The 2021 European Alliance of Associations for Rheumatology/American College of Rheumatology points to consider for diagnosis and management of autoinflammatory type I interferonopathies: CANDLE/PRAAS, SAVI and AGS

Kader Cetin Gedik,[1] Lovro Lamot,[2] Micol Romano,[3] Erkan Demirkaya,[3] David Piskin,[4,5] Sofia Torreggiani,[1,6] Laura A Adang,[7] Thais Armangue,[8] Kathe Barchus,[9] Devon R Cordova,[10] Yanick J Crow,[11,12] Russell C Dale,[13] Karen L Durrant,[9,14] Despina Eleftheriou,[15] Elisa M Fazzi,[16] Marco Gattorno ,[17] Francesco Gavazzi,[7,18] Eric P Hanson,[19] Min Ae Lee-Kirsch,[20] Gina A Montealegre Sanchez,[21] Bénédicte Neven,[22] Simona Orcesi,[23,24] Seza Ozen ,[25] M Cecilia Poli,[26] Elliot Schumacher,[9] Davide Tonduti,[27] Katsiaryna Uss,[1] Daniel Aletaha ,[28] Brian M Feldman ,[29,30] Adeline Vanderver,[7,31] Paul A Brogan ,[15] Raphaela Goldbach-Mansky [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Raphaela Goldbach-Mansky, Translational Autoinflammatory Diseases Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA; goldbacr@mail.nih.gov

KCG, LL and MR contributed equally.

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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 healthcare 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 4 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 standardise and improve care, quality of life and disease outcomes.

INTRODUCTION

Autoinflammatory type I interferonopathies are genetically defined (monogenic or digenic) immunodysregulatory disorders characterised 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, 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 patients with AGS; 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, the 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 characterisation of disease-specific clinical manifestations, and provide evidence supporting the pathogenic role of type I IFN signalling.[1 2 12 13] These developments prompted the Task Force lead by the steering committee (two convenors (PAB, RG-M), a neurologist (AV), two methodologists (BMF, ED) and three paediatric 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 paediatricians, 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 authorising patients' access to various diagnostic tools and treatment options; all with the ultimate goal to harmonise the level of care and to improve quality of life and disease outcomes in this patient population.

METHODS

The European Alliance of Associations for Rheumatology (EULAR)[14] and the American College of Rheumatology (ACR) standardised 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 recognised 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 whom 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 in questions that did not reach a greater than 80% consensus were reviewed and reworded 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, which 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 COVID-19 pandemic, one for CANDLE/PRAAS and SAVI, and one for AGS.

Two conveners (RGM, PAB), three methodologists (BMF, 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, 1 allied health professional and 1 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, 1 allied health professional, 1 SAVI and 1 CANDLE/PRAAS patient presentative, and AGS specific statements were voted on by 14 experts, 1 allied health professional and 1 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 finalised 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, 4 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]

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 counselling with the goal of achieving better clinical outcomes. Patients, their parents and siblings should have access to formal genetic counselling. Genetic counselling 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 harbour any of the disease-causing mutations described here should be referred

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	LoA (0–10) Mean±SD
Overarching principles		**C/S/AGS**	
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 multidisciplinary 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 workup 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 centres that can guide further workup 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 recognised and should be included in the diagnostic workup (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 tables 3 and 4***)***			
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, hyperlipidaemia, glucose intolerance (=metabolic syndrome). ► *Musculoskeletal manifestations*: Arthritis, contractures and myositis. ► *Growth and development*: Growth retardation, osteoporosis, bone development delay, pubertal delay. ► *Haematological manifestations*: Cytopenias (eg, 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 (eg, 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 workup 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 patients with SAVI and CANDLE/PRAAS, disease control should be maintained with the lowest possible dose of glucocorticoid.	2B/2B/2B 4C/4C/NA	9.4±1.2
10	Janus kinase inhibitors (JAKIs) 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			

Continued

Table 1 Continued

		LoE/GoR	LoA (0–10) Mean±SD
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 customised 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 4) ► 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

LoE and GoR are reported separately for each disease.
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 randomised 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'.
*Disease-characteristic clinical features are listed in table 3.
†These two genes were published after the consensus meeting occurred.
‡Clinical symptoms are listed in tables 3 and 4.
C/S/AGS: CANDLE/PRAAS/SAVI/AGS; AGS, Aicardi-Goutières syndrome; CANDLE/PRAAS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; GoR, grade of recommendation; IFN, interferon; JAKI, Janus kinase inhibitors; LoA, level of agreement; LoE, level of evidence; NA, not applicable; SAVI, STING-associated vasculopathy with onset in infancy.

to specialty/research centres that can guide further workup 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 multidisciplinary 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 workup 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) 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 centres 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 standardised 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 (eg, 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

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	eg, *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.

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 harbour a de novo heterozygous missense mutations in the *STING1* gene that confers a gain-of-function by increasing TANK-binding kinase 1-mediated IRF3 phosphorylation 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 signalling cause AGS.[34] These include biallelic null mutations in *TREX1* and *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 type I IFN signalling.[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 note 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 workup, a molecular diagnosis is not established in a patient with suggestive phenotypic features, referral to a research centre of excellence for further evaluation should be considered.

Clinical evaluation

In patients with undifferentiated autoinflammatory diseases or otherwise unexplained systemic inflammation, certain clinical features are suggestive of CANDLE/PRAAS, SAVI or AGS (tables 1 and 3).

The following clinical features are relevant to the workup 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 workup 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 such as pernio ('chilblain lesions') or acral ischaemia presenting as Raynaud's phenomenon, and/or 'purple toes' is suggestive of SAVI[7 44 47] and AGS,[33 52–55] the development of gangrene with prolonged ischaemic attacks is a feature of SAVI[1 7 44] (table 3). 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 patients with AGS.[33 52–55] Moreover, some patients with AGS can have panniculitis as well.[34] Finally, some patients with AGS 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]

Neurological manifestations

Although CANDLE/PRAAS-affected patients present with headaches and may develop aseptic meningitis,[24] neurological 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 workup may include MRI of the brain which identifies best white and grey matter changes.[41] 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 neurological 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

Table 3 Clinical features suggestive of CANDLE/PRAAS, SAVI and AGS

Systemic inflammation	
CANDLE/PRAAS, SAVI, AGS	Clinical features: Recurrent fever, hepatosplenomegaly Laboratory features: Elevated CRP, ESR and IFN signature
Skin manifestations	
CANDLE/PRAAS	Neutrophilic panniculitis, nodular rashes, violaceous annular rashes, lipodystrophy
SAVI	Vasculopathy (ie, chilblain lesions, acral ischaemia ranging from Raynaud's phenomenon to gangrene), loss of digits
AGS	Chilblain lesions, acral lesions (including Raynaud's phenomenon), panniculitis
Neurological manifestations	
CANDLE/PRAAS	Clinical features: Headache, cognitive impairment Lumbar puncture: Sterile pleocytosis Neuroimaging: Basal ganglia calcifications
SAVI	Neuroimaging: Basal ganglia calcifications (rare)
AGS	Clinical features: Subacute or acute onset of neurologic symptoms including developmental delay, irritability, neurological impairment or regression, dystonia and spasticity, focal motor findings, progressive microcephaly, seizures Lumbar puncture: Sterile pleocytosis, elevated CSF neopterin and tetrahydrobiopterin, elevated interferon alpha Neuroimaging: Leukoencephalopathy, cerebral calcifications, early and rapid cerebral atrophy with or without calcification, Moyamoya disease*
Pulmonary manifestations	
CANDLE/PRAAS	Pulmonary hypertension without fibrosis
SAVI	Interstitial lung disease with or without secondary pulmonary hypertension
AGS	Pulmonary hypertension
Hepatic manifestations	
CANDLE/PRAAS	Elevated transaminases, hepatic steatosis
AGS	Elevated transaminases, autoimmune hepatitis
Metabolic and endocrine manifestations	
CANDLE/PRAAS	Hypertension, hyperlipidaemia, glucose intolerance (=metabolic syndrome)
AGS	Hypothyroidism, diabetes insipidus, diabetes
Musculoskeletal manifestations	
CANDLE/PRAAS, SAVI, AGS	Myositis
CANDLE/PRAAS, SAVI, AGS	Arthritis, joint contractures
Growth and development	
CANDLE/PRAAS, SAVI, AGS	Growth retardation, osteoporosis, bone development delay, pubertal delay
Haematological manifestations	
CANDLE/PRAAS, SAVI, AGS	Anaemia, leucopenia, lymphopenia and/or thrombocytopenia
Ophthalmologic manifestations	
CANDLE/PRAAS	Episcleritis and keratitis
SAVI, AGS	Retinopathy, glaucoma
Cardiac manifestations	
AGS	Cardiomyopathy, valve calcifications

