FOP news 24-25

Riccardo Papa
MD, PhD
UOC Reumatologia e Malattie Autoinfiammatorie
IRCCS Istituto Giannina Gaslini
ITALY

Sommario

- Diagnosis
  - Genetics
  - Audiology
  - Laboratory
- Therapy
  - Trials
  - Off-label

Gaslini FOP Clinic

- Offerta di un **team multi-specialistico dedicato** in grado di garantire il più corretto approccio diagnostico e terapeutico a seconda della sintomatologia presentata;

- **Centro coordinatore** che garantisca continuità assistenziale e punto di riferimento per il paziente, la sua famiglia e i medici curanti;

- **Miglioramento della prognosi** – numerosi studi dimostrano che pazienti seguiti nel contesto di una Clinica ricevono cure più aderenti agli standard qualitativi internazionali;

- **Razionalizzazione dei costi** relativi alla diagnosi e cura della malattia, anche quelli a carico di paziente e famiglia;

- Maggiore attenzione all'educazione del paziente e dell'entourage familiare, associata a **supporto psicologico con una figura dedicata**, con conseguente miglioramento dell'aderenza alla terapia;

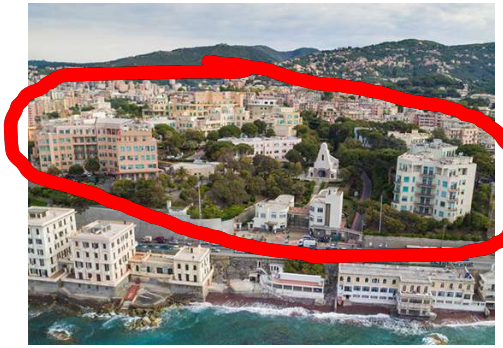
- Possibilità di partecipare a **studi nazionali e internazionali** sulla patologia.

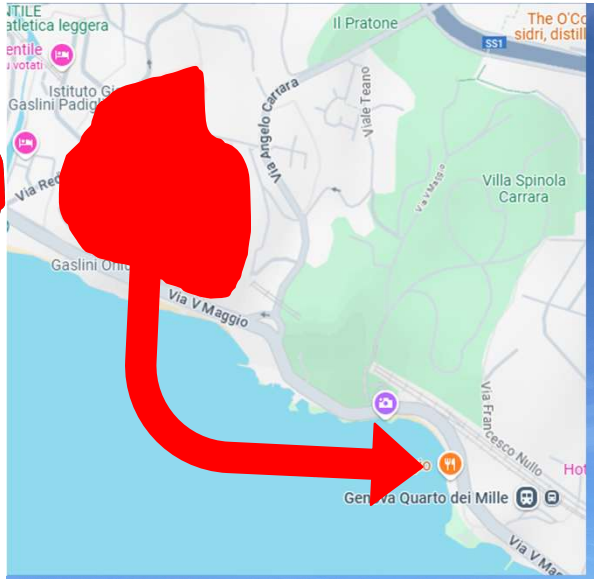
Gaslini FOP Clinic

- Seguiti/valutati 30 pazienti con FOP nel 2024
  - 13 minori <18y
  - 4 nuove diagnosi
  - 2 pazienti con FOP non-classica
  - 2 pazienti liguri

- 2 trial clinici in corso (OPTIMA, FALKON)
  - 12 pazienti arruolati
  - PIVOINE chiuso
  - 3 pazienti trattati long term con off-label

Gaslini FOP Clinic





Summary

- Diagnosis
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Summary

- Diagnosis
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nature communications

Article

https://doi.org/10.1038/s41467-023-37585-8

Enhancer hijacking at the *ARHGAP36* locus is associated with connective tissue to bone transformation

JOURNAL ARTICLE EDITOR'S CHOICE

Matrix metalloproteinase-9 deficiency confers resilience in fibrodysplasia ossificans progressiva in a man and mice

Get access >

Vitali Lounev, Jay C Groppe, Niambi Brewer, Kelly L Wentworth, Victoria Smith, Meiqi Xu, Lutz Schomburg, Pankaj Bhargava, Mona Al Mukaddam, Edward C Hsiao ... Show more

Journal of Bone and Mineral Research, Volume 39, Issue 4, April 2024, Pages 382–398,

Abstract

Single case studies of extraordinary disease resilience may provide therapeutic insight into conditions for which no definitive treatments exist. An otherwise healthy 35-year-old man (patient-R) with the canonical pathogenic ACVR1^{R206H} variant and the classic congenital great toe malformation of fibrodysplasia ossificans progressiva (FOP) had extreme paucity of post-natal heterotopic ossification (HO) and nearly normal mobility. We hypothesized that patient-R lacked a sufficient post-natal inflammatory trigger for HO. A plasma biomarker survey revealed a reduction in total matrix metalloproteinase-9 (MMP-9) compared to healthy controls and individuals with quiescent FOP. Whole exome sequencing identified compound heterozygous variants in *MMP-9* (c.59C > T, p.A20V and c.493G > A, p.D165N). Structural analysis of the D165N variant predicted both decreased MMP-9 secretion and activity that were confirmed by enzyme-linked immunosorbent assay and gelatin zymography. Further, human proinflammatory M1-like macrophages expressing either MMP-9 variant produced significantly less Activin A, an obligate ligand for HO in FOP, compared to wildtype controls. Importantly, MMP-9 inhibition by genetic, biologic, or pharmacologic means in multiple FOP mouse models abrogated trauma-induced HO, sequestered Activin A in the extracellular matrix (ECM), and induced regeneration of injured skeletal muscle. Our data suggest that MMP-9 is a druggable node linking inflammation to HO, orchestrates an existential role in the pathogenesis of FOP, and illustrates that a single patient's clinical phenotype can reveal critical molecular mechanisms of disease that unveil novel treatment strategies.

A Rare Variant Allele of BMPR2 Predisposes to the Onset of a Novel Subtype of Congenital Heterotopic Ossification

Myung-Jin Kim[1], Dayeon Kim[1], Chang Ho Shin[2], Hey Ran Lee[2], Yoon-Young Kim[3], Hyun Mo Ryoo[4], Suk-Won Jin[5,6], Young Yang[1], Won Joon Yoo[2,9], Woong Yang Park[7], Frederick S. Kaplan[8], Aris N. Economides[10], Tae-Joon Cho[2*] and Yonghwan Kim[1*]

[1]Department of Biological Sciences & Research Institute of Women's Health, College of Natural Sciences, Sookmyung Women's University, Seoul 04310, Republic of Korea, [2]Division of Pediatric Orthopaedics, Seoul National University Children's Hospital, Seoul 03080, Republic of Korea, [3]ToolGen, Inc., Seoul 08501, Republic of Korea, [4]Department of Periodontology, School of Dentistry and Dental Research Institute, Seoul National University, Seoul 03080, Republic of Korea, [5]School of Life Sciences, Gwangju Institute of Science and Technology, Republic of Korea, [6]Yale Cardiovascular Research Center, Yale University School of Medicine, New Haven, CT 06511, USA, [7]Samsung Genome Institute, Samsung Medical Center, Seoul 06351, Republic of Korea, [8]Department of Orthopaedic Surgery & Medicine, The Center for Research in FOP and Related Disorders, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA, [9]Department of Orthopaedic Surgery, Seoul National University College of Medicine, Seoul 03080, Republic of Korea, [10]Regeneron Genetics Center, Tarrytown, NY 10591, USA *Co-correspondence

ABSTRACT

Heterotopic ossification, a pathological condition whereby soft tissues transform into skeletal bones, is rare but debilitating disease without any effective treatment. Mutations in *ACVR1* or *GNAS* have been implicated in congenital heterotopic ossification, however, cellular and molecular mechanisms underlying the pathophysiology of heterotopic ossification have not been fully elucidated. Here we report that *BMPR2* is a previously unidentified genetic contributor of the congenital heterotopic ossification. We show that a rare gain of function mutation in *BMPR2* (c.1126G>A, p.E376K) leads to congenital heterotopic ossification. The pathological features of The BMPR2^{E376K} appear to be reminiscent of previously reported fibrodysplasia ossificans progressiva (FOP), yet manifest a number of distinct hallmarks, including lack of stereotypic malformation of the big toes. The BMPR2^{E376K} appears to function as a neomorph, which displays exaggerated responses toward Activin A stimulation by selectively interacting with ACVR1, supporting the idea that dysregulation of ACVR1-mediated Activin A signaling may serve as a critical contributing factor for heterotopic ossification. Taken together, our data illustrate the complex molecular features underlying the pathophysiology of heterotopic ossification, and highlight the importance of BMPR2 as a nexus for ACVR2 and Activin A interaction. Moreover, our findings provide a theoretical framework for developing a novel therapeutic options for heterotopic ossification.

RESULTS

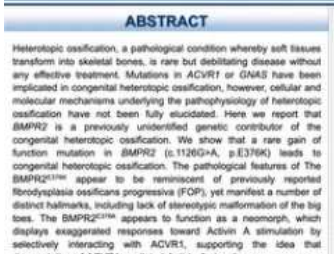


Figure 4. Elucidation on the molecular basis of pathogenicity associated with the BMPR2^{E376K} variant.

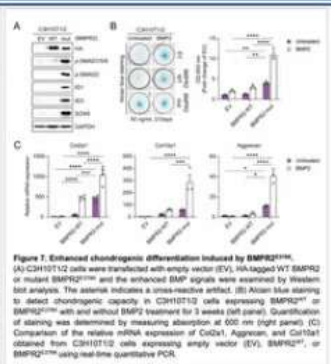


Figure 7. Enhanced chondrogenic differentiation induced by BMPR2^{E376K}.

Figure 5. Staining for detection of osteogenic differentiation.

