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STONEMAN SYNDROME – A DISORDER CAUSING SECOND SKELETON IN THE BODY

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Abstract:

Fibrodysplasia ossificans progressiva (FOP) is a very rare disorder with a worldwide prevalence of approximately 1 in 2 million population. The age of onset is mostly in the first two decades of life, and there is no ethnic, racial, gender, or geographic predilection of FOP. Stone man syndrome is also known Fibrodysplasia ossificans progressiva (FOP) is an extremely rare genetic disorder which is characterised by heterotopic ossification of the connective tissue and congenital malformation of the big toes. Currently this disease exists in 67 countries with 834 confirmed cases across the world. The FOP is caused by the mutation in the gene $ACVR_1$ (ALK_2). The symptoms of FOP are bone forming on muscles, ligaments, and connective tissue, decreased mobility, difficulty eating or speaking, hearing impairment etc., are the symptoms for the FOP. The diagnosis of the FOP can be done by plain X-rays can reveal abnormal osteogenesis after heterotopic ossification manifests. CT scan can also show lesions with typical heterotrophic ossification. MRI can reveal pre-osseous lesions, which appear as soft tissue swelling and skeletal malformations. There is no single effective treatment option available for fibrodysplasia ossificans progressive. Mast cell inhibitors, NSAIDS, amino bisphosphonates, and COX-2 inhibitors are used for treating later flare-ups. We need to spread knowledge to physicians and patients' family members about the disease, as well as its features for early diagnosis and how to prevent flare-up of the disease to promote better quality of life in these patients. This includes most recent updates in the definition, epidemiology, signs and symptoms, etiopathogenesis, and treatment of FOP. We need to educate clinicians and patients' families concerning the disease, as well as its symptoms for early detection and how to prevent flare-ups, in order to improve quality of life.

Key words: *Stone man syndrome, fibrodysplasia ossificans progressiva, COX-2 inhibitors.*

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INTRODUCTION:

Stoneman syndrome also known as Fibrodysplasia Ossificans Progressive (FOP) or Munchmeyer disease, rare genetic disorder of heterotopic ossification (HO), is the severe disabling condition of extra skeletal ossification known to human species. As the name suggests the patient becomes like a stony figure which is caused due to the gene mutation of Activin A receptor, type1 ($ACVR_1$). FOP causes disability in moment through progressive metamorphosis of skeletal muscle and soft connective tissue forming into a second skeleton in the body. The frequency of this disease is approximately 1 in 2 million. Currently this disease exists in 67 countries with 834 confirmed cases across the world. Currently there is no effective treatment to this disease[1-3].

History of FOP

The FOP was first described more than 250 years ago by Guy Patin met with a patient in 1692 and described about it in his letter. A London physician in letter to The Royal Society of Medicine, on 14th April 1736 from John Freke of Saint Bartholomew's Hospital, London Stating: 'There came a boy of healthy look, and about 14 years of age, to ask of us at the hospital, what should be done to cure him of many large swellings on his back, which began about 3 years since, and have continued to grow as large on many parts as a penny loaf particularly on the left side. They arise from all the vertebrae of the neck and reach down to the os sacrum; they likewise arise from every rib of his body, and joining together in all parts of his back, as the ramifications of coral do, they make as it were, a fixed bony pair of bodices.

After 200 years of this incident in 1918, Jules Rosenstirn from Mount Zion Hospital in San Francisco, USA stated: 'One does not wonder that a disease, so baffling in its course from the first causes to its ultimate state, should invite the speculative as well as the patiently investigating observer to lift the obscuring veil and solve this embarrassing puzzle'. FOP is still a medical mystery which is very painful metamorphosis which turns into immobility and a lifelong obstacle for freedom of physical life. Eventually when this disease progresses the life expectancy of the patience gradually decreases as this disease also vital parts of the body[3-7].