*Vasculopathy characterised by progressive narrowing of the terminal intracranial portion of the internal carotid artery and circle of Willis.
AGS, Aicardi-Goutières syndrome; CANDLE/PRAAS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndrome; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; IFN, interferon; SAVI, STING-associated vasculopathy with onset in Infancy.

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 grey 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 workup 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 characterise the immunological features of the central nervous system (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 haemorrhage 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 undercharacterised. 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 per cent of patients with CANDLE/PRAAS 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 hyperlipidaemia at baseline pointing to the role of proteasome dysfunction in the aetiology 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] Patients can develop autoimmune hepatitis, the presence of liver-specific antibodies has been described.[34 62 80]

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 necrotising granulomatous hepatitis, cholestatic hepatitis and cholangitis and multiple biliary cysts are presented.[58 81]

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: hypertriglyceridaemia ≥110 mg/dL, low high-density lipoprotein cholesterol ≤40 mg/dL, abdominal obesity with waist circumference ≥90th percentile (sex specific), hyperglycaemia ≥110 mg/dL, systolic or diastolic blood pressure ≥90th percentile (age, height, sex specific)).[82] In addition, these patients can have increased abdominal girth secondary to intra-abdominal fat deposition.[1 51] The workup 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 83–85] Other endocrine manifestations include central diabetes insipidus, growth hormone deficiency and adrenal insufficiency.[34 83]

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 patients with CANDLE/PRAAS 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.[86] In AGS-affected patients, joint involvement can include a lupus-like arthritis, or progressive arthropathy with joint contractures.[50 87 88] 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) was not common in patients with SAVI but systematic testing has not been performed. Interestingly, the course of the arthritis in SAVI can be destructive, especially in childhood, when associated with RF and anti-CCP antibodies.[7 43]

Growth and development

Many children with chronic inflammation, including patients with type I interferonopathies, have lengths/heights and bone mineral density (BMD) 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 subacute onset most individuals develop profound neurological 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]

Haematological 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 patients with CANDLE/PRAAS and AGS but are also seen in patients with SAVI.[1 8 18 33 50 52 54 60 79 83 89] Thrombocytopenia in patients with AGS can be present during the neonatal period mimicking congenital infection, but also later during the course of the disease associated with other haematological abnormalities such as anaemia and leucopenia.[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.

Ophthalmological manifestations

Patients with type I interferonopathies can develop different types of ophthalmological 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] Glaucoma has been reported in 6.3% of patients with AGS (up to 20.8% of patients with *SAMHD1* mutations), with most cases presenting in the first 6 months of life, in patients who were not receiving glucocorticoids.[34 76] Retinopathy has been described in AGS and SAVI but it remains unclear whether this occurs in the context of secondary mutations.[90]

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*.[91]

Other considerations

Immunodeficiency workup

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.[92] Early manifestations may overlap with non-type I interferonopathy immunodeficiencies. Therefore, a basic immunologic workup should be considered even in the context of a confirmed diagnosis. The workup should include a history of infections and assessment of lymphocyte subsets and immunoglobulin levels, as a minimum.[1 12 93]

Infections in patients with CANDLE/PRAAS can be associated with the development of macrophage activation syndrome (MAS). Opportunistic infections in patients with other CANDLE/PRAAS mutations or SAVI and AGS are rare, although pneumocystis infection has been reported in a patient with SAVI who was not on any immunosuppressive treatment.[89] Furthermore, defects in maturation of CD8+ cells are identified in patients with CANDLE/PRAAS,[2 94] and in some patients with SAVI.[8 57 89] Severe infections are reported in two patients with *POMP* mutations,[94] which may be modified by additional genetic variants.

Points to consider 9–12: treatment focus on optimising 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.

Pharmacological treatment with Janus kinase inhibitors (JAKIs), particularly baricitinib, is widely used to treat patients with type I interferonopathies.[1 95–98] The JAKIs 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 95] In the study by Sanchez *et al*, none of the patients had achieved remission before initiating baricitinib treatment, and 50% of patients with CANDLE/PRAAS achieved lasting remission with no clinical symptoms, normalisation of inflammatory markers on baricitinib, all discontinued glucocorticoids. In addition, patients with CANDLE/PRAAS had improvement in myositis and cytopenias (haemoglobin, lymphocyte and platelets). Moreover, significant clinical improvement, including fewer vasculitis flares, prevention of skin involvement/progression of spontaneous amputations/the development of gangrene, and stabilisation of ILD by preserving pulmonary function, was achieved in patients with SAVI.[1] However, to date, no patient with SAVI treated with JAKI achieved complete remission. Furthermore, JAKIs reduce IFN-α-mediated STAT-1 phosphorylation in a dose-dependent manner in patients with interferonopathy,[26 56] thus demonstrating an in vivo effect of the JAKI on type I IFN signalling. The JAKIs, ruxolitinib and tofacitinib, are also reported as potential treatment options.[44 56 59 98] Population pharmacokinetics and pharmacodynamic analyses in children treated with baricitinib showed a substantially shorter half-life in paediatric than in adult populations requiring more frequent dosing, and led to a proposed weight-based and estimated glomerular filtration rate-based dosing regimen to guide dose adjustments in the growing child.[26] Doses of JAKI used to treat these conditions that were published are summarised in online supplemental table 4. A beneficial effect of JAKI on inflammatory disease manifestations is also observed in patients with AGS, including in an open-label trial. The treatment led to a decrease in interferon signalling genes 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.[95–97] In all instances, pre-existing organ damage is irreparable (ie, the neurological 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[99] and thus it is unclear if these drugs can be recommended.

Viral reactivation including BK viral reactivation has 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.[100 101] 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 data from an open-label trial indicated that patients with AGS who are receiving baricitinib should be monitored closely for thrombocytosis, leucopenia and infection, especially those with underlying thrombotic risk factors or those who are receiving systemic glucocorticoids or immunosuppressive regimens,[95] while no such events were reported in two other reports.[96 97]

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.[102] 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-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, minimising 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, haematologist, 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, orthopaedic 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/PRAAS.[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 4 provides general and disease-specific guidance for the monitoring of disease activity and assessment of organ damage. The monitoring should include (1) assessment of the level of systemic inflammation, and of growth and sexual development, (2) the assessment of general and disease-specific clinical signs and symptoms including the use of validated instruments when available,[1 22 23] (3) monitoring of disease-specific organ manifestations and (4) monitoring of the development of autoimmune features (see online supplemental table 5 for autoantibody associations with organ-specific autoimmune manifestations in CANDLE/PRAAS, SAVI and AGS), cytopenias, treatment-related complications and infections (immunodeficiencies). Preliminary guidance regarding the monitoring of JAKI treatment (tables 3 and 4) is provided but may need to be adjusted as experience with treatment of interferonopathies grows.

All patients should be evaluated at each visit for the presence of disease-specific symptoms and presence of systemic inflammation (table 4).