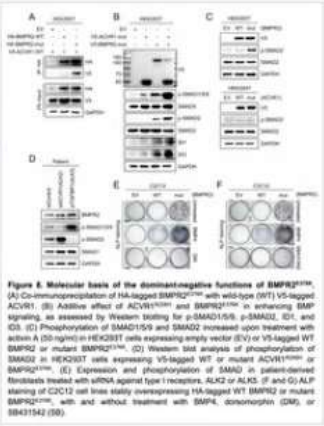


Figure 8. Molecular basis of the dominant-negative functions of BMPR2^{E376K}.

Figure 6. Enhanced chondrogenesis and osteogenesis of BMPR2^{E376K} patient-derived mesenchymal stem cells.

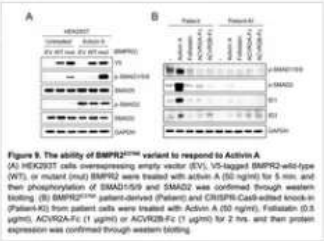


Figure 9. The ability of BMPR2^{E376K} variant to respond to Activin A

SUMMARY

1. We have identified a novel gain-of-function variant as a causative for FOP-like phenotype in a Korean patient.
2. Inappropriate activation of BMPR2 leads to progressive heterotopic ossification within soft connective tissues.
3. BMPR2^{E376K} mutation activates not only SMAD1/5/9 signaling, but SMAD2 signaling cascade as well even in the absence of BMPs.
4. BMPR2^{E376K} mutation induces osteogenic differentiation.
5. BMPR2^{E376K} variant is consistently associated with the ACVR1.
6. These results suggest BMPR2 gene should be enlisted in the targeted sequencing for skeletal dysplasia.

ANDECAL, A Phase 2/3 study to determine the efficacy of the MMP9-inhibitor Andecaliximab to block new heterotopic ossification in fibrodysplasia ossificans progressiva (FOP): Methodology for Part 1 of the Study

Deborah Wenkert,[1] Frederick S. Kaplan,[2] Robert J. Pignolo,[3] Edward C. Hsiao,[4] Mona M Al Mukaddam,[2] Eric Soliman,[1] Victoria Smith,[1] Pankaj Bhargava[1]

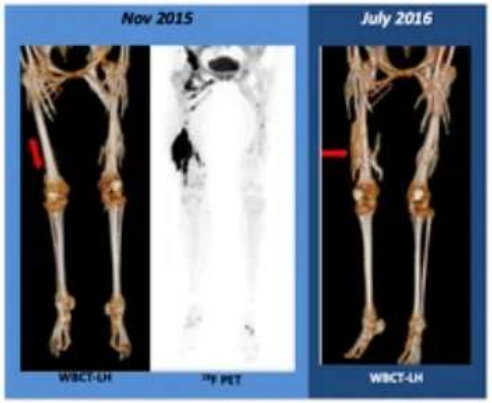
[1] āshibio, Brisbane, USA; [2]Perelman School of Medicine of The University of Pennsylvania, Philadelphia, USA; [3]Mayo Clinic College Of Medicine, Rochester, USA; [4]University of California - San Francisco, San Francisco, USA

Introduction

Fibrodysplasia Ossificans Progressive (FOP):

- An ultra-rare, severely disabling, autosomal dominant disorder, resulting from an activating mutation in activin A type I (*ACVR1*) gene.[1]
- Characterized by painful debilitating inflammatory flare-ups and immobilizing transformation of skeletal muscles, tendons, ligaments, fascia, and aponeuroses[2] into an immobilizing exoskeleton of heterotopic ossification (HO).
- Most patients are confined to a wheelchair by the third decade of life.[3]

Figure 1. Na18F PET/CT[4]



CT and Na^{18}F PET during a suspected flare up in right leg with heterotopic bone detected on a follow-up CT

Current FOP Management &Treatment & Unmet Need:

- Management focuses on early diagnosis & supportive care
- Palovarotene (a retinoic acid receptor gamma agonist) is approved for use in the US, Canada, Australia, and the UAE. Its primary mechanism of action is downstream of the early events leading to HO and flare-ups. It decreases bone morphogenetic protein (BMP) signaling and subsequently inhibits the SMAD1/5/8 signaling pathway.
- Palovarotene provides modest reduction in annualized new HO volume in patients with FOP with no positive effect on flare-ups and cannot be used in girls age <8 years (yrs) nor boys age <10 yrs (a time of active flare-ups and new HO accrual)

Matrix Metalloproteinase-9 (MMP9) & FOP:

- Novel target for FOP, identified through studying a "resilient patient" (Patient-R) who, at age 35 yrs, had minimal flare-ups or heterotopic ossification[5]
- Patient-R carries the classic *ACVR1* mutation (R206H) for FOP and 2 MMP9 gene variants that result in decreased expression and/or activity of MMP9[6].
- MMP9 knock-out abrogates injury-induced HO in a mouse model of FOP, and pharmacologic inhibition with an anti-MMP9 murine antibody inhibited the development of HO[6].

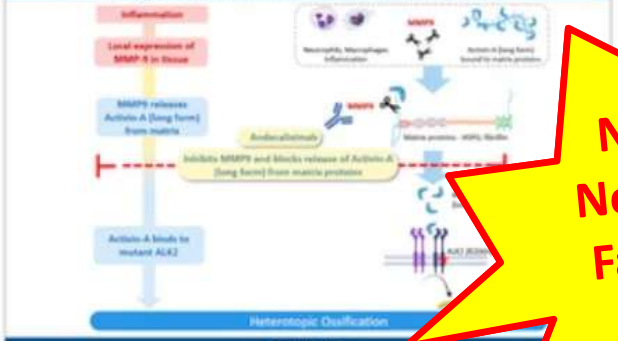
MMP9:

- MMP9 has limited expression in healthy tissues and is associated with chronic inflammation and dysfunctional tissue repair in disease.
- MMP9 releases signaling molecules tethered to the extracellular matrix, such as VEGF, activin A, and potentially BMPs[6], thereby modulating inflammation, neovascularization, and differentiation.

Andecaliximab:

- Humanized monoclonal antibody specific to MMP9[7-11]
- Primary mechanism of action is inhibiting activation of MMP9[7-11]
- Demonstrated a favorable safety profile in prior clinical trials[8,9,11] involving ~1000 adults
- Toxicology studies support the use in ages ≥ 12 yrs; additional toxicology results supporting younger ages should be available before the initiation of ANDECAL Part 2.

Figure 2. Andecaliximab Mechanism of Action



Methods

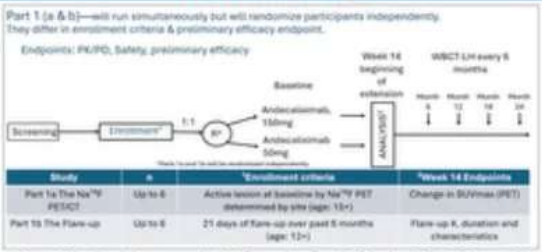
ANDECAL is a Phase 2/3, two-part study of andecaliximab in FOP:

- Part 1 (Part 1a & Part 1b) is the Lead-in Study to assess safety, pharmacokinetics/ pharmacodynamics, and preliminary efficacy
- **Part 1a and Part 1b** are 13-week, double-blind studies (see Figure 3).
- Part 2 (Main Study) is a Phase 2/3 randomized, double-blind, placebo-controlled trial

Enrollment criteria: All participants must have clinical FOP from any activin A receptor type I (ACVR1), pathogenic or likely pathogenic variant, without other potentially confounding chronic disease or active treatment (allowances have been made for use of steroids, etc. per the International Clinical Council [ICC] on FOP guidelines). They must also have evidence of active disease within the past year documented by:

- History of symptoms confirmed by physician as being consistent with flare-up, or
- Physician-confirmed clinical progression (e.g., new HO, or worsening of joint function including new ankylosis).

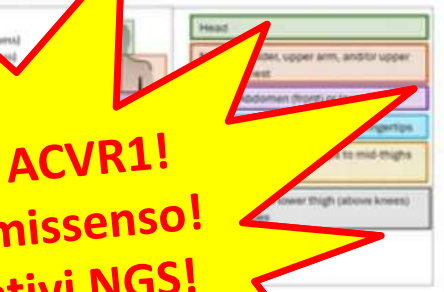
Figure 3. Study Design



In Part 1a and 1b, site visits are required at Screening, Day 1 of dosing, Week 14, every 26 wks while on study treatment, and the Safety Follow-up Visit.

Flare-ups are to be captured by a weekly diary as depicted in Figure 4.

Figure 4. Week[illegible] Flare-up Questionnaire



[illegible] flare-ups or [illegible] MMP9.

[illegible] protects against HO [illegible] se model of anti-MMP9 antibody[6]. ANDECAL, is a [illegible] ng MMP9 in participants with FOP.

Conclusions

Enrollme[illegible] art 1 of AN[illegible] tudy is expected to initiate in the second half of 2024. Part 1 of [illegible]DECAL study [illegible]uate the safety, PK/PD and preliminary efficacy (exploratory) of andecalixim[illegible] participants with FOP and will serve as a lead-in for Part 2 of the study.

References

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Disclosures

Receiving salary and stock options (DW, VS, PB) or consulting fees (ES) from āshibio. Co-inventor on the patent for Methods of Treating HO, including MMP9 as a target (FSK, RJP). Member ICC on FOP and IFOPA Registry Advisory Board (voluntary) (FSK (also founder and past president of ICC), RJP, MMAM, ECH) and Fibrous Dysplasia Foundation (ECH); Research Investigator for āshibio (MMAM, ECH); Clementiapharm (FSK, MMAM, ECH), Incyte (FSK, MMAM), Ascendis (ECH).

Acknowledgements

We thank Maggie Ward for help in creating this poster.

Non solo ACVR1!
Non solo missenso!
Falsi negativi NGS!
Geni correttivi?