Epidemiology and prevalence of FOP

The FOP is an Extremely rare genetic disorder with the frequency of approximately in 1 in 2 million. It affects all ethnicities which does not have any ethnic, racial, gender or geographical conditions. The disease is currently in 67 countries with 837 confirmed cases in which 445 are females and 387 are males and 2 without assigned gender reported in the 2016 global analysis. The most of the cases are in the North America Region (United states, Canada) with 231 cases reported which accounts to 28% of the total cases reported, followed by Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Malta, Norway, Portugal, Netherlands, Spain, Switzerland, Sweden, United Kingdom) with 198 cases accounting to 24% of total cases. Latin America (Argentina, Bolivia, Brazil, Chile, Columbia, Cuba, Ecuador, Guatemala, Honduras, Mexico, Panama, Paraguay, Peru, Uruguay, Venezuela) with 161 cases with 19 % of total cases. Aisa-Pacific (Bangladesh, China & Taiwan, Hong Kong, India, Indonesia, Iran, Israel, Japan, Kazakhstan, Malaysia, North Korea, Pakistan, South Korea, Turkey) with 132 cases accounting to 16% of total cases.

Eastern Europe (Armenia, Belorussia, Bosnia-Herzegovina, Croatia, Estonia, Georgia, Macedonia, Moldova, Poland, Romania, Russia, Serbia, Ukraine) with 87 cases accounting 10% of total cases. Oceania (Australia, New Zealand) with 15 cases accounting 2% and Africa (Egypt, Libya, South Africa, Sudan) with 10 cases accounting to 1% of the total cases. The age group between 20-29 are the ones who got most affected by this disease with 209 cases that is 25%, next comes the age group of 10-19 with the 194 cases and least was recorded between age group of 70-79 with 0.5%. The prevalence of this disease is 0.5 per million individuals and 13 of the 67 countries has more than 0.5 per million individuals. The 13 countries Includes Sweden, Finland, Denmark, United Kingdom, Norway, United States, Poland, Chile, Argentina, Australia, Canada, Netherlands, and Italy has more than 0.5 prevalence rate per million. The trend of seeing the onset of FOP in the age group of 20-29 is due to the delay in diagnosis and detection of the disease in early age and stages[8-11].

Table 1: Epidemiology of FOP by region according to 2016 reports

Region	Number of countries	Cases reported	Percentage (%)
North America	2	231	28
Western Europe	17	198	24
Latin America	15	161	19
Asia-Pacific	14	132	16
Eastern Europe	13	87	10
Oceania	2	15	2
Africa	4	10	1
Total	67	834	100

Table 2: Distribution of FOP in individual according to the age group

Age group (years)	Individual with FOP	Percentage (%)
0-9	97	11.6
10-19	194	23.3
20-29	209	25
30-39	133	15.9
40-49	89	10.7
50-59	47	5.6
60-69	13	1.6
70-79	4	0.5
No data	48	5.8
Totals	834	100

Signs and symptoms

The clinical diagnosis of classical FOP can be defined by two feature one is by the malformation of the great toes; and progression of Heterotopic ossification in the skeletal muscle. Individual with FOP appear to be normal at the of birth but the characteristic malformation of great toes which is present in FOP condition. First decade life the of patient suffering from FOP develop painful and highly inflammatory soft tissue swellings that turns soft connecting tissues, aponeuroses, fascia, ligaments, tendons, and skeletal muscles into bone. Nearly 50% of cases of FOP also have malformations of the thumbs like the big toe. To due to the excessive conversion of the skeletal muscles into the bone there is a restriction in the mobility.

