LDH, lactate dehydrogenase; LFTs, liver function tests; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PAH, pulmonary arterial hypertension; PFTs, pulmonary function tests; SAVI, STING-Associated vasculopathy with onset in Infancy; TSH, thyroid stimulating hormone.

All patients should be evaluated at each visit for the presence of disease-specific symptoms and presence of systemic inflammation (table 3).

Chronic inflammation and chronic glucocorticoid treatment negatively affect bone health, (e.g., osteoporosis), growth (stunting) and development.[1] These parameters should be monitored regularly, as well as cardiac (e.g., hypertension) and ophthalmologic complications of chronic glucocorticoid use.

Patients with CANDLE/PRAAS should also be monitored for headaches, skin and musculoskeletal disease, development of metabolic syndrome (hypertension, hyperglycemia, and hepatic steatosis) and for development of primary pulmonary hypertension. Pulmonary hypertension can be insidious in onset. Although ILD is rare, it should be screened for at baseline and monitored as indicated by PFTs and low radiation chest CT. Ophthalmologic and dental

assessment may be required in patients with eye inflammation and hypodontia and tooth eruption problems.[1 2 5 9 18 36 37 39 51]

Patients with SAVI may require wound care (including wound culture as necessary), and close assessment of ILD and the development of secondary pulmonary hypertension. Patients should be screened for systemic hypertension, otolaryngology, ophthalmology, and dental disease at baseline and be followed as indicated. Patients should be instructed in self-care, including keeping peripheries warm, and in emergency management of acute ischemic digits (e.g., with – but not limited to – intravenous fluids, pentoxyphylline, or intravenous vasodilators), prompt use of antibiotics if infection is suspected, and meticulous wound care.[1 8 102]

Patients with AGS are monitored for progression of neurologic disease including gross and fine motor function and cognitive function using validated scales when available.[22 23] Patients with *SAMHD1* mutations require yearly MRI and MR angiography studies to screen for intracerebral artery disease (e.g., Moyamoya).[49 74 77] Patients should be monitored for the development of systemic hypertension, pulmonary hypertension and cardiomyopathy.[78] Other complications include autoimmune hepatitis[25 82] and autoimmune endocrinopathies, most frequently hypothyroidism.[34] Other manifestations that can develop insidiously include glaucoma and epilepsy, and should be monitored as clinically indicated.[76 103] Neurologic tone abnormalities in non-ambulatory patients can lead to joint dislocation and scoliosis and should be monitored. Families should be instructed in prevention of skin complications, physical therapy, management of disturbed sleep-wake patterns and irritability commonly seen in AGS. Families can also participate in home stretching programs, and appropriate positioning of children with tone abnormalities.

Antinuclear antibodies (ANA) are seen in up to 62.5% of SAVI patients[8] and in up to 23% of AGS patients[62] , but are less frequent in CANDLE patients. Antineutrophil cytoplasmic antibodies (ANCA) are, intermittently, elevated in up to 71% of SAVI patients and 18 % of AGS patients.[8 62] Moreover, antiphospholipid antibodies are present in patients with CANDLE/PRAAS, SAVI and AGS[1 7 62] ; and RF positivity is reported in patients with SAVI (see above). Urinalysis for kidney dysfunction and screening for autoimmunity based on the disease symptoms are recommended as kidney disease is reported mostly in patients with AGS[50 62 79] and SAVI.[8 104 105] Renal pathology prior to treatment with JAKI should be assessed by a baseline renal ultrasound and urine protein/creatinine ratio (or albumin/creatinine ratio).

All patients and families should have access to formal genetic counselling and may require social and other support. Supportive care, including adaptive equipment (e.g., orthoses, walkers, wheelchairs, seating equipment, etc.), may be required.

Treatment during infections including COVID-19

Disease flares and progression can occur if immunosuppressive treatment is held[106] and disease can flare in the context of an infection. Thus, any patient who develops an acute infection (or other complications) may require adjustment of immunosuppressive treatment (and/or institution of other supportive treatment), which should be conducted only under expert supervision. In line with these suggestions, recently published ACR guidance recommends continuing or initiating immunosuppressants when indicated in patients with pediatric rheumatic diseases in the context of exposure to SARS-CoV-2 or if experiencing asymptomatic SARS-CoV-2 infection. Immunosuppressants may be temporarily delayed or withheld if a patient has symptomatic COVID-19.[107]

Vaccination

Whether vaccination may trigger disease flares in interferonopathies is an important and currently unanswered question. There are no data suggesting that patients with CANDLE/PRAAS and SAVI develop disease flares to routine childhood vaccinations and the Task Force therefore recommended compliance with local regulations when patients are not treated with immunosuppressive treatments or glucocorticoids. No such consensus was achieved for AGS: the safety of vaccines in this population is not fully evaluated, and anecdotal reports of vaccine induced neurological regression were concerns debated by the Task Force. No specific recommendation on vaccination for AGS was therefore possible. In line with general EULAR guidance, the Task Force recommends avoiding live vaccines in patients with CANDLE/PRAAS, SAVI, and AGS while on treatment with JAKI or other immunosuppressive medications.[108]

Ribonucleic acid (RNA) based SARS-Cov-2 vaccines are not live vaccines, suggesting that they may be safe for immunosuppressed patients. Whether vaccines against COVID-19 have the potential to provoke a disease flare is unknown, theoretical concerns about disease flare in type I interferonopathies caused by RNA vaccines exist. There are currently no data, to back specific recommendations.