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

Table 4 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, tachypnoea, 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 until 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 (dyslipidaemia), fasting glucose, Haemoglobin 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	At baseline and then as needed
	PFTs	Every 3–6 months As needed
AGS		
Neurological 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 At baseline and then as needed Yearly 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, immuno-deficiency and JAK inhibitor-related complications		
Autoimmunity and cytopenias and immunodeficiency	Screening for autoimmunity (autoantibodies as indicated), CBC with differential (screening for anaemia, thrombocytopenia, leukopenias) History of infections, lymphocyte subsets, immunoglobulin levels.	Every 6–12 months and when indicated
	Consider immunology or haematology referral	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, creatine kinase; CRP, C-reactive protein; 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 normalised ratio; JAK, Janus kinase; LDH, lactate dehydrogenase; LFTs, liver function tests; MRA, magnetic resonance angiography; PAH, pulmonary arterial hypertension; PFTs, pulmonary function tests; SAVI, STING-associated vasculopathy with onset in infancy; TSH, thyroid-stimulating hormone.

Patients with CANDLE/PRAAS should also be monitored for headaches, skin and musculoskeletal disease, development of metabolic syndrome (hypertension, hyperglycaemic 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 ischaemic digits (eg, with, but not limited to, intravenous fluids, pentoxyphylline or intravenous vasodilators), prompt use of antibiotics if infection is suspected, and meticulous wound care.[1 8 103]

Patients with AGS are monitored for progression of neurological 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 (eg, 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 83] and autoimmune endocrinopathies, most frequently hypothyroidism.[34] Other manifestations that can develop insidiously include glaucoma and epilepsy, and should be monitored as clinically indicated.[76 104] Neurological 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 programmes, and appropriate positioning of children with tone abnormalities.

The heightened type I interferon-mediated autoimmune response contributes to the development of autoantibodies and autoimmune diseases[105] (see online supplemental table 5). Antinuclear antibodies (ANA) are seen in up to 62.5% of patients with SAVI,[8] in up to 42% of patients with CANDLE/PRAAS[1 2 5 9 18 39 51 93] and 23% of patients with AGS.[62] Moreover, antiphospholipid antibodies are present in patients with CANDLE/PRAAS, SAVI and AGS.[1 7 62] Antineutrophil cytoplasmic antibodies (ANCA) are, intermittently, elevated in up to 71% of patients with SAVI and 18% of patients with AGS[8 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.[8 106 107] Antibodies associated with specific autoimmune diseases including autoimmune arthritis, pauci-immune glomerulonephritis, autoimmune cytopenias, thyroiditis and/or hepatitis have been described in CANDLE/PRAAS, SAVI or AGS with variable frequencies (online supplemental table 5). As it remains difficult to diagnose these diseases based on clinical symptoms, regular screening for autoantibodies as outlined in table 4 is currently recommended. 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 (eg, orthoses, walkers, wheelchairs, seating equipment), may be required.

Treatment during infections including COVID-19

Disease flares and progression can occur if immunosuppressive treatment is held[108] 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 paediatric 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.[109]

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 the 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.[110] Treatment discontinuation can result in withdrawal flares. In general, we suggest following recommendations for other autoimmune and inflammatory rheumatic diseases,[110 111] we however currently do not advise treatment adjustments for treatments recommended for the type I interferonopathies including JAKI.

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 characterised 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 box 1. The cost and availability of genetic testing, interferon signature assays and JAKI treatment are substantial barriers that currently prevent optimised care for patients with interferonopathies. Furthermore, patients with the autoinflammatory interferonopathies CANDLE/PRAAS, SAVI and AGS live in many different

Box 1 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 sensitive biomarkers of progression of organ disease (including central nervous system).
- 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 viraemia.
- 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 (eg, 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.

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 standardise the level of care by characterising the diagnostic and therapeutic tools that can improve care.

Author affiliations
[1]Translational Autoinflammatory Diseases Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA
[2]Department of Pediatrics, University Hospital Centre Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia
[3]Division of Paediatric Rheumatology, Department of Paediatrics, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada
[4]Department of Epidemiology and Biostatistics, Schulich School of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada
[5]London Health Sciences Center, Lawson Health Research Institute, London, Ontario, Canada
[6]UOC Pediatria a Media Intensità di Cura, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Lombardia, Italy
[7]Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
[8]Pediatric Neuroimmunology Unit, Neurology Service, Sant Joan de Deu Children's Hospital, and IDIBAPS-Hospital Clinic, University of Barcelona, Barcelona, Spain
[9]Autoinflammatory Alliance, San Francisco, California, USA
[10]Aicardi-Goutieres Syndrome Americas Association, Manhattan Beach, California, USA
[11]Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Molecular Medicine, University of Edinburg, Edinburg, UK
[12]Laboratory of Neurogenetics and Neuroinflammation, Institut Imagine, Université de Paris, Paris, Île-de-France, France
[13]Kids Neuroscience Centre, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia
[14]Kaiser San Francisco Hospital, San Francisco, California, USA
[15]Great Ormond Street Institute of Child Health, University College London, London, UK
[16]Child Neurology and Psychiatry Unit, Department of Clinical and Experimental Sciences ASST Civil Hospital, University of Brescia, Brescia, Italy
[17]Center for Autoinflammatory diseases and Immunodeficiencies, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[18]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy
[19]Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, Indiana, USA
[20]Department of Pediatrics, Medical Faculty Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[21]Intramural Clinical Management and Operations Branch (ICMOB), Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA
[22]Necker Children's Hospital, Assistance Publique-Hôpitaux de Paris, Université de Paris, Institut Imagine Institut des Maladies Genetiques, Paris, Île-de-France, France
[23]Child Neurology and Psychiatry Unit, IRCCS Mondino Foundation, Pavia, Italy, Italy
[24]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Lombardia, Italy
[25]Pediatric Rheumatology, Hacettepe University, Ankara, Turkey
[26]Department of Pediatrics, Facultad de Medicina Clinica Alemana Universidad del Desarrollo, Santiago, Chile
[27]Child Neurology Unit, COALA (Center for Diagnosis and Treatment of Leukodystrophies), V. Buzzi Children's Hospital, Milano, Italy
[28]Department of Rheumatology, Medical University of Vienna, Vienna, Austria
[29]Division of Rheumatology, Hospital for Sick Children, Toronto, Ontario, Canada
[30]Department of Pediatrics, Faculty of Medicine, University of Toronto Institute of Health Policy Management and Evaluation, Toronto, Ontario, Canada
[31]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

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Twitter Seza Ozen @drsezaozen

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ORCID iDs
Marco Gattorno http://orcid.org/0000-0003-0704-1916
Seza Ozen http://orcid.org/0000-0003-2883-7868
Daniel Aletaha http://orcid.org/0000-0003-2108-0030
Brian M Feldman http://orcid.org/0000-0002-7813-9665
Paul A Brogan http://orcid.org/0000-0001-6178-6893
Raphaela Goldbach-Mansky http://orcid.org/0000-0001-7865-5769

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CONTENTS

I. Supplementary Methods

1. Task force meetings proceedings:

Per European Alliance of Rheumatology Associations (EULAR) and American College of Rheumatology (ACR) standard operating procedures (SOPs) the following steps were followed.