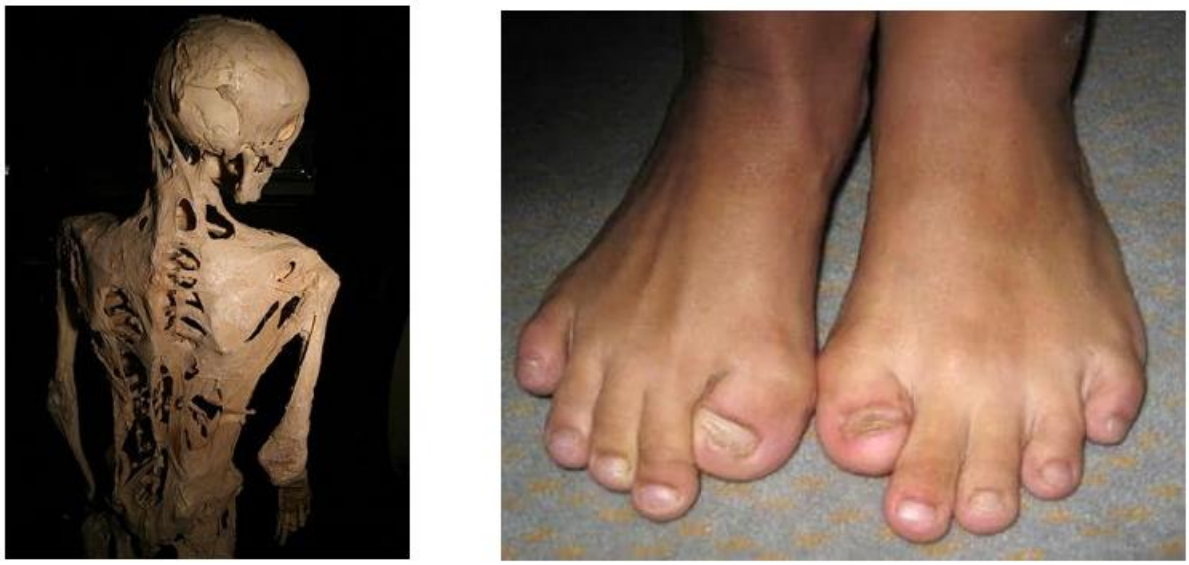

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Figure 1: The clinical manifestation of the Fibrodysplasia Ossificans Progressiva. A) Damaged skeletal muscle turning into bone due to the FOP, B) Deformation of the great toes indicating the FOP condition at the early stages.

Sometimes patient suffering from FOP may have some difficulties in eating, speaking, hearing impairment. There are few red to purple colour lesions present on the neck and back and sometimes present on the limbs which are often mistaken to be tumours these are most common in the patient suffering with FOP. Skeletal muscles like tongue, diaphragm and extraocular muscles may turn into bone, but FOP do not affect the Cardiac Muscle and smooth muscle. Later progression of disease occurs in the appendicular, ventral, distal and caudal regions.

Bone Formation is a periodic, but disability is progressive in the patient life. Most of the patients at end of their life they require assistance and a wheel chair to perform their daily activities. Severe weight loss takes place due to lowing of ankylosis of the jaw. Pneumonia or right-side heart failure complication may happen due to rigid fixation of the chest wall. The average age for survival of the patient is 45 years and death often result from complication of thoracic insufficiency syndrome (TIS)[11,12].

Pathophysiology of FOP

FOP is an autosomal disorder, caused due to the mutation of $ACVR_1$ gene. The full form of $ACVR_1$ is Activin A receptor type I. It is also known as ALK_2, located in chromosome 2q23-q24 and encodes for the 509 amino acid protein (UniProtKB: Q044771). This $ACVR_1$ gene encodes for bone morphogenetic pathway type I receptor which belongs to the family TGF-β receptor superfamily. The mutation on the $ACVR_1$ gene causes the FOP specially on R206H codon. Mutation on the $ACVR_1$ Causes the substitution of R206H codon from arginine to histidine in $ACVR_1$ protein, resulting in the abnormal activation, leading to the transformation of connective tissue and muscles in a bone which includes cartilage and skeletal muscles as these tissues contains $ACVR_1$ which is responsible for the growth and development of the muscle. As $ACVR_1$ is a type of BMP receptor. Bone morphogenetic protein (BMP) receptors are serine- threonine kinase receptors and TGF-β family proteins bind to these receptors for paracrine signalling.

In 2006 it was found that the Arg206His (R206H) $ACVR_1$ gene mutation was responsible for FOP. R206H mutation results in ligand-independent BMP signalling and enhances BMP responsiveness via increased SMAD1/5/8 signalling. When ligands which are responsible for the growth bind with the $ACVR_1$ receptors, intracellular signalling is regulated by the regulatory molecules called as Receptor regulated SMAD (mothers against decapentaplegic) shortly R-SMAD. These are those transcriptional factors which are responsible for transduce the extracellular ligand signalling from cell membrane bound to $ACVR_1$ receptors which targets the $ACVR_1$ genes. There are numerous SMAD molecules that are signalled by distinct signalling molecules, including SMAD1/2/3/5/8, which are R-SMAD's, and SMAD4, which is also known as a common partner SMAD (Co-SMAD), which aids in intracellular signalling when R-

SMAD's are activated. I-SMADs, also known as inhibitory SMADs (SMAD6/7) compete with SMAD4 to modulate $ACVR_1$-regulated transcription.
TGF type 1 monomer and TGF type 2 monomer are the two monomeric receptor subunits of TGF superfamily receptors. Type 2 monomers feature extracellular cysteine rich regions for ligand binding, which induces dimerization of type 2 receptors and signalling recruitment of type 1 receptors owing to type 2 receptor kinase activity. phosphorylates serine residues in the intracellular domain of type 1 receptors, generating a heterotetrametric complex, attracts R-SMADs, and binds to tetrameric complexes at the type 1 receptor's L-45 region.