Summary

- Diagnosis
  - Genetics
  - Audiology
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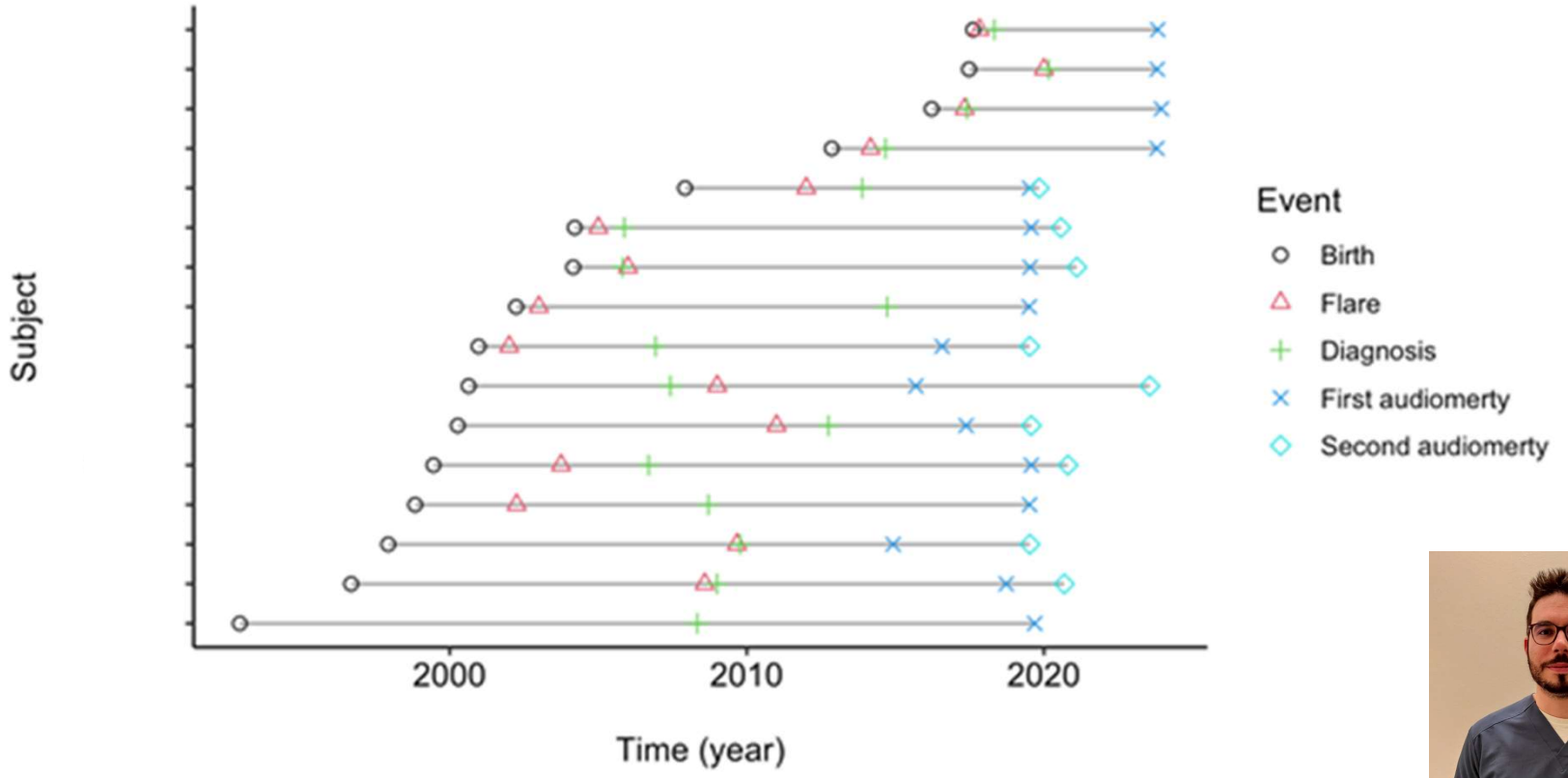
Audiology



T. Cacco et al. JBMR Plus 2025

Audiology

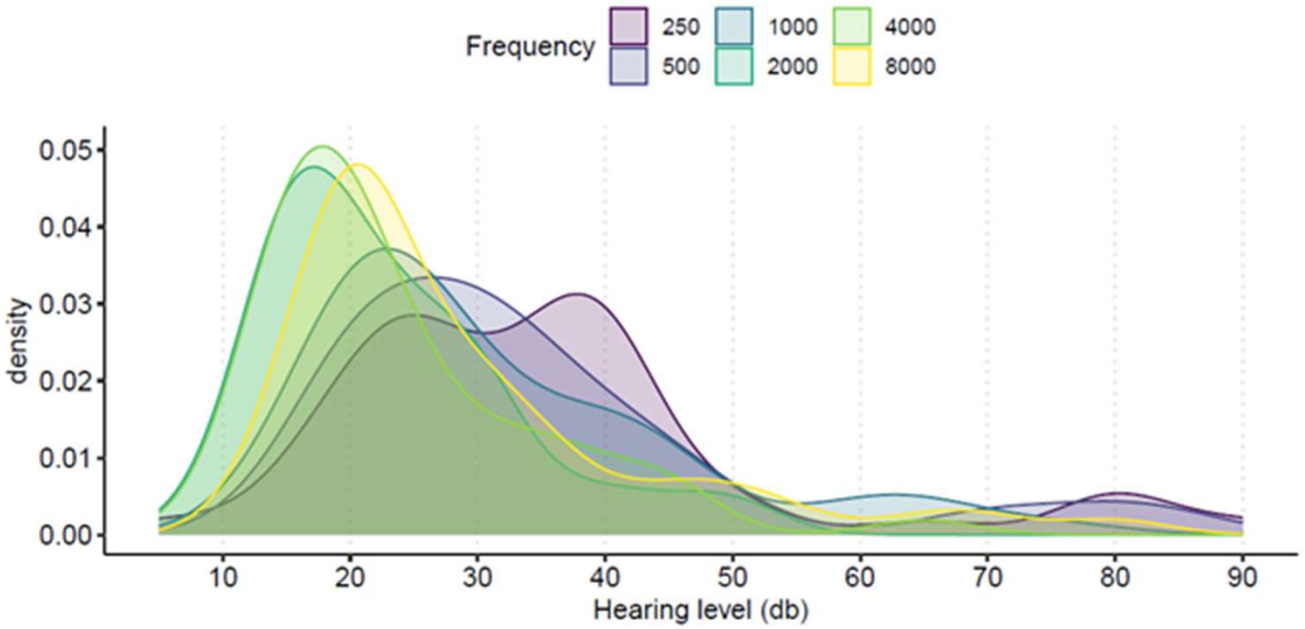


Figure 2: Distribution of hearing level by frequency

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Audiology

- Longer disease history is associated with a statistically significant worse hearing loss
- High frequencies mainly involved
- Male show a statistically significant greater drop than female (hormonal effect as well as in otosclerosis?)
- The position of the high-frequency receptors within the cochlea, near the oval window, makes them more exposed to damage than the low-frequency receptors located deeper in the cochlea
- Only a non-classic FOP patient presented a mixed hypoacusia with a sensorineural component, currently not deserving hearing aids

T. Cacco et al. JBMR Plus 2025

Summary

- Diagnosis
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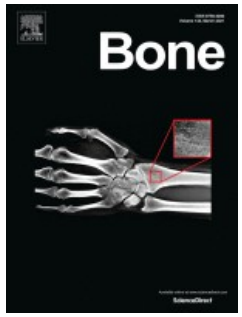
IL-1RA as biomarker for flares



Dott.ssa A. Bertoni

No new flare-up in Clinic this year!!

R. Papa et al. Bone 2024

IL-1RA as biomarker for flares

Nikishina et al. Pediatric Rheumatology (2023) 21:92
https://doi.org/10.1186/s12969-023-00856-1

Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Successful experience of tofacitinib treatment in patients with Fibrodysplasia Ossificans Progressiva

Biomarkers

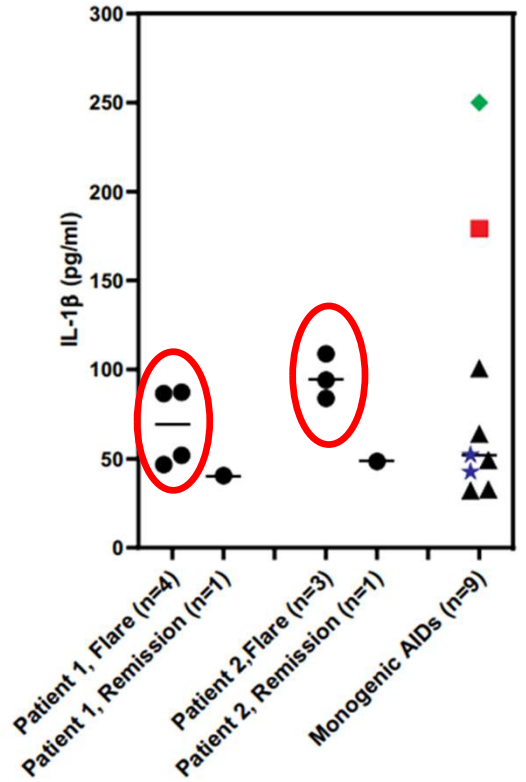
We analyzed repeatedly the spectrum of several serum biomarkers in a small group of patients with FOP (n=5) in paired serums before and under the tofacitinib treatment. During the trial, the levels of IL1RA decreased in 4/5 (80%) and increased in 1/5 (20%). The levels of IL18 decreased in 1/5 (20%), increased in 1/5 (20%), and were unchangeable in 3/5 (60%). The levels of IL10 increased in 3/5 (60%), decreased in 1/5 (20%), and were stable in 1/5 (20%). The levels of IL-6 decreased by 3/5 (60%) and increased by 2/5 (40%).