- August 2019 (NIH Bethesda): A face-to-face meeting was convened to define the focus of the task force and identify the target population.
- A EULAR task force was established and consisted of: nine pediatric rheumatologists (including one delegate of the EULAR young rheumatologists' network EMEUNET), seven neurologists, a neurologist and geneticist (double board certified), two geneticists, an immunologist, a health care professional, three fellows, three patient representatives (one for each disease) from the autoinflammatory alliance (n=2) and the Aicardi Goutières Syndrome Americas Association (AGSAA) (n=1) and three methodologists .
- Systematic literature review (SLR): A systemic literature review was conducted by three research fellows (KCG, MR, LL), with support from a librarian and epidemiologist (DH and DP), and a senior methodologist (ED) to identify relevant literature published before September 2020. The search was performed using PubMed, Embase and the Cochrane Library up to and including August 2020. Overall, 2961 references pertaining to the 3 diseases were identified, 71 of which were finally included (or for SAVI, 13/875 references, for CANDLE/PRAAS 12/801 references and for AGS 55/1297).
- Based on the SLR results, statements were drafted by the expert group. Two rounds of pre-consensus meeting Delphi questionnaires were sent using REDCap (https://projectredcap.org/software/), a secure Web-based system with the technical help of the University of Toronto. The purpose was to develop draft statements regarding the diagnosis, treatment, and long-term management of CANDLE/PRAAS, SAVI and AGS that

were circulated to be considered as potential points to consider. The task force members were asked to indicate their agreement with each statement (in the first round) and with draft statements that were circulated in the second survey with yes/no and, were given a free text option and suggestions to capture all relevant items. Responses were anonymous. Draft statements with 80% or higher agreement were retained for voting at the consensus meeting, and draft statements, that did not achieve 80% agreement, were marked for further discussion and refinement at the two consensus meetings.

- Delphi questionnaires: The Delphi technique, which uses a series of well-defined mail questionnaires, with the first one laid out broadly to avoid any biases, and the subsequent ones based on the results of the prior ones, was used to generate draft statements. Two surveys have been conducted through RedCap, a secure Web-based system, with the technical help of the University of Toronto. The first semi-structured, anonymous Delphi questionnaire was sent to 28 Task Force members, 22 were also voting members, (KU was a voting member but was not sent the questionnaire). The task force was asked to indicate "yes/no" to proposed questions and members were also given a free text option and asked to provide comments to existing questions and to add additional questions that they considered important to be addressed. If a statement reached ≥80% agreement in the first Delphi survey, the statement was included for discussion to the consensus meetings. The second Delphi questionnaire/survey was sent to the same 28 Task Force members who participated in the first Delphi survey. Similarly, participants were asked to indicate their agreement by answering "yes or no" to questions and were given to possibility to add comments in a free text option. After the second Delphi questionnaire, draft statements for all questions that had achieved a higher than 80% agreement were generated by the steering committee members.

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Draft statements were also written for questions that had achieved between 20% to 80% agreement. All draft statements were distributed to the Task Force members prior to the consensus meeting. The lower percentage of consensus/agreement was indicated for draft statements that achieved less than 80% agreement. The draft statements with >80% agreement were discussed and voted on first at the consensus meetings, and those with a lower level of agreement were discussed next and generated longer discussions, more refinements and some draft statements ended up being ultimately excluded.

- Most Task Force members responded to the Delphi surveys within one week. Those who had not responded were sent daily reminders individually. For both rounds of Delphi questionnaires, a 100% response rate was achieved. The questionnaire data and the results from the SLR were used to generate draft statements that were discussed in two consensus meetings.
- Due to the coronavirus pandemic 2019 (COVID-19) travel restrictions prohibited face-to-face meetings. The two consensus meetings were thus held virtually online. One consensus meeting included voting members with expertise in CANDLE and SAVI and was held on October 8, 2020, and one with members with expertise in AGS on October 19, 2020.
    - The SLR results were presented by the fellows for each disease and discussed during the consensus meetings.
    - The draft statements that were distributed to the task force members prior to each consensus meeting were discussed, refined, and voted on.
    - Overarching statements and statements pertaining to both groups were voted on in both consensus meetings while statements pertaining to only CANDLE or SAVI and AGS were voted on in the respective meetings only.

  - Statements with between 20% and 80% agreement were chosen for ongoing discussion and possible major revision during the second part of the consensus meeting, while the rest (<20% agreement) were dropped and were not included as points to consider statements. A methodologist (BMF) trained in nominal group technique, and a EULAR methodologist (ED) led the voting members attending the virtual consensus meeting through the consensus process. The voting members included, the two conveners (RGM, PB), 1 allied health professional (KU) and 3 experts (MLK, BN, DE) attended both meetings, and the rest of the expert panel (CP, SO[1], GAMS, EPH, TA, LAA, AV, MG, RCD, YJC, DT, FG, SO[2], EF) and patient advocates (DRC, KB, ES) attended one meeting based on their disease specific experience/expertise.
  - The voting panel consisted of 23 people (19 experts, one allied health professional and three patient representatives [one for each disease]). During the consensus meetings, the joint statements were voted on by all members of the voting panel. However, CANDLE/SAVI specific statements were voted on by ten experts, one allied health professional, one SAVI and one CANDLE patient representative. The AGS specific statements were voted on by 14 experts, one allied health professional and one AGS patient representative.
- Reaching consensus: All statements included in the tables that reached the minimum 80% consensus were retained in the final formulation of the recommendations. If one of the sub-statements did not reach that threshold in the pre-consensus Delphi or at the consensus meetings, it was discussed and reworded or modified with the aim of achieving a secondary 80% consensus. If the 80% level was not achieved in any way, the statement was eliminated.

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Eliminated statements were listed in the procedural materials that are available upon request. The proportion of agreement (80-100%) among the task force at the end of the second conference was recorded.

- A post-consensus meeting questionnaire with the finalized statements was distributed among all voting members of both consensus meetings and a level of agreement was obtained based on marking on a scale from 0 to 10, with 0 indicating no agreement and 10 indicating full agreement. Using those data, the mean and standard deviation (SD) of level of agreement for each statement was calculated.
- The manuscript was reviewed and approved by all task force members and the EULAR executive committee before submission.

2. Search Terms

a) ***Search Terms for SAVI***

(((((SAVI syndrome) OR STING associated vasculopathy) OR stimulator of IFN genes-associated vasculopathy) OR severe pulmonary fibrosis [Title/Abstract]) OR TMEM173[Title/Abstract])

b) ***Search Terms for CANDLE/PRAAS***

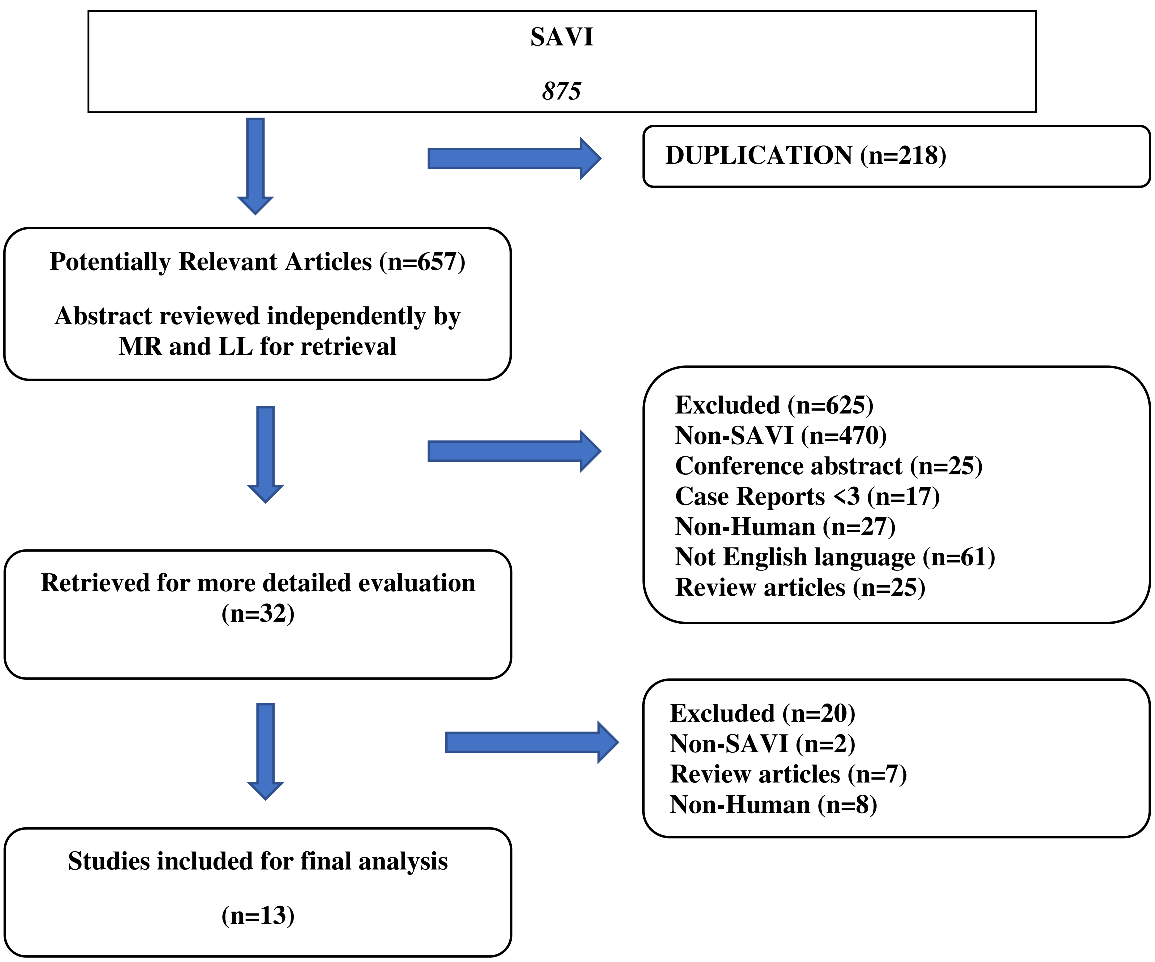
((((((((CANDLE syndrome) OR (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature)) OR proteasome associated autoinflammatory syndrome) OR PRAAS) OR CANDLE/PRAAS) OR PSMB8 gene) OR (Joint contractures Muscular atrophy microcytic anemia and Panniculitis Associated lipodystrophy)) OR Nakajo-Nishimura syndrome) OR Japanese autoinflammatory syndrome [Title/Abstract])