R-SMAD recruitment is aided by SARA proteins, which attach the cell membrane and assist RSMADs in binding to type 1 receptors. Type 1 receptor kinase activity phosphorylates R-SMADs, creating a conformational change at their MH2 domain (active RSMAD). When R-SMAD is activated, it signals the binding of Co-SMAD, resulting in the formation of the R-SMAD Co-SMAD Complex, which transcribes the genes that govern osteogenesis, neurogenesis, and ventral mesoderm specification. Activin-A is a ligand for TGF receptors, which drive intracellular signalling via SMAD2/3. However, in the R206H mutation, activin-A activates SMAD1/5/8, enhancing endochondral ossification and chondrogenesis which is ligand independent BMP signalling. As a result, secondary skeleton building (heterotopic ossification) occurs in the soft tissues, restricting movement[12-14].

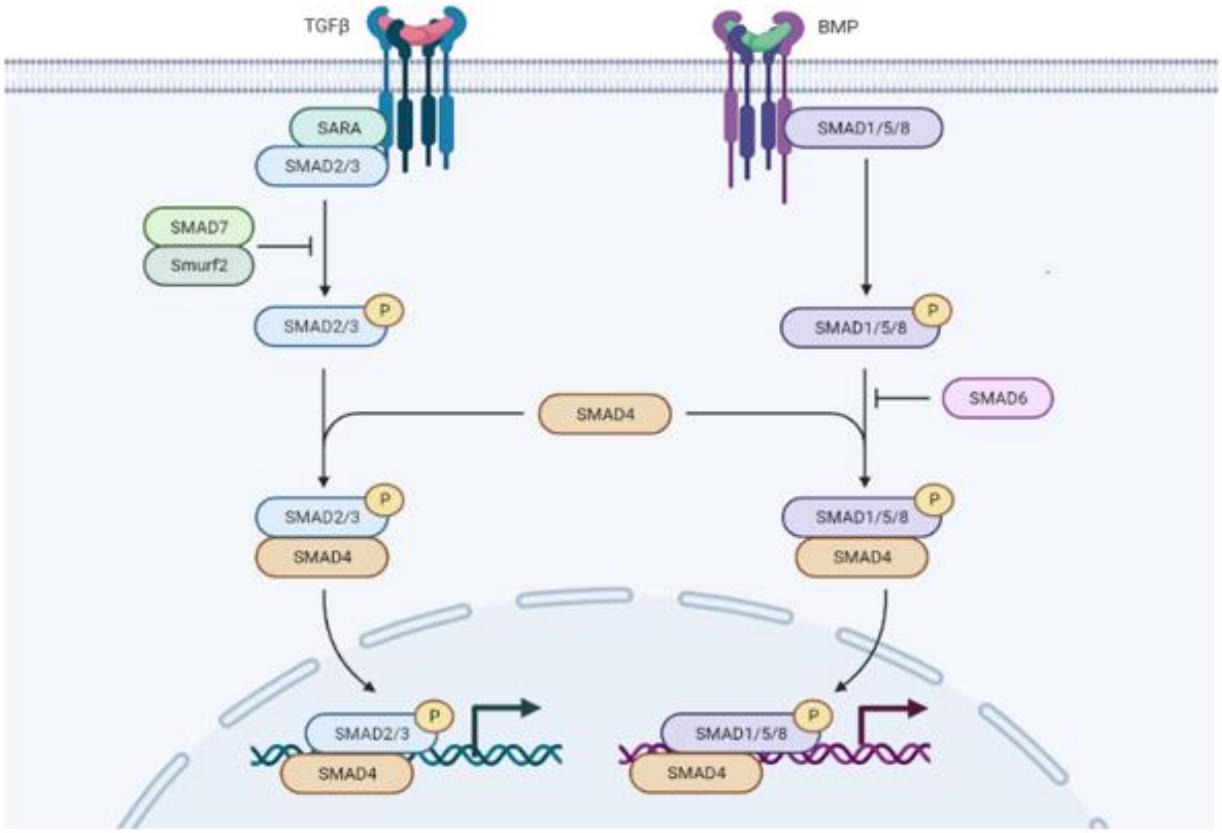

Figure 2: Mutation of ACVR1 Gene causing the change of cartilage and skeletal muscle into bone