Rheumatology, 2024, **63**, 2597–2604
https://doi.org/10.1093/rheumatology/keae255
Advance access publication 11 May 2024
Original Article

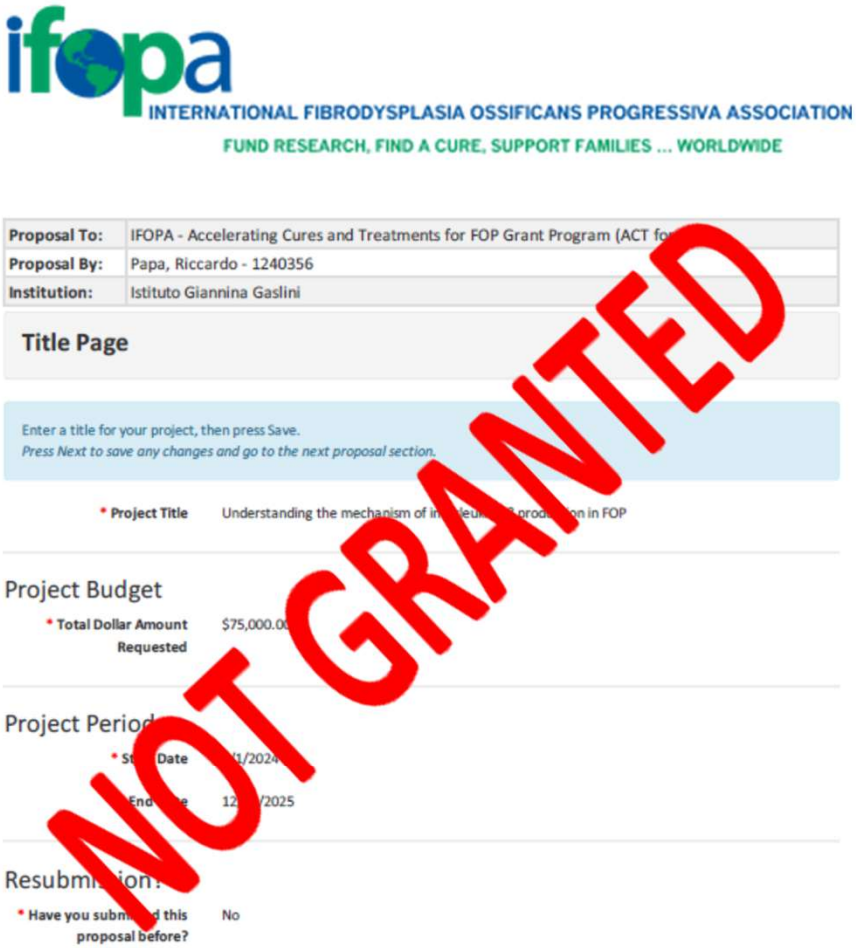
British Society for Rheumatology RHEUMATOLOGY OXFORD

Basic science

Long-term use of interleukin-1 inhibitors reduce flare activity in patients with fibrodysplasia ossificans progressiva



IL-1RA as biomarker for flares



ifopa
INTERNATIONAL FIBRODYSPLASIA OSSIFICANS PROGRESSIVA ASSOCIATION
FUND RESEARCH, FIND A CURE, SUPPORT FAMILIES ... WORLDWIDE

Proposal To:	IFOPA - Accelerating Cures and Treatments for FOP Grant Program (ACT fo
Proposal By:	Papa, Riccardo - 1240356
Institution:	Istituto Giannina Gaslini

Title Page

Enter a title for your project, then press Save.
Press Next to save any changes and go to the next proposal section.

* **Project Title** Understanding the mechanism of in eu 6 prod on in FOP

Project Budget

* **Total Dollar Amount Requested** $75,000.0

Project Period

* St Date /1/2024
End e 12 /2025

Resubm ion?

* **Have you subm d this proposal before?** No

NOT GRANTED

ACT for FOP Results
4 messaggi

Danielle Kerkovich <danielle.kerkovich@ifopa.org> 28 marzo 2024 alle ore 19:40
A: Riccardo papa <papariccardo86@gmail.com>

Dear Dr. Papa,

Thank you so much for applying to the IFOPA ACT for FOP grant program. Unfortunately, the IFOPA is unable to fund your proposal due to the availability of funds and concerns raised by the reviewers.

The reviewers agree that inflammatory symptoms during FOP flare-ups are clinically relevant and the fact that anti-inflammatory therapies are only partially effective, demands a deeper understanding of the mechanisms underlying flare-ups in FOP. To this end, the PI's goal of analyzing the role of the IL-1 pathway in the pathogenesis of FOP is laudable and the methods proposed are reasonable. However, the reviewers do not have sufficient information within the proposal to rest assured that a sufficient number of patients are available for the study and because a statistical assumptions/plan is not presented, the reviewers cannot recommend funding of the proposal with confidence.

Thank you again for your work, time, and attention to FOP. If you have any questions, please don't hesitate to reach out to me at the number or email below. We like your proposal, are impressed by your work and believe this is an important line of inquiry to pursue in FOP research. We hope that you will resubmit during the next cycle after addressing the statistical concerns of the reviewers.

All my best,

Danielle

Danielle M Kerkovich, PhD
Director of Research Development and Partnerships
International Fibrodysplasia Ossificans Progressiva
danielle.kerkovich@ifopa.org
+1-202-812-6462

PS I would like to apologize for the unexpected delay in completing the review process. Your time and efforts are valuable and we resolve to address the hurdles that prevented us from notifying applicants sooner.

IL-1RA as biomarker for flares

FONDAZIONE Telethon

Application Form

Summary

Reference number	6150
Institution	Istituto Giannina Gaslini - IRCCS
Lead Applicant	Dott. Riccardo Papa
Total Requested	€37,000.00

General Remarks

Fondazione Telethon ETS received 273 applications for the Round 4 of the Multiround Call for research projects. Projects were reviewed according to the policies and procedures set by Fondazione Telethon and stated in the Call for Application.

Seven projects were considered not eligible because they did not meet the relevance requirements specified in our call for proposals. Given the number of applications received, Fondazione Telethon decided to proceed with a triage phase: 128 applications were rejected while 138 underwent the phase II "Full review". Specifically, 96 Basic track applications and 42 PoC track applications underwent full review.

For the Basic track, applications with an average score ≥ 3.8 plus 3 projects with a discordant score were discussed. For the PoC track, applications with an average score ≥ 3.6 plus 1 project with a discordant score were discussed.

Based on these criteria, 76 applications were discussed during the Fondazione Telethon Scientific Committee study section: 46 for the Basic Track and 30 for the POC Track. After discussion, all members assigned a new score to the projects. Given the available funds, Fondazione Telethon will fund 36 projects: 25 for the Basic Track and 11 projects for the POC Track.

This review report provides the anonymous written comments of all the Reviewers and a summary of the plenary discussion when occurred.

Although Fondazione Telethon is willing to relay the views of its reviewers, it is not prepared to discuss the individual reviewer's opinions.

If you have questions about Fondazione Telethon's policy and procedures, please contact the Telethon Research Office.

Project Description

This proposal focuses on a very rare disease characterized by heterotopic ossification, known as Fibrodysplasia Ossificans Progressiva (FOP). FOP is associated with neofunctional mutations in the ACVR1 gene, which lead to episodic endochondral bone formation triggered by the local release of Activins. Currently, there is no globally validated cure, and anti-inflammatory drugs have traditionally been used to prevent flare-ups of bone formation.

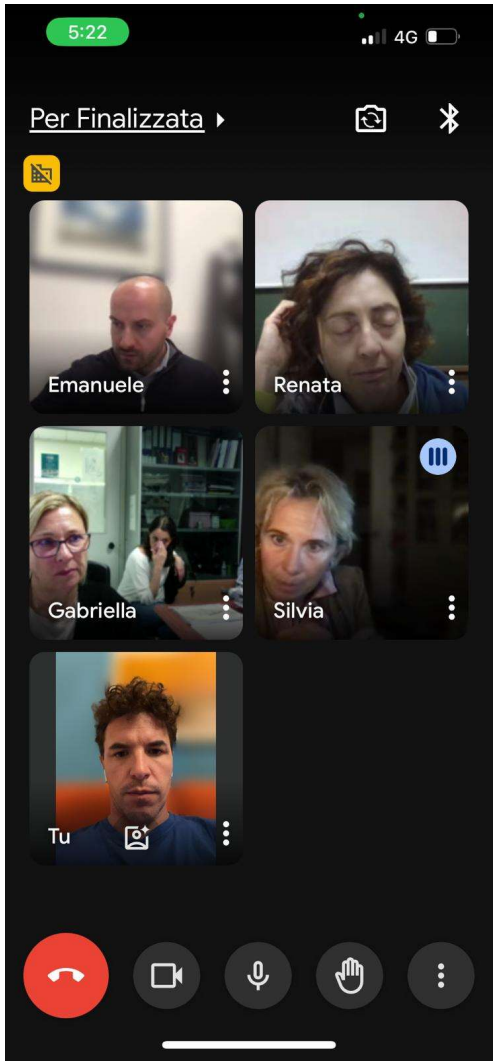
Building on a case report that noted elevated peripheral IL-1β levels in FOP patients during flare-ups, the proposed work plan aims to further validate this finding and characterize the expression of IL-1β, as well as the response to IL-1β inhibitors, in primary monocytes obtained from FOP patients. While exploring the IL-1β axis in FOP is of interest, the proposed study is quite exploratory and superficial, lacking significant impact on patient outcomes. The focus on monocytes, without testing the effects of IL-1β inhibition on in vitro osteochondrogenic differentiation models, limits the study's scope.