c) ***Search Terms for AGS***

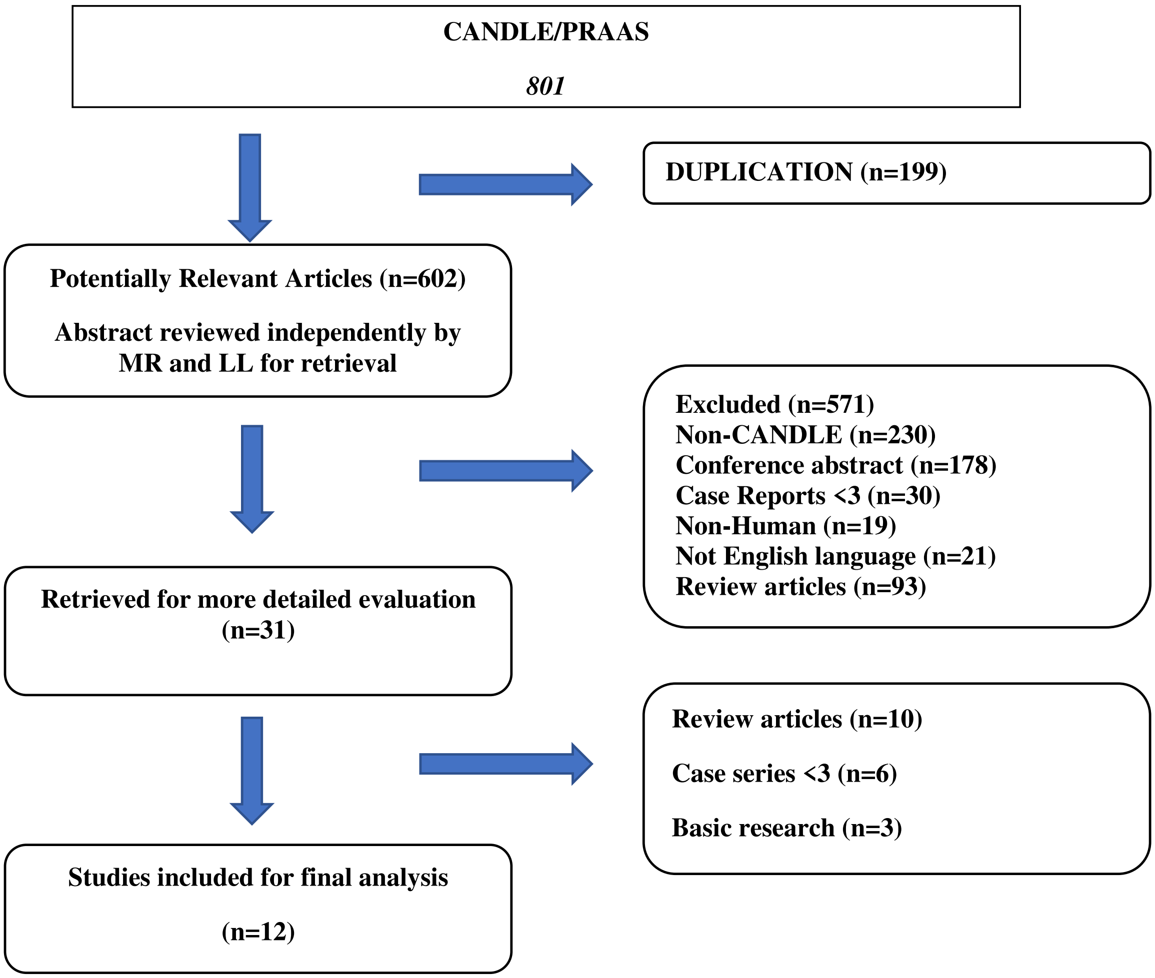
(Familial Infantile Encephalopathy with Intracranial Calcification and Chronic Cerebrospinal Fluid Lymphocytosis OR Cree Encephalitis OR Encephalopathy with Basal Ganglia Calcification OR Aicardi Goutières syndrome OR Pseudotoxoplasmosis syndrome OR Pseudo-TORCH syndrome OR Aicardi-Goutières Syndrome 1 OR Aicardi-Goutières Syndrome 2 [Title/Abstract])