Diagnosis
FOP is a rare genetic disorder which causes immobility in the body which does not have any viable treatment that can cure and prevent the progression. Early clinical scepticism of FOP is based on deformed great toes, which can aid in early clinical diagnosis and treatment by averting adverse repercussions later in life. The radiographic imaging findings are used to make the diagnosis. Atypical bone scans reveal heterotopic ossification. Magnetic resonance imaging also aids in early detection prior to ossification; early diagnosis is advantageous in avoiding unneeded intrusive investigations such as biopsies and intramuscular injections, which would worsen the illness condition's development with inflammation. As a result, thorough awareness of this illness state is

critical for radiologists to prevent such intrusive tests. Palpation demonstrates soreness in all visible masses as well as stiffness in all abdominal and paraspinal muscles.

Laboratory test Shows a subtle rise in erythrocyte sedimentation rate, and conventional biochemical assessments of bone mineral metabolism are normally normal, albeit serum alkalinity is elevated. Phosphatase activity may be elevated, particularly during illness flare-ups. During illness flare-ups that coincide with the pre-osseous angiogenic phase of fibroproliferative lesions, urinary basic fibroblast growth factor levels may be raised. The genetic testing can also be used in the diagnosis. A particular mutation in the $ACVR_1$ gene (Activin A receptor, type I) can be used to confirm FOP. Most people with classic FOP have a particular mutation in the $ACVR_1$ gene. DNA taken from blood or saliva samples is commonly used in genetic testing.

The diagnosis is confirmed by imaging tests such as computed tomography and radiography that reveal heterotopic bones. Multiple ectopic osseous growths in the soft tissues of the posterior parts of the neck, chest, and abdomen wall can be seen on radiographs of the neck, chest, and foot.

Radiographs of the hands and knee may reveal short first metacarpals with bilateral and sharp bony outgrowths in the medial aspects of the tibia, which are called pseudo exostoses due to their close resemblance to osteochondromas (exostoses). Radiographs of the feet may show bilateral hallux valgus deformity, deformity great toe, short first metatarsal with normal cervical vertebral bodies and posterior elements, giving a strong suspicion of FOP[14,15].

Misdiagnosis of FOP

Although incorrect diagnoses of FOP are frequent, they can be prevented by looking for an early indication of great toes in a person. Clinical professionals frequently misdiagnose FOP as aggressive juvenile fibromatosis, dermatomyositis, lymphedema, or soft-tissue sarcoma. Additionally, FOP needs to be distinguished from nonhereditary (acquired) heterotopic ossification (HO) and other genetic disorders of HO.

Progressive osseous heteroplasia (POH) is a rare genetic condition of progressive heterotopic ossification (HO) that is characterized by cutaneous ossification. It is primarily a childhood condition that progresses with the involvement of subcutaneous and deep connective tissues, including muscle and fascia, without the presence of multiple features of Albright hereditary osteodystrophy (AHO) or hormone resistance. Congenital deformity of the great toes, perosseous inflammation known as "flare-ups," and the lack of cutaneous ossification distinguish FOP from POH. Thus, the radiographic characteristics of FOP include soft tissue ossification and joint malformations. The presence of proximal medial tibial osteochondromas and abnormalities of the great toes, thumbs, cervical spine, and proximal femurs might further confirm the diagnosis.

Management and treatment of FOP

For FOP, there is currently no effective medical intervention to stop, prevent, or reverse heterotopic ossification. In FOP, damaged tissue, and muscle exhibit aberrant expression of an enzyme necessary for bone repair, which promotes lymphocyte recruitment and excessive BMP-4 production, both of which lead to the development of new bone. Research is underway to inhibit the hyperactive $ACVR_1/ALK_2$ signaling pathway, which would obstruct heterotopic ossification particularly.

Currently, supportive therapy for FOP is based on early diagnosis, preventing iatrogenic harm and injuries, giving conservative analgesic relief during painful flare-ups, maintaining residual functions, and ultimately utilizing surgery as a last resort. When there is severe discomfort, joint restriction, or nerve compression, surgical excision may be recommended. When myositis ossificans is mature, as evidenced by elevated bone density in x-ray results and normal erythrocyte sedimentation rate and alkaline phosphatase level, surgery is usually recommended. At the onset of flare-ups, corticosteroids are recommended as the first line of therapy. Within the first 24 h of a flare-up, a quick 4-day course of high-dose corticosteroids may help lessen the severity of tissue edema and inflammation that are frequently observed in the early stages of the disease.