The work plan consists of three aims. In Aim 1, the applicant will collect blood samples from FOP patients during their routine follow-up visits over a period of 24 months. These samples will be assayed for IL-18, IL-1RA, IL-6, and TNFR1 levels alongside those of healthy controls. In Aim 2, peripheral blood mononuclear cells (PBMCs) will be isolated from FOP patients, challenged, and analyzed for cytokine production, as well as for the activation of ASC, caspase-1, and Gasdermin D. In Aim 3, IL-1β and inflammasome inhibitors will be tested on previously isolated PBMCs, using the aforementioned parameters as readouts.

Outcome of the Review Process

Based on the criteria mentioned in the "General Remarks" section, this Application was not discussed during the plenary meeting and this Research Project will not be funded.

IL-1RA as biomarker for flares



Ministero della Salute

Ex-Direzione generale della ricerca e dell'innovazione in sanità
BANDO RICERCA FINALIZZATA 2024
esercizio finanziario anni 2022-2024 - Letter of intent (LOI)

Project title:
Decoding Immune-Mediated Pathways in Heterotopic Ossification of Fibrodysplasia Ossificans Progressiva Using Multi-Model Platforms

Project duration (months): 36

Project Code:

Principal Investigator: Brunelli Silvia

Research Type:
a) Theory-enhancing: sviluppare procedure innovative e nuove conoscenze utili al miglioramento delle opportunità di prevenzione, diagnosi, trattamento, riabilitazione anche attraverso...

Applicant Institution: Fondazione IRCCS San Gerardo dei Tintori

Project Acronym: IMPACT-FOP

Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

LETTER OF INTENT

MDC primary: Ortopedia

MDC secondary: Pediatria

Project Classification IRG: Musculoskeletal, Oral and Skin Sciences

Project Classification SS: Skeletal Biology Structure and Regeneration - SBSR

Project Keyword 1: Nature of musculoskeletal injuries, disorders/diseases of developmental, infectious, degenerative, traumatic, and/or age-related etiologies. This includes sports-related and repetitive motion disorders, and the wear, injury-induced, and degenerative changes manifest in articular and meniscal cartilage.

Project Keyword 2: Heterotopic ossification

Project Keyword 3: Inflammasome

Project Request: **Animals:** [X] **Humans:** [X] **Clinical trial:** [ ]

The object/s of this application is/are under patent copyright Y/N: [ ]

Project total financing request to the MOH: € 450.000

Operative Units

	INSTITUTION	Department/Division/Laboratory	Role in the project
1	Fondazione IRCCS San Gerardo dei Tintori	SCHOOL OF MEDICINE AND SURGERY-UNIV. MILANO BICOCCA	Coordinator Responsible Aim 2
2	IRCCS Istituto Giannina Gaslini	UOC Medical Genetics/UOC reumathology	Responsible Aim1, collaborator in Aim 3
3	IGB A. Buzzati Traverso, CNR	Institute of Genetics and Biophysics "Adriano Buzzati Traverso"	Responsible Aim3

IL-1RA as biomarker for flares

E-RDERA European Rare Diseases Research Alliance

Date and signature of the partners involved:

SANCHEZ DUFFHUES GONZALO - 30958263X
Digitally signed by SANCHEZ DUFFHUES GONZALO - 30958263X
Date: 2025.02.13 12:55:56 +01'00'

G. Sanchez-Duffhues,
Oviedo (Spain), 13/02/2025.

F. Ventura Pujol,
Barcelona (Spain), 13/02/2025

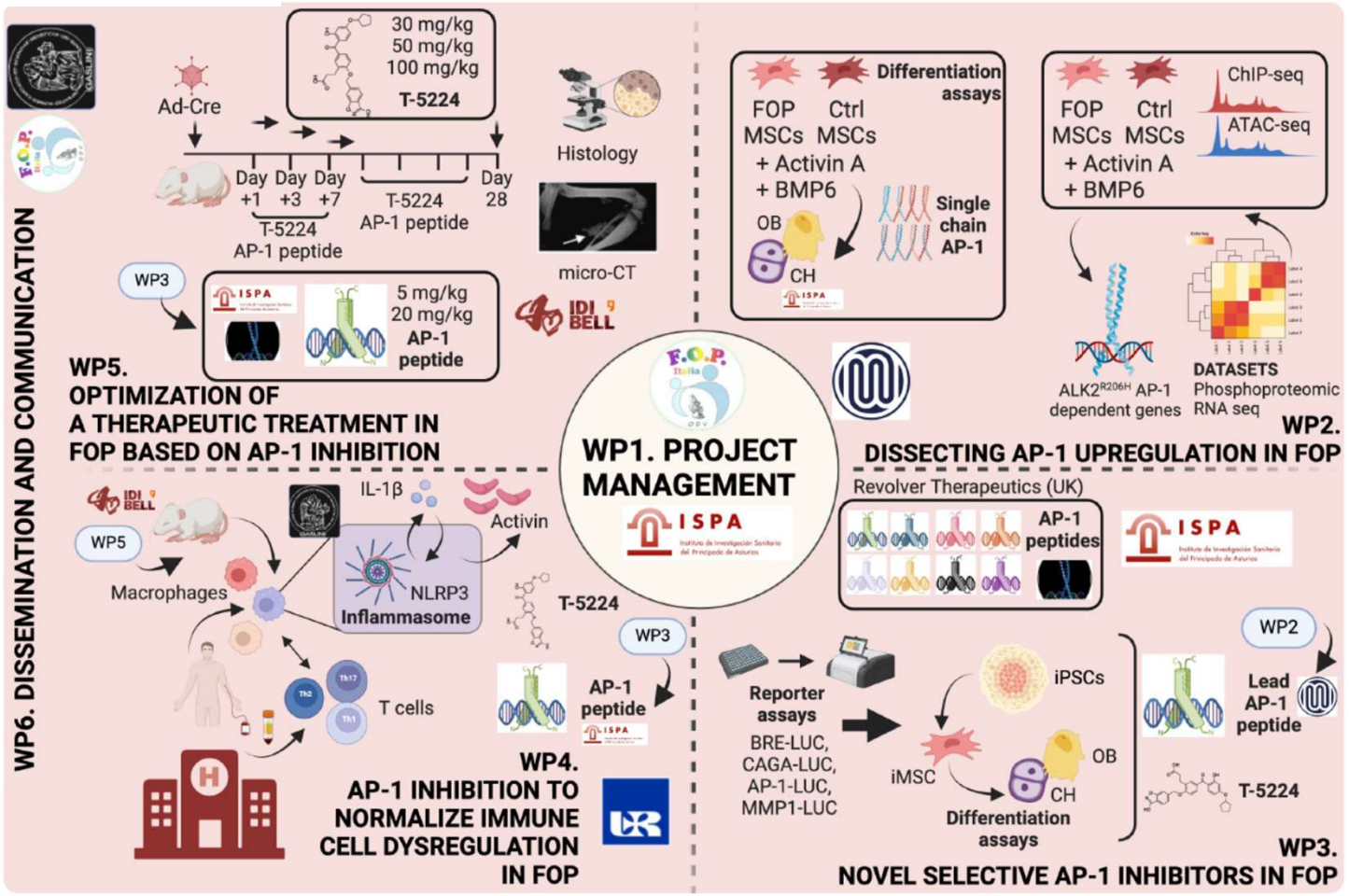
L. Bakiri
Vienna (Austria), 13/02/2025

Uniwersytet Rzeszowski
Kierownik
Laboratorium Badań Translacyjnych
w Medycynie
prof. dr hab. n. med. i n. o zdr. Jacek Tabarkiewicz

J. Tabarkiewicz,
Rzeszow (Poland), 13/02/2025

Riccardo Papa

R. Papa,
Genova (Italy), 13/02/2025



IL-1RA as biomarker for flares

Dr. Andrea del Fattore

Head of the Bone Physiopathology Research Unit

Genetics and Rare Diseases Research Division

Bambino Gesù Children's Hospital IRCCS, Rome, Italy

Summary

- Diagnosis
  - Genetics
  - Radiology
  - Laboratory
- Therapy
  - Trials
  - Off-label