3. Flowcharts

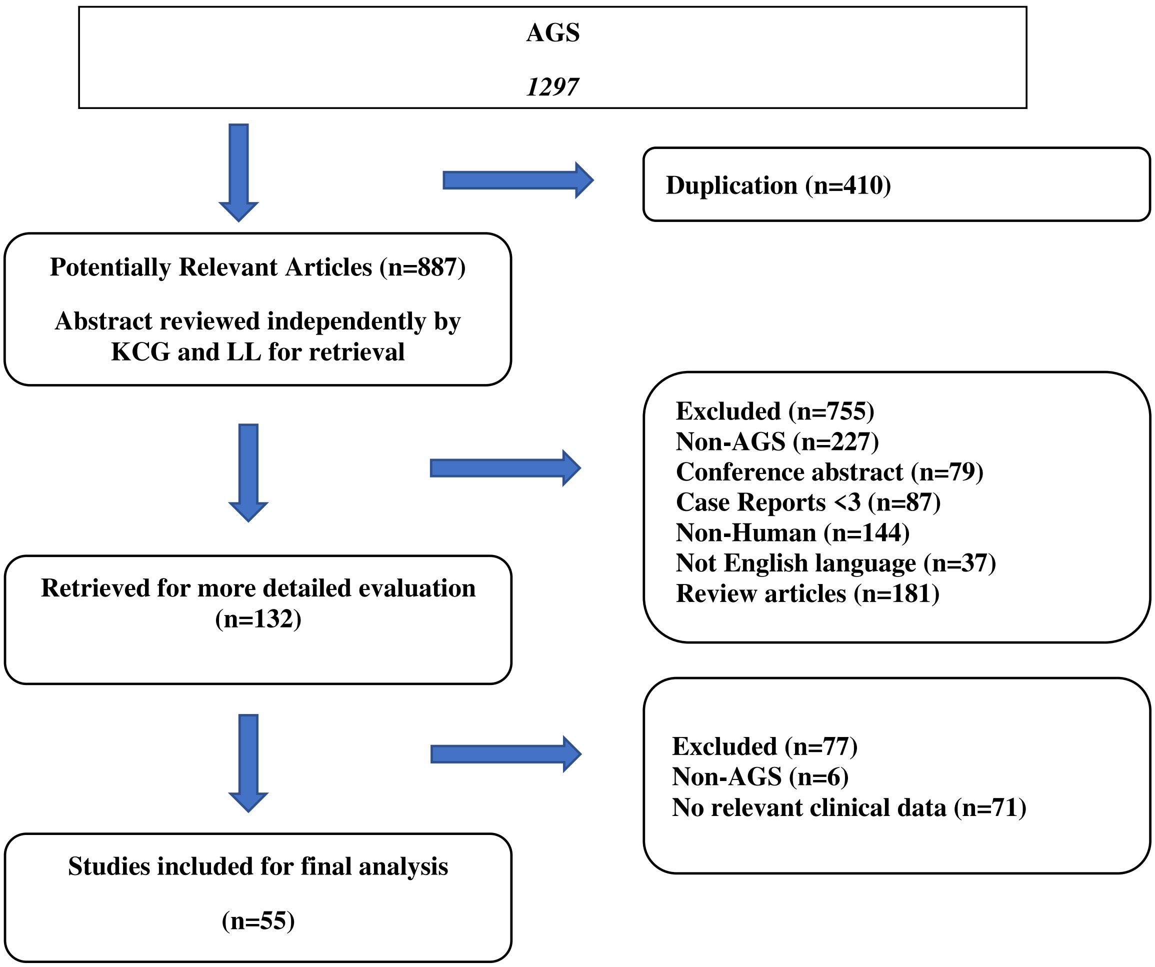
a. ***Flowchart for SAVI***



b) ***Flowchart for CANDLE/PRAAS***



c) *Flowchart for AGS*



II. Supplementary Tables

Supplementary table 1. Included articles for SAVI for final analysis

1	**Frémond ML et al**. Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with *TMEM17*3-activating mutations in 3 children. ***J Allergy Clin Immunol. 2016.***
2	**Jeremiah N et al.** Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. ***J Clin Invest, 2014.***
3 A	**Kim H et al.** Pharmacokinetics, Pharmacodynamics, and Proposed Dosing of the Oral JAK1 and JAK2 Inhibitor Baricitinib in Pediatric and Young Adult CANDLE and SAVI Patients. ***Clin Pharmacol Ther, 2018.***
3 B	**Sanchez GA et al.** JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. ***J Clin Invest, 2018.***
4	**Liu Y et al.** Activated STING in a vascular and pulmonary syndrome. ***N Engl J Med, 2014.***
5	**Melki I et al.** Disease-associated mutations identify a novel region in human STING necessary for the control of type I interferon signaling. ***J Allergy Clin Immunol, 2017.***
6	**Picard C et al.** Severe Pulmonary Fibrosis as the First Manifestation of Interferonopathy (*TMEM173* Mutation). ***Chest, 2016.***
7	**Volpi S et al.** Efficacy and Adverse Events During Janus Kinase Inhibitor Treatment of SAVI Syndrome. ***J Clin Immunol, 2019.***
8	**Konig N et al.** Familial chilblain lupus due to a gain-of-function mutation in STING. ***Ann Rheum Dis, 2018.***
9	**Tang Xiaolei, et al.** "STING-Associated Vasculopathy with Onset in Infancy in Three Children with New Clinical Aspect and Unsatisfactory Therapeutic Responses to Tofacitinib." **Journal of Clinical Immunology (2019): 1-9**
10	**Clarke S. L. N., et al.** "Type 1 interferonopathy presenting as juvenile idiopathic arthritis with interstitial lung disease: report of a new phenotype." **Pediatric Rheumatology 18 (2020): 1-5.**
11	**Keskitalo Salla, et al.** "Novel *TMEM173* mutation and the role of disease modifying alleles." ***Frontiers in immunology*** **10 (2019): 2770.**
12	**Lin Bin, et al.** "A novel *STING1* variant causes a recessive form of STING-associated vasculopathy with onset in infancy (SAVI)." ***Journal of Allergy and Clinical Immunology*** **(2020).**

SAVI, STING-associated vasculopathy with onset in infancy.

Supplementary table 2. Included articles for CANDLE/PRAAS for final analysis

1 A	**Argarwal AK et al.** *PSMB8* encoding the beta5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. ***Am J Hum Genet, 2010.***
1 B	**Garg A et al.** An autosomal recessive syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy. ***JCEM, 2010.***
2	**Al-Mayouf SM et al.** Monogenic interferonopathies: Phenotypic and genotypic findings of CANDLE syndrome and its overlap with C1q deficient SLE. ***International Journal of Rheumatic Diseases, 2018.***
3	**Arima K et al.** Proteasome assembly defect due to a proteasome subunit beta type 8 (*PSMB8*) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome. ***Proc Natl Acad Sci U S A, 2011.***
4	**Brehm A et al.** Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. ***J Clin Invest, 2015.***
5 A	**Kim H et al.** Pharmacokinetics, Pharmacodynamics, and Proposed Dosing of the Oral JAK1 and JAK2 Inhibitor Baricitinib in Pediatric and Young Adult CANDLE and SAVI Patients. ***Clin Pharmacol Ther, 2018.***
5 B	**Sanchez GA et al.** JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. ***J Clin Invest, 2018.***
6	**Kitamura A et al.** A mutation in the immunoproteasome subunit *PSMB8* causes autoinflammation and lipodystrophy in humans. ***J Clin Invest, 2011.***
7	**Liu Y et al.** Mutations in proteasome subunit beta type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. ***Arthritis Rheum, 2012.***
8	**Torrelo A et al.** Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. ***J Am Acad Dermatol, 2010.***
9	**de Jesus Adriana A., et al.** "Distinct interferon signatures and cytokine patterns define additional systemic autoinflammatory diseases." ***The Journal of Clinical Investigation*** **130.4 (2020).**
10	**Ayaki Takashi, et al.** "Myositis with sarcoplasmic inclusions in Nakajo–Nishimura syndrome: a genetic inflammatory myopathy." ***Neuropathology and Applied Neurobiology*** **(2020).**

CANDLE/PRAAS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/ proteasome-associated autoinflammatory syndrome.