Restricted use of corticosteroids is recommended when treating flare-ups involving the jaw, submandibular region, and major joints. since of their recurrent nature and extended length, corticosteroids are often not utilized for the symptomatic treatment of flare-ups involving the back, neck, or trunk since it can be challenging to determine when they begin. Prednisone is often given as a single daily dosage of 2mg/kg. If a second round of corticosteroids is required, a gradual reduction in dosage should come next. Limiting children's opportunities for physically involved play may help prevent falls. To reduce the risk of injury from falls in children, techniques such as

modifying activities, using ambulatory devices, improving household safety, and wearing protective headgear are recommended.

The goal of physical rehabilitation is to enhance activities of daily life by avoiding passive range of motion, which increases the risk of illness flare-ups. Consultations with occupational therapists and vocational educators might be beneficial. Mast cell inhibitors, NSAIDS, amino bisphosphonates, and COX-2 inhibitors are used for treating later flare-ups. Many drugs, such as imatinib, a human anti-activin A-neutralizing antibody, dorsomorphin, palovarotene, rapamycin, are in clinical trials, and suitable drugs may be available in the coming future concerning the better understanding of the mechanism of onset of fibrodysplasia ossificans progressiva.

The use of corticosteroids should be restricted to treatment of flare-ups that affect major joints, the jaw, or the submandibular area. Corticosteroids should not be used for symptomatic treatment of flare-ups that involve the back, neck, or trunk, owing to the long duration and recurring nature of these flare-ups and the difficulty in assessing the true onset of such flare-ups. When prednisone is discontinued, a nonsteroidal anti-inflammatory drug or a Cox-2 inhibitor (in conjunction with a leukotriene inhibitor) may be used symptomatically for the duration of the flare-up. None of these drugs avoided the progression of the disease in our patient[13,15,16].

Ongoing clinical research on FOP

Target inhibition of the $ACVR_1$ receptor, $ACVR_1$ ligand, BMP intracellular signaling, and inflammatory triggers of disease activity have been the focus of several studies to create therapeutic medicines. Recently, there have been exciting developments in novel therapy techniques for FOP. Exogenous retinoid agonists can efficiently and quickly inhibit chondrogenesis since retinoid signaling is often reduced throughout this process. In a transgenic mouse model of familial orthoplasia, retinoic acid receptor agonists (PARα or RARγ) experimentally suppressed the chondrogenesis of heterotopic ossification; the RARγ agonists were much more efficient in this regard.

Palovarotene, a highly selective RARγ agonist, has been assessed in a previous clinical study for α-1-antitrypsin-induced emphysema and has a well-established safety profile. It is one of the medications in the RARγ family. In a mouse model of FOP, palovarotene prevents heterotopic ossification while preserving limb development and mobility. Another set of phases 2 trials is assessing the efficacy of palovarotene in treating hereditary multiple exostoses by inhibiting the growth of osteochondromas. Clementia Pharmaceuticals started phase 2 clinical studies in 2014 to assess the safety and effectiveness of palovarotene as a therapy for FOP. Comparing the amount of heterotopic ossification development between patients who received treatment and those who did not was the main goal.

Palovarotene reduced patient-reported pain, the time it took for flare-ups to resolve, and the proportion of FOP patients that develop heterotopic ossification. The phase three experiment is going on right now. Palovarotene is a recognized teratogen that can stunt a child's growth and cause deformities in the limbs of the developing baby. Palovarotene may also increase your risk of pancreatitis, hearing loss, visual impairment, mouth ulcers, UV sensitivity, and dry skin. Throughout the studies, these side effects are meticulously observed.

The $ACVR_1$ receptor misinterprets activin A due to the R206H mutation, resulting in a signal indicating the presence of BMP ligands. When activin A was injected, the $ACVR_1$ mutant mice experienced increased heterotopic ossification across their skeletons; in contrast, the animals administered with an activin A blocking antibody did not experience heterotopic ossification. Therefore, activin A is a necessary secreted factor that must be present for the onset of heterotopic ossification in FOP, and inhibiting activin A may stop heterotopic bone from forming. Following preclinical research, a clinical study is now being conducted on adult patients with FOP to evaluate the safety, tolerability, and effectiveness of REGN 2477 (garetosmab), an antibody that binds to activin A and suppresses its action.

