"Knowing and Treating Kosaki/Penttinen syndrome" international collaborative consortium: recommendations for follow-up, natural history and a real-life observational study about safety and efficacy profile of tyrosine kinase inhibitors"

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SUMMARY

Background: Five years have passed since the formation of the multidisciplinary consortium "Knowing & Treating Kosaki and Penttinen Syndromes", two ultra-rare degenerative multisystem syndromes caused by heterozygous activating variants in *PDGFRB*. Neurological, orthopedic, and vascular deterioration can occur. Case reports of patients treated with tyrosine kinase inhibitors (TKIs) suggest that these drugs may be a therapeutic option in the future. The bi-annual remote meetings provide an opportunity to share knowledge on these syndromes.

Material & methods: The consortium has validated standardized follow-up guidelines, established a database to improve the natural history, and evaluated the real-world safety and efficacy profile of tyrosine kinase TKI by comparing treated and untreated patients.

Results: 18 teams in 13 countries have joined the consortium. More than 25 patients have now been identified worldwide, either published or unpublished; 7 of them were treated with a TKI. The guidelines include retrospective and prospective sections for each organ affected by the disease and are based on literature and expert opinion. They also include recommendations to standardize the assessment of the efficacy and safety of treatments prescribed under compassionate use.

Conclusion: The consortium welcomes new teams on an ongoing basis and aims to be as broad and inclusive as possible. Recommendations are especially useful in such ultra-rare degenerative diseases. The real-life observational study seems to be an appropriate model to improve knowledge, including the assessment of treatment efficacy when the prevalence of the disease does not allow the setting up of clinical trials.

INTRODUCTION

Kosaki Overgrowth Syndrome (KOGS) is an extremely rare multisystem disorder described in 2015, coinciding with the identification of its molecular basis through exome sequencing[1]. This clinical

entity is characterized by a deregulation of cell proliferation mediated by Platelet-Derived Growth Factor (PDGF), particularly in mesenchymal tissues, which explains the clinical picture: coarse facial features, tall stature, cutaneous and ungual involvement with thin, hyperelastic skin leading to hypertrophic and hyperkeratotic scars with nail dystrophy. These relatively constant signs are accompanied by progressive and evolving features such as skeletal (e.g., scoliosis and craniosynostosis, early osteoporosis), neuroanatomical (e.g., periventricular white matter anomalies, Dandy-Walker malformation, cerebellar dysgenesis, and arachnoid cysts), ophthalmological (e.g., pterygia, which may be recurrent), and neuropsychological symptoms (e.g., psychomotor retardation, intellectual disability with neurological deterioration, and mood disorders). Recent descriptions of adult patients have reported the existence of vascular complications such as aneurysms of the cervico-encephalic, coronary or renal arteries, which have a significant impact on patient morbidity and mortality. The case-reports of about fifteen patients with this condition have been published[1–12].

Penttinen syndrome (PS), first described clinically in 1997[13], is a genetic progeroid syndrome that is also very rare. It is clinically characterized by the childhood occurrence of prematurely aged appearance of certain organs and tissues (lipoatrophy, amyotrophy, thin, translucent skin, thinning hair, etc.), as well as the delay or premature senescence of physiological processes such as bone maturation, with marked acro-osteolysis and osteopenia, delayed tooth eruption and joint contractures in the hands and feet. The molecular basis of the disease was described in 2015[14]. The literature reports around ten patients worldwide[7, 13–20].