Supplementary table 3. Included articles for AGS for final analysis

1	**Adang LA, et al.** Developmental Outcomes of Aicardi Goutières Syndrome. ***Journal of Child Neurology, 2020.***
2	**Adang LA, et al.** Development of a neurologic severity scale for Aicardi Goutières Syndrome. ***Mol Genet Metab, 2020.***
3	**de Jesus AA et al.** Distinct interferon signatures and cytokine patterns define additional systemic autoinflammatory diseases. ***The Journal of Clinical Investigation, 2020.***
4	**Lhamtsho D et al.** Novel RNASEH2C mutation in multiple members of a large family: insights into phenotypic spectrum of Aicardi-Goutières Syndrome. ***BMJ Neurology Open, 2020.***
5	**Rice GI et al.** Genetic and phenotypic spectrum associated with *IFIH1* gain-of-function. ***Hum Mutat. 2020.***
6	**Vanderver A, et al.** Janus Kinase Inhibition in the Aicardi-Goutières Syndrome. ***N Engl J Med, 2020.***
7	**Videira G et al.** Diagnosis of Aicardi-Goutières syndrome in adults: a case series. ***Movement Disorders Clinical Practice, 2020.***
8	**Garau J et al.** Molecular Genetics and Interferon Signature in the Italian Aicardi Goutières Syndrome Cohort: Report of 12 New Cases and Literature Review. ***J Clin Med, 2019.***
9	**Moreno Medinilla EE et al.** Aicardi-Goutières syndrome: Phenotypic and genetic spectrum in a series of three cases. ***An Pediatr (Barc), 2019.***
10	**Meesilpavikkai K et al**. Efficacy of Baricitinib in the Treatment of Chilblains Associated with Aicardi-Goutières Syndrome, a Type I Interferonopathy. ***Arthritis & rheumatology, 2019.***
11	**Samanta D et al.** Multiple Autoimmune Disorders in Aicardi-Goutières Syndrome. ***Pediatric neurology, 2019.***
12	**Tonduti D et al.** Spontaneous MRI improvement and absence of cerebral calcification in Aicardi-Goutières syndrome: Diagnostic and disease-monitoring implications. ***Molecular Genetics and Metabolism, 2019.***
13	**Zimmermann N et al.** Assessment of Clinical Response to Janus Kinase Inhibition in Patients with Familial Chilblain Lupus and *TREX1* Mutation. ***JAMA Dermatol, 2019.***
14	**Adang LA et al.** Aicardi Goutières syndrome is associated with pulmonary hypertension. ***Molecular Genetics and Metabolism, 2018.***
15	**Al Mutairi F et al.** Phenotypic and Molecular Spectrum of Aicardi-Goutières Syndrome: A Study of 24 Patients. ***Pediatric Neurology, 2018.***
16	**Hebbar M et al.** p.Arg69Trp in *RNASEH2C* is a founder variant in three Indian families with Aicardi–Goutières syndrome. ***American Journal of Medical Genetics, 2018.***
17	**Rice GI et al.** Reverse-Transcriptase Inhibitors in the Aicardi–Goutières Syndrome. ***NEJM, 2018.***
18	**Armangue T et al.** Neonatal detection of Aicardi Goutières Syndrome by increased C26:0 lysophosphatidylcholine and interferon signature on newborn screening blood spots. ***Mol Genet Metab, 2017.***
19	**Rice GI, et al.** Genetic, Phenotypic, and Interferon Biomarker Status in ADAR1-Related Neurological Disease. ***Neuropediatrics, 2017.***

20	**Wang BX et al.** Interferon-Stimulated Gene Expression as a Preferred Biomarker for Disease Activity in Aicardi–Goutières Syndrome. ***Interferon & Cytokine Research, 2017.***
21	**Cattalini M et al.** Exploring Autoimmunity in a Cohort of Children with Genetically Confirmed Aicardi–Goutières Syndrome. ***J Clin Immunol, 2016.***
22	**La Piana R et al.** Neuroradiologic patterns and novel imaging findings in Aicardi-Goutières syndrome. ***Neurology, 2016***
23	**Stellitano LA et al.** Leukodystrophies and genetic leukoencephalopathies in childhood: a national epidemiological study. ***Neurology, 2016.***
24	**Yarbrough K et al.** The Importance of Chilblains as a Diagnostic Clue for Mild Aicardi–Goutieres Syndrome. ***American Journal of Medical Genetics, 2016.***
25	**Bursztejn AC et al.** Unusual cutaneous features associated with a heterozygous gain-of-function mutation in *IFIH1*: overlap between Aicardi– Goutières and Singleton–Merten syndromes. ***Br J Dermatol, 2015.***
26	**Crow YJ et al.** Characterization of Human Disease Phenotypes Associated with Mutations in *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR*, and *IFIH1*. ***American Journal of Medical Genetics, 2015.***
27	**Uyur-Yalçın E et al.** Clinical and neuroradiologic variability of Aicardi-Goutiéres syndrome: Two siblings with *RNASEH2C* mutation and a boy with *TREX1* mutation. ***The Turkish Journal of Pediatrics, 2015.***
28	**Vanderver A et al.** Early onset Aicardi Goutières syndrome: MRI pattern Recognition. ***J Child Neurol, 2015.***
29	**Abe J et al.** A nationwide survey of Aicardi-Goutières syndrome patients identifies a strong association between dominant *TREX1* mutations and chilblain lesions: Japanese cohort study. ***Rheumatology, 2014.***
30	**Crow YJ et al**. Mutations in *ADAR1, IFIH1*, and *RNASEH2B* Presenting as Spastic Paraplegia. ***Neuropediatrics, 2014.***
31	**Livingston JH, et al.** A type I interferon signature identifies bilateral striatal necrosis due to mutations in *ADAR1*. ***J Med Genet, 2014.***
32	**Oda H, et al.** Aicardi-Goutières syndrome is caused by *IFIH1* mutations. ***Am J Hum Genet, 2014***.
33	**Ramantani G et al.** Epilepsy in Aicardi Goutières syndrome. ***European Journal of Pediatric Neurology, 2014.***
34	**Rice GI, et al.** Gain-of-function mutations in *IFIH1* cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. ***Nat Genet, 2014.***
35	**Abe J et al.** Heterozygous *TREX1* p.Asp18Asn mutation can cause variable neurological symptoms in a family with Aicardi-Goutières syndrome/familial chilblain lupus. ***Rheumatology, 2013.***
36	**Livingston JH et al.** Recognizable phenotypes associated with intracranial calcification. ***Developmental Medicine & Child Neurology, 2013.***

37	**Izzotti A et al.** Different Mutations in Three Prime Repair Exonuclease 1 and Ribonuclease H2 Genes Affect Clinical Features in Aicardi-Goutières Syndrome. J ***Child Neurol, 2012.***
38	**Ostergaard E et al.** A novel RNASEH2B splice site mutation responsible for Aicardi–Goutières syndrome in the Faroe Islands. ***Acta Pædiatrica, 2012.***
39	**Rossler L et al.** Aicardi-Goutières syndrome with emphasis on sonographic features in infancy. ***Pediatric Radiology, 2012.***
40	**Xin B et al.** Homozygous mutation in *SAMHD1* gene causes cerebral vasculopathy and early onset stroke. ***Proc Natl Acad Sci U S A, 2011.***
41	**Ramesh VA et al.** Intracerebral large artery disease in Aicardi–Goutières syndrome implicates *SAMHD1* in vascular homeostasis. ***Developmental Medicine & Child Neurology, 2010.***
42	**Ramantani G el al.** Expanding the Phenotypic Spectrum of Lupus Erythematosus in Aicardi-Goutières Syndrome. ***Arthritis & Rheumatism, 2010.***
43	**Thiele H et al.** Cerebral Arterial Stenoses and Stroke: Novel Features of Aicardi-Goutières Syndrome Caused by the Arg164X Mutation in SAMHD1 Are Associated with Altered Cytokine Expression. ***Human Mutation, 2010.***
44	**Izzotti A et al.** Interferon-Related Transcriptome Alterations in the Cerebrospinal Fluid Cells of Aicardi-Goutières Patients. ***Brain Pathology, 2009.***
45	**Izzotti A et al.** Brain damage as detected by cDNA-microarray in the spinal fluid of patients with Aicardi-Goutières syndrome. ***Neurology, 2009.***
46	**Uggetti C et al.** Aicardi-Goutières Syndrome: Neuroradiologic Findings and Follow-Up. ***American Journal of Neuroradiology, 2009.***
47	**Rice G et al.** Heterozygous mutations in TREX1 cause familial chilblain lupus and dominant Aicardi-Goutières syndrome. ***American Journal of Human Genetics, 2007.***
48	**Rice G et al.** Clinical and Molecular Phenotype of Aicardi-Goutières Syndrome. ***The American Journal of Human Genetics, 2007.***
49	**Lanzi G et al.** The natural history of Aicardi–Goutières syndrome: Follow-up of 11 Italian patients. ***Neurology, 2005.***
50	**Abdel-Salam GMH et al.** Aicardi-Goutières syndrome: clinical and neuroradiological findings of 10 new cases. ***Acta Paediatrica, 2004.***
51	**Crow YJ et al.** Congenital Glaucoma and Brain Stem Atrophy as Features of Aicardi–Goutières Syndrome. ***American Journal of Medical Genetics, 2004.***
52	**Blau N et al.** Cerebrospinal fluid pterins and folates in Aicardi-Goutières syndrome: a new phenotype. ***Neurology, 2003.***
53	**Lanzi G et al.** Aicardi-Goutières Syndrome: a description of 21 new cases and a comparison with the literature. ***European Journal of Pediatric Neurology*, 2002.**
54	**Crow YJ et al.** Aicardi-Goutières Syndrome Displays Genetic Heterogeneity with One Locus (AGS1) on Chromosome 3p21. ***American Journal of Human Genetics, 2000.***

55	**Goutières F et al.** Aicardi-Goutières Syndrome: An Update and Results of Interferon-a Studies. ***Annals of Neurology, 1998.***

AGS, Aicardi-Goutières syndrome.