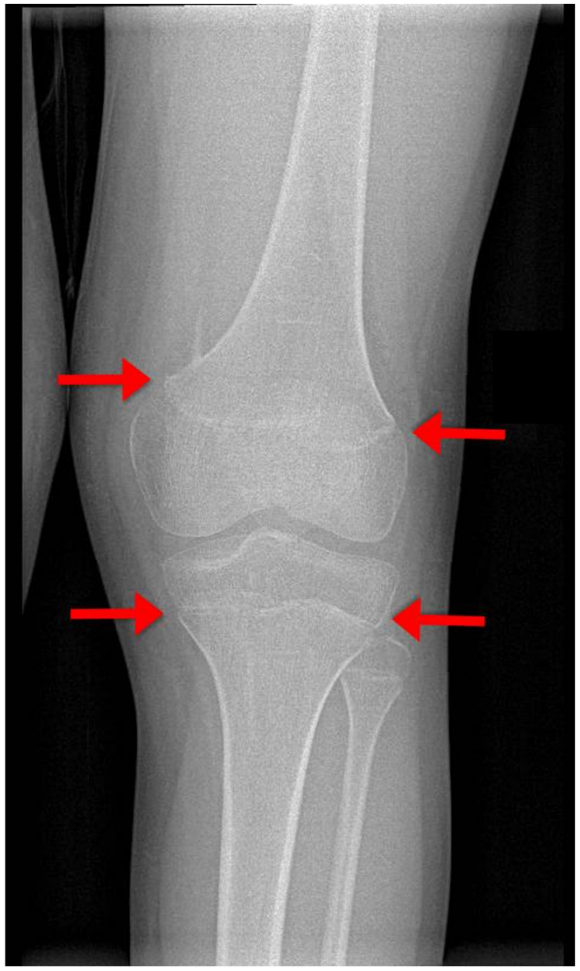
Summary

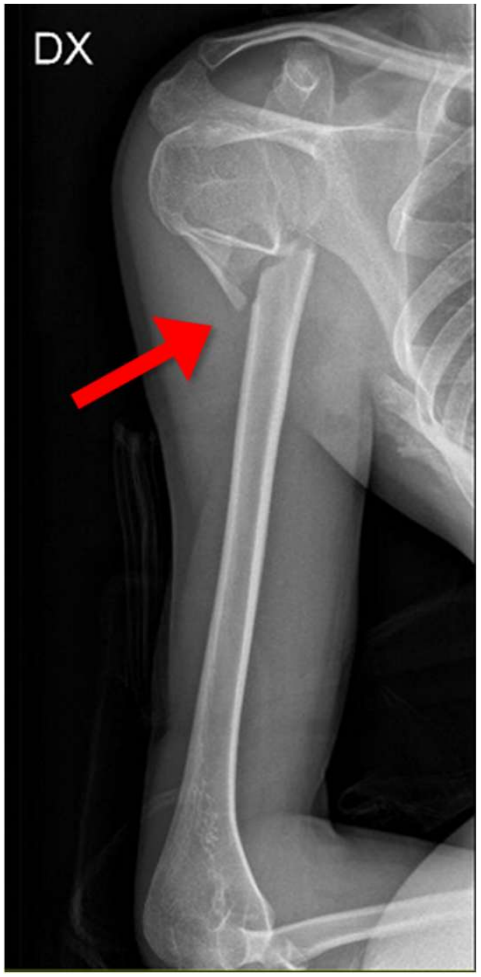
- Diagnosis
  - Genetics
  - Radiology
  - Laboratory
- Therapy
  - Trials
  - Off-label

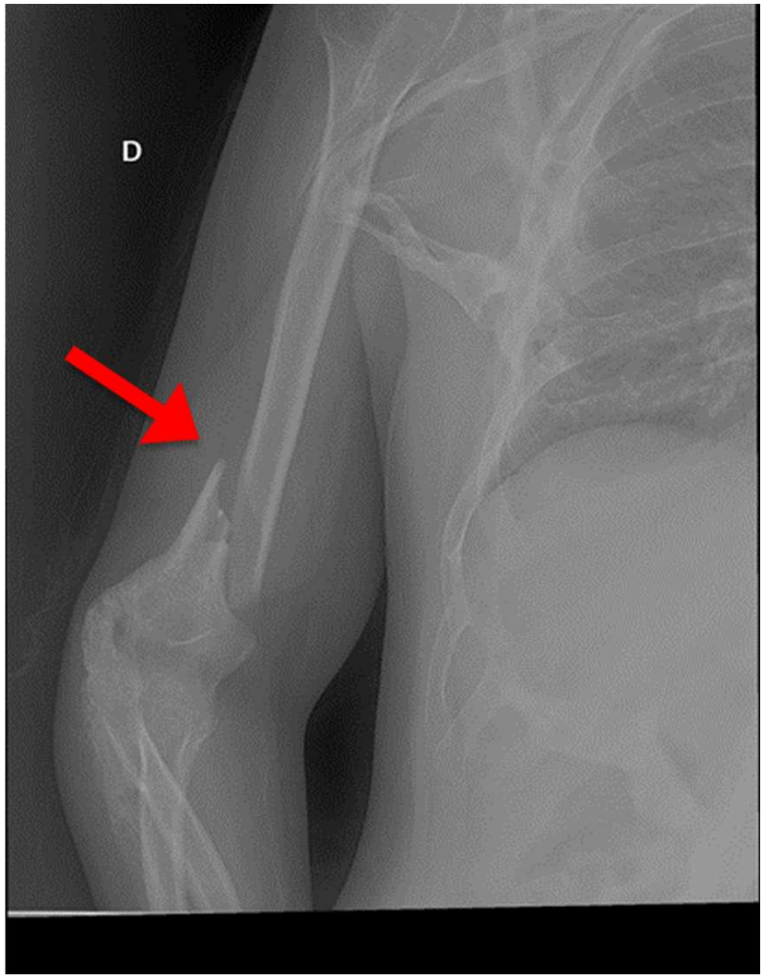
Trials

- Palovarotene (PIVOINE) os – **end in NOV 2024**
  - approved in USA, Canada, Emirates and Australia
  - Not approved in Europe

Trials







Trials

- Palovarotene os (PIVOINE) – **end in NOV 2024**
  - approved in USA, Canada, Emirates and Australia
  - Not approved in Europe

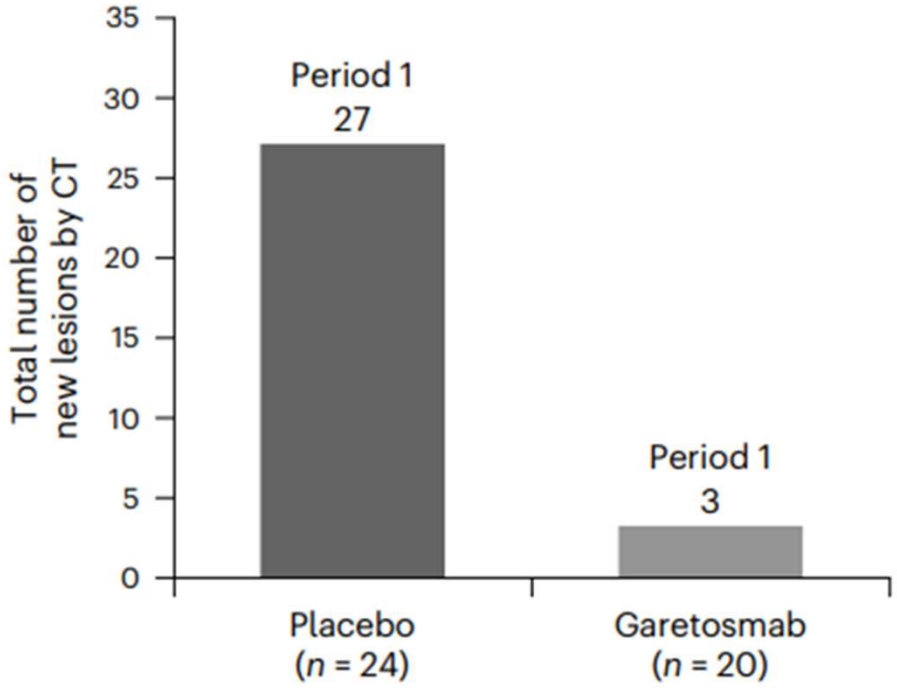
- Garetosmab iv (OPTIMA) – fase 3 - ongoing
  - 10 adult patients enrolled in Italy; <18y early 2026?
  - No major safety concerns **by now**

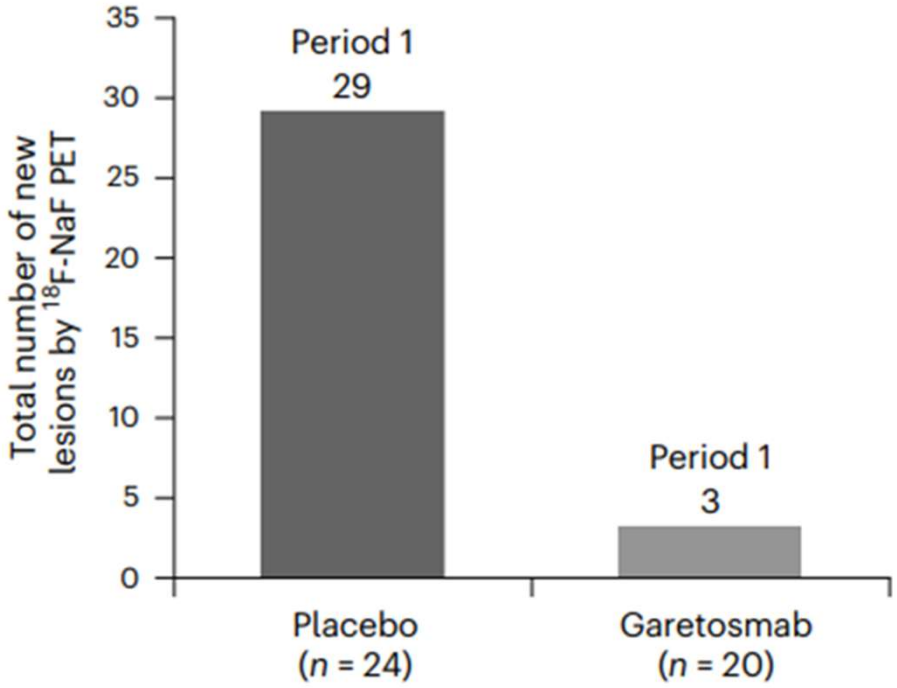
- Fidrisertib os (FALKON) – fase 2 - ongoing
  - <15y in JUN 2024 – 1 pediatric patient enrolled in Italy

- Zilurgisertib os (PROGRESS) – fase 2 - Roma
- Saracatinib os (STOPFOP) – fase 2 - Nord UE
- Andecaliximab sc (ANDECAL) – fase 2 - USA
- Rapamycin (?) – fase 2 - Japan

Article https://doi.org/10.1038/s41591-023-02561-8

Garetosmab in fibrodysplasia ossificans progressiva: a randomized, double-blind, placebo-controlled phase 2 trial





M. Di Rocco et al. Nature Medicine 2023

Summary

- Diagnosis
  - Genetics
  - Radiology
  - Laboratory
- Therapy
  - Trials
  - Off-label

Off-label

30 May 2024

Updated statement regarding off label medications for the management of FOP, from the International Clinical Council (ICC) on FOP

This statement updates the recommendations from the ICC to include several new publications, and brings attention to an important potentially severe medication interaction with palovarotene.