The molecular basis of Kosaki and Penttinen syndromes are germline activating variants of the *PDGFRB* gene, which encodes PDGFRβ. Activating variants in this gene may also account for an entity responsible for more incomplete signs, restricted to one or few organs, such as isolated extreme corneal vascularisation[21], ocular pterygium-digital keloid dysplasia[29], or other distinct phenotypes such as infantile myofibromatosis (multiple benign tumors of the subcutaneous tissue, bones and thoracic or abdominopelvic viscera) and cerebral vascular aneurysms. In both cases, patients may

present with constitutional or somatic variants[22–25]. Although different clinical entities have been used to classify diseases associated with specific germline-activating variants of *PDGFRB,* some patients share the same symptoms for these different syndromes. For example, some patients initially diagnosed with Kosaki syndrome have developed one or more myofibromas[24], some patients with infantile myofibromatosis have later developed vascular aneurysms[26], and some individuals present crossed clinical features between Kosaki and Penttinen syndromes[24, 27]. Some complex presentations cannot be classified in a defined entity[28]. It is now suggested that patients with germline activating *PDGFRB* variants may share several features that could be grouped into a single entity[24].

Tyrosine kinase inhibitors (TKIs) targeting PDGFRβ (imatinib, dasatinib, sunitinib) are widely prescribed for the treatment of hematological malignancies or certain types of solid tumors with aberrant activation of PDGFRβ, with well-known toxicity profiles. *In vitro* cellular studies have demonstrated the ability of various TKIs to inhibit the pathway of several *PDGFRB* variants. As a result, some teams have proposed compassionate treatment based on these functional results. To date, nine patients with myofibromatosis and four patients with KOGS or PS have been treated with a TKI with encouraging safety and efficacy results published in the literature[3, 7, 9, 20]. However, these data were regularly collected over short periods of time, and long-term follow-ups were not allowed (between 8 weeks and 18 months for KOGS and PS patients). In addition, a patient with ocular digital keloid dysplasia did not respond to treatment with imatinib[29]. In addition, to optimize therapeutic management and the choice of TKI molecule, it has been proposed to carry out *in vitro* studies on patient fibroblasts to determine which molecule would be the most effective in blocking the PDGFRβ signaling pathway[20]. Different groups have explored the physiopathology of PDGF receptor variants in cellular or mouse models[24, 27, 30–32]. The initial characterization of *PDGFRB* variants in cellular assays showed that they activate the receptor signaling in the absence of ligands[33]. Constitutive activation of the receptor in mesenchymal cells of bones, skin, blood vessels and adipose tissue could explain most disease features. This was confirmed by experiments in mice carrying a *Pdgfrb* gain-of-function

mutation, which induces a phenotype that is reminiscent of KOGS and PS, at least to some extent[30]. Activation of the transcription factor STAT1 is a key regulator of this phenotype and may play a specific role in Penttinen syndrome[29, 30, 32].

Despite encouraging results, access to treatment for these patients may be limited. For example, not all national healthcare systems provide access to treatment through the compassionate use program. In addition, some physicians and/or patients' families or patients themselves may be reluctant to initiate treatment due to the lack of data on the safety of TKIs in these syndromes and the absence of a standardized therapeutic protocol. The ultra-rare nature of the disease would make a therapeutic trial set up extremely challenging. To understand whether treatments can improve patients' symptoms, or at least slow the progression of the disease and reduce vascular risk, long-term and standardized data collection, with a good understanding of the natural history of the disease, is needed. To this end, an international consortium has been set up with a dual objective. The first is to establish guidelines for the follow-up patients. The second is to set up a database with the aim of: i) collecting real-life data to describe the natural history of patients with KOGS/PS and related conditions, with their clinical heterogeneity and complications, and ii) comparing the evolution of treated and untreated patients to assess the safety and efficacy of TKIs in this group of diseases. This article describes the implementation of these tools and the proposed data analysis plan.

METHODOLOGY

Creation of the consortium

An international multidisciplinary consortium was set up in 2019 by Professor Laurence FAIVRE (University Hospital of Dijon Burgundy and ERN ITHACA) with the aim of monitoring treated and untreated KOGS/PS patients and related conditions. This group of experts was initiated by bringing together all the authors of at least one published article on the syndrome (clinical or biological), but also by a call for contributions (European Reference Network (ERN) ITHACA, European Society of

Human Genetics (ESHG)). A dedicated website (www.kosakipenttinen.org) permits prospective contacts via clinicians or families. In some cases, contact was made at the request of a family member who had heard about the consortium through social media. The consortium meets online every 6 months and regularly welcomes new members.