CONCLUSION

The aim of these points to consider is to address the unmet need to provide guidance for healthcare professionals involved in the care of patients with the recently characterized type I interferonopathies, CANDLE/PRAAS, SAVI and AGS. A lack of high-level evidence is a limitation to these points to consider and reflect the challenges of studying novel, ultra-rare

diseases. To address these challenges the Task Force generated guidance statements based on results from a thorough SLR and on specialists'/experts' opinions where evidence was lacking or was insufficient. The Task Force included various specialists with broad expertise in relevant clinical areas and representing different regions, disease interests, and practice environments.

Important areas of future research are outlined in table 4. The cost and availability of genetic testing, interferon signature assays, and JAKI treatment are substantial barriers that currently prevent optimized care for patients with interferonopathies. Furthermore, patients with the autoinflammatory interferonopathies CANDLE/PRAAS, SAVI, and AGS live in many different countries and are managed in different healthcare systems. These points to consider address the multiple challenges of managing patients with these ultrarare diseases, by providing guidance on improving clinical recognition, support for decision-making on genetic testing as well as treatment and long-term management. These points to consider were developed to increase awareness of these diseases, and to standardize the level of care by characterizing the diagnostic and therapeutic tools that can improve care.

Table 4 Research agenda
To define autoinflammatory disease outcomes, including: Develop validated remission criteria for each disease including patient reported outcome measures. Develop minimal disease activity criteria. Validate identify sensitive biomarkers of progression of organ disease (including CNS).
To further assess efficacy of Janus kinase inhibitors (JAKI) and other Type I IFN targeted therapies.
To assess long-term safety with treatment of JAKI. Assess long-term effect of chronic BK viral reactivation. Recommend monitoring guidance including frequency of BK viral loads measurements and management of BK viremia.
To assess requirement of viral prophylaxis on JAKI.
To identify novel therapeutic targets and better treatments.
To validate an interferon signature to diagnose and monitor patients (e.g., number of interferon response genes to include, sensitivity and specificity of score).
To evaluate the effect of vaccination in triggering or exacerbating disease activity in patients with type I interferonopathies while on or off treatments with immunosuppressive medications and/or glucocorticoids.
To identify new genetic causes for interferonopathies

CNS, central nervous system.

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This project is part of a series of "points to consider" consensus efforts to standardize the diagnosis, treatment, and long-term monitoring of patients with the 3 major groups of known autoinflammatory diseases including a. the IL-1 mediated diseases CAPS, TRAPS, MKD and DIRA, b. the autoinflammatory interferonopathies CANDLE, SAVI and AGS and c. the on early diagnosis, treatment, and long-term monitoring of inflammatory conditions with the potential progression to HLH/MAS.

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The Autoinflammatory Alliance substantially contributed to an international meeting and workgroup organization in August 2019 that developed the outline of the points to consider project. The funds for this preceding international meeting were largely due to patient fundraisers, online fundraising and the work of countless volunteers who made this project possible.

Contributions

All authors contributed to the formulation of the points to consider. In details, the steering committee of the Task Force (RGM, PB, AV, BF, ED) defined the research questions for the SLR. A systematic literature review was conducted by KCG, MR, LL with support from a librarian and epidemiologist (DH and DP) under supervision of a senior methodologist (ED). KCG, LL, MR extracted the data. RGM, PB and AV synthesized the results form SLR and Delphi questionnaires and generated draft statements. The manuscript was drafted by KCG, LL and MR and revised by RGM, PB, AV, ED and BF. DA oversaw the proceedings and provided advice of this points to consider project as EULAR methodologist. All other authors participated in the taskforce meetings, in two pre-meeting Delphi questionnaires, suggested and agreed upon the research questions, read the final statements prior to the manuscript, discussed results and made contributions to the text. All authors approved the final version of the manuscript.

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Competing Interest

EF: received NIH Grant “Clinical Outcomes in Aicardi Goutières Syndrome” (Grant number 5U01NS106845-02) and participated in an advisory board of Biogen. EH: Spouse employed by Eli Lilly and received stock options in 2019 and 2020. SO1: NIH Grant “Clinical Outcomes in Aicardi Goutières Syndrome” (Grant number 5U01NS106845-02) and participated in advisory board of Biogen. CP: received consulting and lecture fees from Novartis. BF: is associate editor of Arthritis and Rheumatology and member of the ACR guidance document committee. AV:

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