The International Clinical Council (ICC) on FOP clinicians are aware of several recent publications describing the off-label use of potent medications for managing inflammation in FOP. These potential treatments include the use of anakinra (1), canakinumab (1; 2), tofacitinib (3), and imatinib (4; 5). These reports appear to show some benefits, particularly with managing FOP flares and flare pain.

In addition, there are recent reports of medications such as minocycline (6), momelotinib (7), and pacritinib (8) that have activity in animal models of FOP or that may directly target ACVR1 activity. There are no clinical data regarding the risks or benefits of these therapies for managing patients with FOP.

Off-label

- Sirolimus (mTOR inhibitor) os
  - Japanese trial
  - Reported experience of 2 patients by Kaplan et al.

- Tofacitinib (JAK inhibitor) os
  - 12 patients

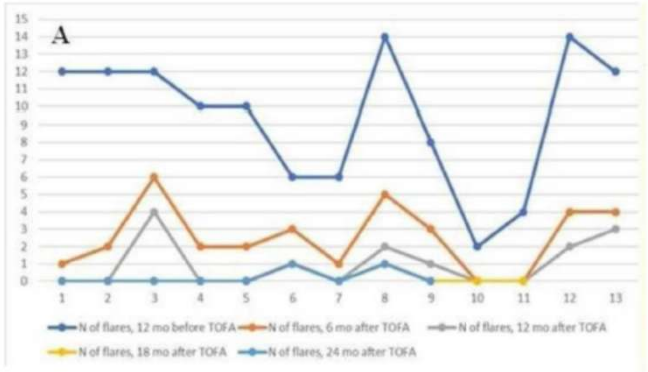
Off-label

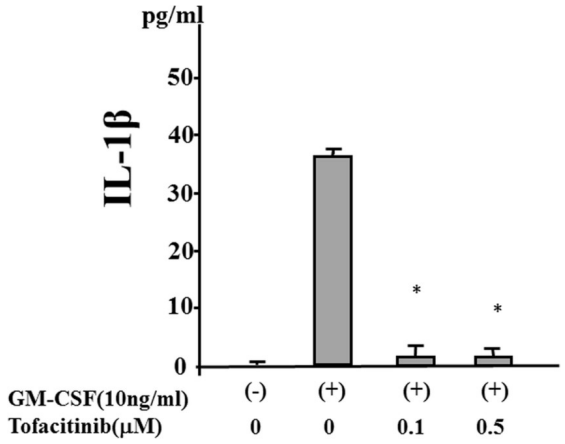
Nikishina et al. Pediatric Rheumatology (2023) 21:92
https://doi.org/10.1186/s12969-023-00856-1

Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Successful experience of tofacitinib treatment in patients with Fibrodysplasia Ossificans Progressiva





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D., for the ORAL Surveillance Investigators*

CONCLUSIONS

In this trial comparing the combined tofacitinib doses with a TNF inhibitor in a cardiovascular risk–enriched population, risks of MACE and cancers were higher with tofacitinib and did not meet noninferiority criteria. Several adverse events were more common with tofacitinib. (Funded by Pfizer; ORAL Surveillance ClinicalTrials .gov number, NCT02092467.)

Furuya *et al. Arthritis Research & Therapy* (2018) 20:196
https://doi.org/10.1186/s13075-018-1685-x

Paediatric rheumatology

CLINICAL SCIENCE

Safety and efficacy of tofacitinib for the treatment of patients with juvenile idiopathic arthritis: preliminary results of an open-label, long-term extension study

The use of JAK inhibitors, including tofacitinib, has been associated with herpes zoster events in adult patients with immune-mediated diseases such as rheumatoid arthritis, PsA and ulcerative colitis.[39–42] In the current study, herpes zoster infection did occur and appeared more frequent than what has been previously reported in JIA with biological DMARDs.[2–8] Herpes zoster events with tofacitinib occurred at an estimated mean rate of 0.58 per 100 patient-years of tofacitinib exposure in JIA. Notably, two of the four patients who experienced herpes zoster had been vaccinated against varicella zoster virus, while the other two patients had experienced varicella zoster prior to study start. This observation might prompt clinicians to carefully educate families regarding the risk of herpes zoster.

In ORAL Surveillance, cardiovascular risk-enriched adult patients with rheumatoid arthritis demonstrated a higher rate of MACE and cancers with tofacitinib, compared with tumour necrosis factor inhibitors[43]; risk differences of these outcomes were confined to patients who were ≥65 years of age, and/or long-time current/past smokers,[44] and those who had a history of atherosclerotic cardiovascular disease (MACE only).[45] While the current LTE study did not observe any cases of MACE or malignancies in a population of patients with JIA, and indeed, these differentiating risk factors are less applicable to the JIA population, the safety findings of ORAL Surveillance warrant a precautionary approach to apply these findings across all JAK inhibitors and all approved disease states, until data from additional dedicated safety studies (of sufficient size and duration) establish that this is not appropriate.

RESEARCH ARTICLE Open Access

Tofacitinib inhibits granulocyte–macrophage colony-stimulating factor-induced NLRP3 inflammasome activation in human neutrophils

Off-label

- Sirolimus (mTOR inhibitor) os
  - Japanese trial
  - Reported experience of 2 patients by Kaplan et al.
- Tofacitinib (JAK inhibitor) os
  - 12 patients
- Canakinumab (IL-1 inhibitor) sc
  - 4 patients

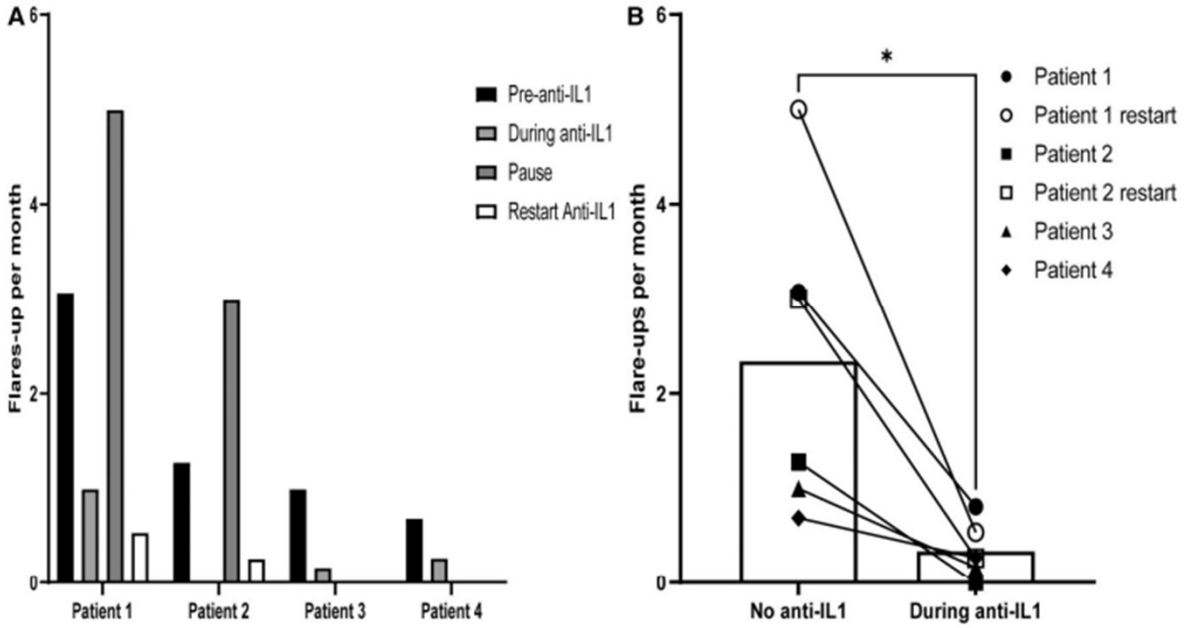
Off-label

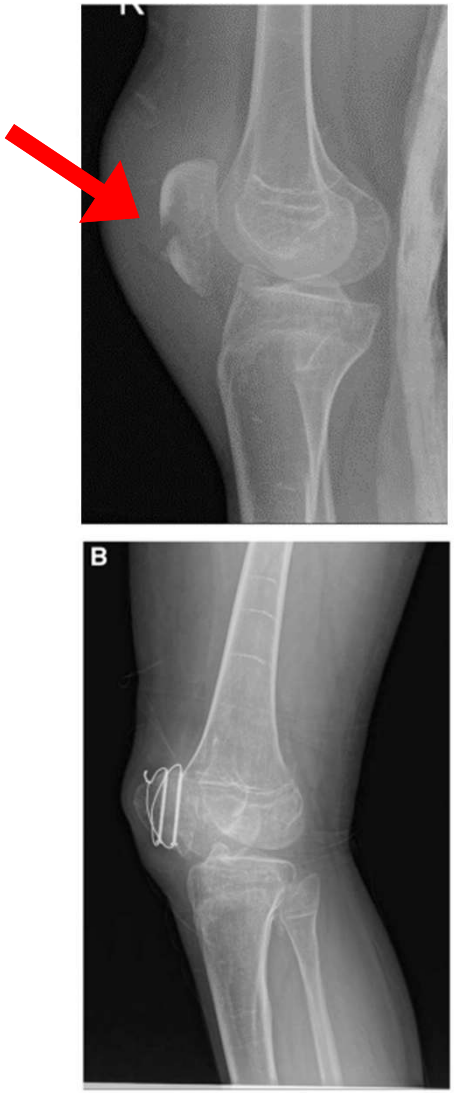
Rheumatology, 2024, **63**, 2597–2604
https://doi.org/10.1093/rheumatology/keae255
Advance access publication 11 May 2024
Original Article