Implementation of recommendations for follow-up

The Consortium met for the first time in September 2023 to validate follow up and standard of care recommendations for patients treated, or not, with TKI. Special attention was given to vascular follow-up. These recommendations were proposed based on existing patients' follow-up data and experts' experience.

Setting up a database

An electronic case report form (CleanWeb) was developed to collect anamnestic, clinical, biological, iconographic and quality-of-life data. Patient data will be entered into the database prospectively, with a reconstruction of the medical history, and retrospectively for deceased patients. The elements used to assess the response to treatment will be the same as those collected to evaluate the evolving natural history. The consortium suggested adding scales for treatment monitoring.

Regulatory procedures

In accordance with Article 65 paragraph 1 of the French Data Protection Act, authorization of the National Commission on Data Processing and Freedom (CNIL) is not required, as the data subjects will have consented to the processing. In accordance with Article 35 of the GDPR, the creation of a health database requires the preparation of the Data Protection Impact Assessment (DPIA), in order to assess

the risks of data processing and to address any potential breaches that may occur. For patients in the European Union, this information letter and consent form will mention the purposes of the database, the rights set out in the General Data Protection Regulation (GDPR), and the contact details of the responsible data controller with whom patients can exercise their rights, in particular the Data Protection Officer (DPO) of the University Hospital of Dijon. The regulatory procedures include a consortium agreement, with a data protection annex in the form of a Data Transfer Agreement (DTA). Each site is responsible for compliance with local regulatory requirements and translating the information letter and consent form into their local language.

Creating the Data Analysis methodology

The methodology of this project is based on a quasi-experimental approach. The aim is to include in the database data from patients already identified as well as those who will be recognized prospectively in the future, regardless of whether they are receiving treatment at the time of inclusion or not. The decision to treat or not to treat will remain at the discretion of the patient/their legal representative and the referring physician, and will depend on the current regulations in the country (compassionate use authorization or not).

First, the database will help to define the natural history of untreated patients or, for treated patients, the natural history up to the start of treatment, based on an international cohort with the most complete data collection possible. In the long term, our quasi-experimental approach, based on standardized follow-up and centralized data collection as recommended by the consortium's expert group, should allow us to compare the evolving natural history of treated and untreated patients

RESULTS

Consortium

As of July 2024, the consortium consists of 18 international teams in 13 countries with at least one patient with the disease or are involved in functional studies of the PDGFBR pathway (Figure 1, www.kosakipenttinen.org).

eCRF

The electronic case report form is now available to all consortium members, and is designed to collect the following data:

For all patients: i) demographic data; ii) presence and age of onset of various clinical signs and complications; iii) various additional examinations recommended for the initial assessment of the extent of the disease, and for follow-up the following: iv) number and type of interventions required and established patient's follow-up; v) quality of life study (questionnaire and pain assessment).

For treated patients, the following standardized recommendations were agreed upon by consensus: vi) information on current and previous treatment, posology and adherence to treatment (schedule); vii) assessment of drug safety; viii) assessment of treatment efficacy; ix) decision to perform, or not, *in vitro* functional studies to test patient sensitivity to different TKIs, as per Bredrup et al.. Assessment of treatment efficacy was proposed according to the management methods (additional tests, biology, etc.) and clinical follow-up agreed upon by the consortium, including quality of life measures adapted to the patient's clinical condition. The Goal Attainment Scaling (GAS) is recommended to assess treatment response. Its criteria are based on the patient's expectations at baseline[34, 35]. The CGI scale could also be completed (Clinical Global Impressions – Severity (CGI-S) and Clinical Global Impressions – Improvement (CGI-I).

Each patient's referring physician will be responsible for entering data into the database. Project coordinators will be responsible for monitoring the data entry rate and sending alerts when information is missing to ensure quality and coordinated follow-up.