Through aberrant BMP signaling activation in vitro and endochondral ossification in vivo, activin A promotes the chondrogenesis of induced mesenchymal stromal cells produced from FOP patients-derived induced pluripotent stem cells (FOP-iPSCs). preventing the action of mTOR1 kinase. In both FOP-iPSC-based heterotopic ossification model mice and FOP-model mice, rapamycin therapy reduced heterotopic ossification. In Japan, a phase 2 clinical trial for an open-label extension study and a 6-month randomized placebo-controlled study is now accepting participants. Using the Japanese version of the health evaluation Questionnaire or Childhood Health Assessment Questionnaire, objective physical function evaluation serves as the primary endpoint for assessing the efficacy of rapamycin.

Saracatinib, commonly referred to as AZD0530, is an experimental medication that was first created to potentially treat cancer patients. By directly inhibiting BMPR-I kinase activity, Saracatinib prevents the serum activation of Id1, a transcriptional factor mediated by Smad 1/5/8 phosphorylation. Additional studies showed that Saracatinib was also efficient in inhibiting the heterotopic ossification or bone formation in several FOP animal models, as well as the improved chondrogenesis of FOP-iPSCs. In the Netherlands, the UK, and Germany, a phase 2A proof of concept research is suggested that consists of a 6-month randomized placebo-controlled study plus a 12-month open label extension study utilizing historical data[10,12,17].

Future directions and recommendations

One of the key future directions in the development of novel therapeutic targets for FOP is the continued identification and validation of targets. Advanced techniques such as genomics, proteomics, and high-throughput screening can aid in the identification of potential targets. By studying the genetic and protein profiles of individuals with FOP, researchers can identify specific molecules or pathways that are dysregulated in the disease. Validating these targets through in vitro and in vivo studies, as well as utilizing animal models that accurately recapitulate FOP characteristics, will be crucial in confirming their therapeutic potential.

As novel therapeutic targets for FOP are identified and experimental treatments are developed, rigorous safety and efficacy assessments are essential. Preclinical studies provide valuable insights into the potential risks and benefits of new treatments. These studies should encompass various aspects, including toxicity assessments, pharmacokinetics, and pharmacodynamics evaluations. Animal models that accurately represent FOP pathophysiology will be crucial in assessing the safety and efficacy of potential treatments. Moving forward, clinical trials will play a crucial role in evaluating the safety and efficacy of experimental therapies in human subjects. Rigorous trial designs, including randomized, double-blind, placebo-controlled studies, will be necessary to establish the effectiveness of new treatments. Long-term follow-up assessments will be vital to monitor treatment outcomes, including disease progression, quality of life, and adverse effects.

The successful translation of novel therapeutic targets into effective treatments for FOP requires the optimization of delivery methods. Gene therapy approaches, such as CRISPR-Cas9 and RNAi, rely on efficient and targeted delivery of therapeutic agents to the affected tissues. Finding effective ways to deliver these agents directly to the site of abnormal bone formation will be crucial for maximizing their therapeutic potential. Various delivery methods can be explored, including viral vectors, nanoparticles, and exosome-based approaches. Each method has its advantages and limitations in terms of efficiency, safety, and target specificity. Ongoing research should focus on optimizing these delivery methods to ensure effective and precise targeting of therapeutic agents to the affected tissues in FOP.

CONCLUSION:

Stoneman syndrome is a rare genetic disorder which turns the skeletal muscles and connective tissue into bone. Currently there is no proper treatment for this disease. The present treatment options being used for reduce the patient complaints and gives symptomatic relief are using mast cell inhibitors, NSAIDS, amino bisphosphonates, and COX-2 inhibitors are used for treating later flare-ups. Currently the research is going on the drugs like saracatinib, rapamycin, palovarotene, imatinib, a human anti-activin A-neutralizing antibody, dorsomorphin for better treatment of FOP. However, ongoing research and clinical trials provide hope for improved management strategies and treatment options. Future directions include further identification and validation of targets, rigorous assessment of safety and efficacy, optimization of delivery methods, patient selection and stratification, and exploration of combination therapies. Through unraveling the complex mechanisms of FOP and developing targeted therapies, the goal of improved outcomes, disease modification, and ultimately finding a cure for FOP can be pursued.

Competing interests

The authors declare that they have no competing interests.

Ethical approval

Not required

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