British Society for Rheumatology RHEUMATOLOGY OXFORD

Basic science

Long-term use of interleukin-1 inhibitors reduce flare activity in patients with fibrodysplasia ossificans progressiva





Off-label

Arthritis & Rheumatology
Vol. 76, No. 6, June 2024, pp 949–962
DOI 10.1002/art.42808

American College of Rheumatology
Empowering Rheumatology Professionals

Clinical Characteristics of Cryopyrin-Associated Periodic Syndrome and Long-Term Real-World Efficacy and Tolerability of Canakinumab in Japan: Results of a Nationwide Survey

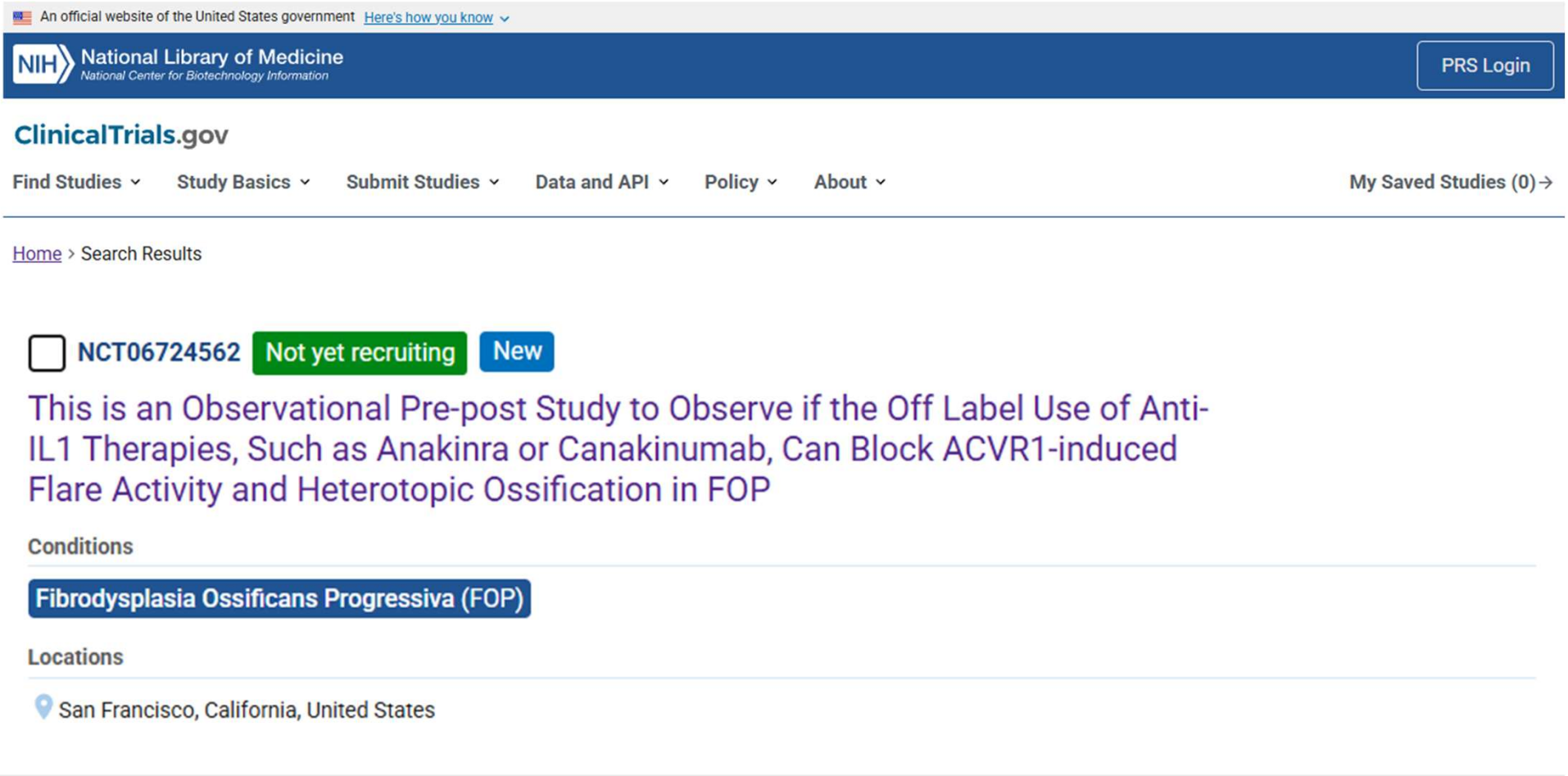
Objective. We assess the clinical characteristics of patients with cryopyrin-associated periodic syndrome (CAPS) in Japan and evaluate the real-world efficacy and safety of interleukin-1 (IL-1) inhibitors, primarily canakinumab.

Methods. Clinical information was collected retrospectively, and serum concentrations of canakinumab and cytokines were analyzed.

Results. A total of 101 patients were included, with 86 and 15 carrying heterozygous germline and somatic mosaic mutations, respectively. We identified 39 mutation types, and the common CAPS-associated symptoms corresponded with those in previous reports. Six patients (5.9% of all patients) died, with four of the deaths caused by CAPS-associated symptoms. Notably, 73.7% of patients (100%, 79.6%, and 44.4% of familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and chronic infantile neurological cutaneous articular syndrome/neonatal onset multisystem inflammatory disease, respectively) achieved complete remission with canakinumab, and early therapeutic intervention was associated with better auditory outcomes. In some patients, canakinumab treatment stabilized the progression of epiphysial overgrowth and improved height gain, visual acuity, and renal function. However, 23.7% of patients did not achieve inflammatory remission with crucial deterioration of organ damage, with two dying while receiving high-dose canakinumab treatment. Serological analysis of canakinumab and cytokine concentrations revealed that the poor response was not related to canakinumab shortage. Four inflammatory nonremitters developed inflammatory bowel disease (IBD)—unclassified during canakinumab treatment. Dual biologic therapy with canakinumab and anti–tumor necrosis factor-α agents was effective for IBD– and CAPS-associated symptoms not resolved by canakinumab monotherapy.

Conclusion. This study provides one of the largest epidemiologic data sets for CAPS. Although early initiation of anti–IL-1 treatment with canakinumab is beneficial for improving disease prognosis, some patients do not achieve remission despite a high serum concentration of canakinumab. Moreover, IBD may develop in CAPS after canakinumab treatment.

Off-label


An official website of the United States government Here's how you know
NIH National Library of Medicine
National Center for Biotechnology Information
PRS Login
ClinicalTrials.gov
Find Studies
Study Basics
Submit Studies
Data and API
Policy
About
My Saved Studies (0)
Home > Search Results
NCT06724562
Not yet recruiting
New
This is an Observational Pre-post Study to Observe if the Off Label Use of Anti-IL1 Therapies, Such as Anakinra or Canakinumab, Can Block ACVR1-induced Flare Activity and Heterotopic Ossification in FOP
Conditions
Fibrodysplasia Ossificans Progressiva (FOP)
Locations
San Francisco, California, United States

Off-label

Eligibility Criteria

Description

Inclusion Criteria:

- Patients with a clinical presentation consistent with FOP and a genetic diagnosis of classical FOP (ACVR1R206H variant) (2), male or female aged 6-17 years old.
- Patients with unusually severe FOP disease activity. This will be determined by FOP flare frequency of >6 flares per year, which is 3 times higher than the reported average in prior FOP studies ; or by a persistent flare that has failed to resolve after 3 months of standard-of-care therapy.
- Patients whose primary medical team has decided that rescue therapy with an anti-IL1 medication should be initiated. Once the primary medical team has decided that anti-IL1 therapy should be pursued, the subject will be told about this clinical-observational study and enrolled in the pre-treatment phase while access to the anti-IL1 therapy is being obtained by the clinical management team.
- Ability to participate in all assessments, including blood draws, radiology assessments, and travel. Age 6 is chosen as the lower limit to avoid the need for anesthesia for whole body CT in younger subjects.
- No history of unexplained infections, known autoimmune disease, or contraindication to anti-IL1 therapy.
- Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

Exclusion Criteria:

- Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
- Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
- Inability to travel to site for assessments
- Pre-existing autoimmune or autoinflammatory disease (aside from FOP)
- Inability to tolerate assessments (such as phlebotomy)
- Unexplained infections
- Current participation in an interventional trial, or study of a potentially disease modifying medication
- Inability to take medications as prescribed by managing physician

Ages Eligible for Study

6 Years to 17 Years (Child)

Sexes Eligible for Study

All

Accepts Healthy Volunteers

No

Sampling Method

Non-Probability Sample

Conclusions

- Nuovi geni associati a ossificazione eterotopica
- In programma esperienze di laboratorio per approfondire il meccanismo infiammatorio alla base delle riacutizzazioni di malattia
- Trials di fase 2 e 3 con farmaci (forse) efficaci e (per ora) sicuri
- Farmaci off-label per i pazienti non arruolabili nei trials che presentano frequenti riacutizzazioni e/o uso frequente di cortisone
- Futura possibilità di chirurgia ortopedica mirata nei pazienti con malattia controllata

UOC Reumatologia e Malattie Autoinfiammatorie

Dir. Dott. Marco Gattorno

Prof. Dott. Stefano Volpi

Dott. Roberta Caorsi

Dott. Riccardo Papa

Dott.ssa Caterina Matucci-Cerinic

Laboratorio Immunologia

Dott.ssa Ignazia Prigione

Dott.ssa Federica Penco

Dott.ssa Arinna Bertoni

Dott.ssa Cristina Scarone

UOC Genetica Medica

Prof.ssa Renata Bocciardi

UOC Radiologia

Dott. Luca Basso

Dott. Luca Tovt

UOC Psicologia

Dott.ssa Elena Pescio

UOC Otorinolaringoiatria

Dott. Tommaso Cacco

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Grazie per l'attenzione

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