Follow-up recommendations (table 1)

Follow-up recommendations consist of a full initial assessment, including: i) a clinical examination (including evaluation of laxity, contractures and blood pressure, growth parameters including arm span, photographs), ii) various specialty examinations (dermatologic, orthopedic, dental, ophthalmologic evaluation, hearing tests, electrocardiogram).

Biologic tests include thyroid function tests and molecular testing if not already performed.

Imaging tests include renal ultrasound, cardiac ultrasound, doppler of the supraaortic trunks (detection of aneurysms of medium-caliber vessels) that should be performed by an expert team, injected Angioscan or AngioMRI of the total aorta up the supra-aortic trunks and the skull base synchronized with the ECG (detection of aneurysms of medium caliber vessels), cerebral MRI with injection for detection of intracranial aneurysms, dural MRI, osteodensitometry. All examinations should be performed at baseline except injected Angioscan which is to be performed only in patients > 15 years of age if there is no clinical suspicion of a vascular complication, taking into account the radiation risk; and osteodensitometry from mid-adolescence.

Some tests that are not part of a routine evaluation, such as muscle testing (Medical Reach Council, MRC, scale) and walking distance (6-minute walk test), have been included in the database when available.

The type and frequency of additional evaluation varies according to the context and clinical manifestations. Some tests are suggested to be performed annually to every 5 years, others depending on symptoms. Experts have suggested that some examinations are optional: cerebral CT scan in case of suspected craniosynostosis; electroencephalography in case of presumed epilepsy; EOS or other X-rays (hands, skull) depending on the clinical need (risk of radiation); IQ test in case of school difficulties, behavioral tests in case of suspected abnormal behavior.

Ideally, patient-reported outcomes, including pain assessment (numerical scale from 1 to 10), quality of life assessment (Short Form (36) Health Survey (SF36) for adults, PedsQL questionnaires for children, if available in the local language), should be obtained at each visit.

Goal Attainment Scaling (GAS) is recommended every 3 months for treated patients. At the initial visit, a CGI Severity Scale and at each visit, a CGI Improvement Scale are also suggested to be performed by the physician. Cellular studies to test the efficacy of TKI could be conducted before treatment initiation, or in case of no or insufficient response, if the variant has never been tested for treatment response.

Regulatory procedures

The consortium agreement, including a Data Transfer Agreement (DTA), is currently in the approval process. The study has been approved in France by the National Institute of Health and Medical Research - INSERM Ethics Committee (approval n°23-1042). The English version of the information letter and the informed consent form have been provided to all partners. Each participating site is now responsible for verifying compliance with the necessary ethical and/or regulatory requirements applicable in its own country, and will be responsible for translating and adapting the study documents into its local language.

Analysis methodology

The primary and secondary objectives are summarized in Table 2.

Inclusion criteria are as follows:

- Patients with Kosaki/Penttinen syndrome or related disorders, with an identified pathogenic or probably pathogenic constitutional mutation of the *PDGFRB* gene;
- Patients or legal representatives willing to participate in this database project;

The exclusion criteria are as follows:

- Patients with isolated myofibromatosis;

- Lack of identification of a mutation of interest in the *PDGFRB* gene;
- Refusal by patients or representatives to undergo regular clinical evaluation;
- Patients or legal representatives who do not wish to participate in this database project.

Inclusion and exclusion criteria do not depend on whether or not patients are receiving treatment.

Although enrollment in this registry will not change diagnostic and therapeutic management, particularly concerning initiation of treatment with a TKI, patients will be compared between those treated and those not treated with a TKI. Analyzing data from untreated patients will allow us to investigate the determinants of treatment initiation, and compare their evolving natural history with that of patients treated with TKIs.

The main statistical analysis will be descriptive. Qualitative data (such as gender, adherence to follow-up recommendations defined as 80% adherence to the expert group recommendations, etc.) will be presented as proportions, and quantitative data will be presented as means and standard deviations.