Supplementary Table 4. Summary of janus kinase inhibitor (JAKI) dosing regimens published in the literature

	Weight class (kg)	**Minimum/maximum doses based on published literature (mg/kg/day)***	**References**
Baricitinib			
CANDLE/PRAAS	10-20	0.3/0.8	Sanchez et al.,[1] Kim et al.,[2] Boyadzhiev et al.[3]
	20-40	0.15/0.4	Sanchez et al.,[1] Kim et al.[2]
	>40	NA/0.25	Sanchez et al.,[1] Kim et al.[2]
SAVI	10-20	0.3/0.8	Kim et al.[2]
	20-40	0.15/0.4	Sanchez et al.,[1] Kim et al.[2]
	>40	NA/0.25	Sanchez et al.,[1] Kim et al.[2]
AGS	4.5-8.5	0.12/0.44, age < 6 months 0.24/0.89, age $\geq$ 6 months	Vanderver et al[4]
	8.5-20	0.3/0.8	Vanderver et al.[4], Kim et al.[2]
	20-40	0.15/0.4	Vanderver et al.[4], Kim et al.[2]
	>40	NA/0.25	Vanderver et al.[4], Kim et al.[2]
Ruxolitinib			
CANDLE/PRAAS	10-20	no data available	NA
	20-40	0.5 /0.75	de Jesus et al.[5]
	>40	no data available	NA
SAVI	10-20	0.5/1	Raffaele et al.[6], Frémond et al.[7]
	20-40	0.25/1.25	Volpi et al.[8], Frémond et al.[7]
	>40	no data available	NA
AGS	10-20	0.2/0.8	Tungler et al.[9], Mura et al.[10]
	20-40	no data available	NA

	>40	no data available	NA
Tofacitinib**		No dosing data per weight were reported	NA

*Dosing regimens proposed here are based on normal renal function. Most of them are based on eGFR calculations using bedside Schwartz formula for children <18 years and Cockcroft-Gault equation for adults (≥18 years)
https://www.kidney.org/professionals/KDOQI/gfr_calculatorPed
https://www.kidney.org/professionals/kdoqi/gfr_calculatorCoc
**Published data for tofacitinib is incomplete. No published dosing data for CANDLE and AGS are available and one paper reports on tofacitinib in two SAVI patients. Both patients (13 months and 64 months) received 2.5 mg BID and both were reported have failure to thrive[11]
AGS, Aicardi-Goutières Syndrome; CANDLE/PRAAS, Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature/Proteasome-Associated Autoinflammatory Syndrome; kg, kilogram; mg, milligram; NA, not available; SAVI, STING-associated vasculopathy with onset in infancy.

The dosing listed in the table is based on published data; the respective articles are listed. Only reports that included the patient's weight and dosing regimen were included. For baricitinib, a formal pharmacokinetic (PK) analysis in patients with CANDLE, SAVI and AGS allowed for estimation of the exposure and PK profile at the doses listed. Dose adjustment for reduced renal function were also provided.[2] None of the treatments are approved by FDA or EMA for the treatment of CANDLE, SAVI or AGS.

The dosing regimens summarized in this supplementary table were reviewed by all members in the task force and reflective current practice by the expert physicians who are treating these patients.

Long-term safety assessments for treatment with JAKIs have not firmly been established. Follow outcomes and safety data have been published for baricitinib.[1 4] For the other janus kinase inhibitors (JAKI) long-term safety data on the doses published and summarized in the table has not been established yet. Until further safety data are available, all the patients should be monitored for BK viral load in urine and blood.

Close safety monitoring is required and includes the following labs in most research studies:

Safety labs every 3 months for JAK inhibitors (see also table 3):

- Complete blood count (CBC) with differential with reticulocyte count
- Renal function (serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR) (bedside Schwartz calculation for patients < 18 years of age), creatinine clearance, standard urinalysis, beta 2 microglobulin
- Liver function tests (alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, gamma glutamyl transferase (GGT))
- BK virus test (blood and urine)
    - Every 3-6 months
    - Additional follow-up is recommended for patients with suspected renal impairment
- Other: Electrolytes and glucose and Chemistry profile (creatinine kinase, uric acid) and Lipid panel (cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides)
- Tuberculosis (purified protein derivative (PPD) skin test or QuantiFERON) test yearly.

Supplementary Table 5. Summary of the autoantibodies and related clinical features of autoimmune disease in CANDLE/PRAAS, SAVI and AGS that has been published in the literature

a. Antibodies that were elevated but not associated with clinical disease in CANDLE/PRAAS, SAVI and AGS	
c-ANCA (low titer) p-ANCA (low titer) dsDNA (low titer)	Transient elevations of dsDNA or c-ANCA or p-ANCA positive antibodies have been reported in patients with SAVI but were not associated with disease severity and patients did not develop immune complex-mediated glomerulonephritis nor vasculitis.[1 12]

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	Anti-dsDNA antibodies have not yet been reported in the context of hypocomplementemia.
ANA (low titer) Anti-phospholipid antibodies (low titer)	Up to 62.5% of patients with SAVI[12], up to 42% of patients with CANDLE/PRAAS[1 13-19] and up to 23% of patients with AGS[20] have positive ANA. Antiphospholipid antibodies are present in patients with CANDLE/PRAAS (up to 43%), SAVI and AGS.[1 20 21]
b. Antibodies that were elevated and associated with autoimmune disease in CANDLE/PRAAS, SAVI and AGS	
RF and anti-CCP	Rheumatoid factor (RF) positivity was reported in 57% of SAVI patients with joint symptoms[12] while anti-cyclic citrullinated peptide (anti-CCP) was present in some patients but systematic testing has not been performed.[21 22]
p-ANCA (high titer)	Necrotizing pauci-immune crescentic glomerulonephritis has recently been described in three patients with confirmed SAVI, in two with measured antibodies with high titer p-ANCA.[23 24]
Coomb's test (antiglobulin test) anti-platelet antibodies	One CANDLE patient with Evans Syndrome[25] and two CANDLE patients with autoimmune hemolytic anemia have been reported.[5 17]
anti-thyroid peroxidase	Hypothyroidism is present in AGS, one study reporting aggregate data describes that as much as 4% of affected patients can infrequently develop antibodies directed against the thyroid gland with (sub)clinical thyroiditis[26]. In SAVI, the positivity of anti-thyroid peroxidase (TPO) antibodies can be associated either with hypo- or hyperthyroidism.[27]
Liver-specific antibodies	Autoimmune hepatitis and the presence of liver-specific antibodies (that can include anti-nuclear, anti F-actin, and anti-smooth muscle antibodies) have been described in AGS.[26 28]

ANA, antinuclear antibodies; AGS, Aicardi-Goutières syndrome; ANCA, anti-neutrophil cytoplasmic antibodies; anti-CCP, anti- cyclic citrullinated peptide; CANDLE/PRAAS, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature / proteasome-associated autoinflammatory syndrome; dsDNA, double stranded DNA, RF, rheumatoid factor; SAVI, STING-associated vasculopathy with onset in infancy.

There is insufficient data on the value of monitoring autoantibody titers for assessing response to treatment.

Supplementary References to Supplementary Tables 4 and 5.

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