Changes in quality of life and symptom burden will be analyzed based on a univariate and multivariate parameters to identify the predictors of clinical improvement or worsening. Treatment with TKIs will be included in the multivariate analysis.

Discussion

We have described here the creation of an international consortium to improve the knowledge of KOGS/PS syndromes. The first objective is to propose recommendations for patient follow-up. The second is to establish a database to collect real-life data and to describe the natural history of patients with KOGS/PS. This is all the more important given the clinical heterogeneity of patients, particularly in terms of complications. This standardized collection of real-world data will enhance our ability to evaluate the safety and efficacy of TKIs in patients with this group of diseases. Although particularly cumbersome, this type of approach seems to be very important for patients with ultra-rare diseases

where no national approach is sufficient to increase the knowledge. For example the Banque Nationale de Données Maladies Rares (National Data Bank for Rare Diseases), which includes all French patients followed up in a rare disease reference center, has only three patients. We believe that the creation of this registry will be beneficial for monitoring patients suffering from this polymorphic, progressive and sometimes severe, disease and, in particular, for providing an initial characterization of the expected benefits and risks of treatment with TKIs, which are PDGFRβ inhibitors, currently approved for other indications. If the existing literature data are sufficient to allow TKIs to be prescribed under compassionate use, they are not sufficient to properly characterize the risk-benefit balance. The extreme rarity of the disease makes the design of a therapeutic trial to reposition a molecule particularly complex. In this case, structuring a standardized real-life evaluation provides us with an appropriate approach to make a first robust assessment of the risk-benefit ratio of TKIs in the context of compassionate use in this indication. Published data on patients' clinical histories show a short follow-up period and an absence of standardized follow-up or objective monitoring data, which would be insufficient to draw conclusions[3, 7, 9, 20]. Ultimately, we should be able to determine the efficacy and safety of TKIs in the short and long term.

This work will also allow us to update the initial follow-up recommendations.

In conclusion, by bringing together all professionals involved in caring for patients with KOGS/PS, this international consortium aims to improve knowledge of the natural history of these diseases and to adapt mid-term recommendations for the follow-up and management of patients.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics

The study has been approved in France by the National Institute of Health and Medical Research - INSERM Ethics committee (CEE/IRB approval n°23-1042 on 14th November 2023).

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Figure and table legends

Figure 1: International teams in the Kosaki/Penttinen consortium, spread over 13 countries and managing at least one patient with the disease, published or not, or involved in functional studies on the PDGFBR pathway.

Table 1: Recommendations for follow-up (initial assessment and follow-up) for Kosaki/Penttinen syndrome, including recommendations for treatment follow-up

Table 2: Primary and secondary objectives of the consortium

Figure 1: International teams in the Kosaki/Penttinen consortium, spread over 13 countries and managing at least one patient with the disease, published or not, or involved in functional studies on the PDGFBR pathway.

Table 1 : Recommendations for follow-up (initial assessment and follow-up) for Kosaki/Penttinen syndrome, including recommendations for treatment follow-up

	Initial work-up at DIAGNOSIS	Follow-up	Frequency	Age at beginning	Follow-up IF TREATED	Frequency
Clinical exam including evaluation of laxity, contractures and blood pressure	+	+	Annual or more frequent according to clinical severity	From diagnosis	+	1, 2, 3 months and every 3 months
Growth parameters including arm span	+	+	Annual	From diagnosis	+	1, 2, 3 months and every 3 months
Photographs	+	+	Annual or more frequent if rapid changes	From diagnosis	+	1, 2, 3 months and every 3 months
Dermatological exam	+	+	Annual	From diagnosis	+	Unchanged
Orthopedic follow-up	+	+	Annual if clinical features	From diagnosis	+	Unchanged
Dental exam	+	+	Annual or more frequent according to clinical presentation	From diagnosis	+	Unchanged
Ophthalmology (including split lamp to evaluate the cornea)	+	+	Annual or more frequent according to clinical presentation	From diagnosis	+	Unchanged
Hearing tests	+	+ If hearing problems	If needed according to the presentation	From diagnosis	+	Unchanged
Thyroid tests	+	+	Annual	infancy	+	Unchanged

Molecular testing	+					
Walking perimeter (6-minute walk test)	+ if possible	+ if possible	Annual	School age	+	1, 2, 3 months and every 3 months
Muscular testing (echelle Medical Reach Concil (MRC), if detailed needed Manual muscle Test (MMT))	+ if possible	+ if possible	Annual	6 years	+ if muscular manifestations	1, 2, 3 months and every 3 months
Renal ultrasound	+	+ If needed	If needed according to the presentation	From diagnosis	+	Unchanged
Cardiac ultrasound/ electrocardiogramm	+	+	2 years if normal or according to manifestations	From diagnosis	+	Unchanged
Doppler of supraaortic trunks (detection of aneurysms of medium-calibre vessels) ***Should be performed by an expert team***	+	+	2 years if initially normal or according to manifestations	From diagnosis	+	Annual
Injected angioscan of the total aorta up the supra-aortic trunks and the base of the skull synchronised with the ECG (detection of medium calibre vessels aneurysms)* *** AngioMRI could be an alternative but need different MRI to perform**	+	+	Every 5 years if normal According to the presentation if aneurysms	From age 15 years (radiations)	+	Unchanged

an analysis of the whole aorta						
Cerebral MRI with injection (detection of intracranial aneurysms)	+	+	Every 5 years* or more frequent if neurological manifestations * if general anesthesia needed, TBD	From diagnosis	+	Unchanged
Dural MRI	+	+ If clinical manifestations			+	Unchanged
Cerebral CT scan	Only if signs of craniosynostosis if needed for surgical intervention			At diagnosis		
Electroencephalography	+ If suspicion of seizures	+ If suspicion of seizures	According to clinical presentation	From diagnosis	-	-
OES	If clinically needed	If clinically needed	Annual if clinically needed	From diagnosis	+	Unchanged
Other X-rays (hands, cranial)	If clinically needed (radiations)	If clinically needed	According to the evolution of manifestations	To be discussed in childhood (radiations)	+	Unchanged
Osteodensitometry	+	+	5 years More frequent if anomalies	Mid adolescence	+	Unchanged
IQ testing	+	+ If degradation	If degradation	From age 6 years	+	Unchanged

	if cognitive impairement					
Behavioural tests	If clinically needed, test adapted to the clinic	If clinically needed, test adapted to the clinic	If needed	Beginning of manifestations		
Evaluation of pain (numeric scale from 1 to 10)	+ if possible	+ if possible	At each visit	From diagnosis	+	Weekly
Evaluation of quality of life For adults, Short Form (36) Health Survey (SF36) For children, PedsQL questionnaires	+ if possible	+ if possible	At each visit	From diagnosis	+	1, 2, 3 months and every 3 months
Goal Attainment Scaling (GAS)					+	1, 2, 3 months and every 3 months
Cellular assays to establish the variant pathogenicity (based on in vitro PDGFRB mutagenesis)					+ if the variant is novel	At diagnosis
Cellular assays to test the efficacy of TKI					+ if not done for the variant of the patient in the previous literature	Before initiation or if plateau effect

Table 2: *Primary and Secondary Objectives*

Primary objective	**Secondary objectives**
Characterize the evolving natural history of clinical manifestations in patients with Kosaki/Penttinen syndrome or related disorders.	1. Evaluate the clinical, paraclinical and contextual factors associated with the decision to treat with TKIs 2. Evaluate the efficacy of TKIs in patients with Kosaki/Penttinen syndrome or related disorders. 3. Evaluate the safety of TKIs in patients with Kosaki/Penttinen syndrome or related disorders. 4. Assess the interest and feasibility of using an *in vitro* approach with cell cultures prior to treatment initiation or in cases of insufficient therapeutic response to select the most appropriate TKI, for patients who received it before treatment.