REVIEW ARTICLE

Fibrodysplasia Ossificans Progressiva: Molecular Mechanism, Drug Development and Current Clinical Trials

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ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic human disease characterized by abnormal bone formation in muscle and soft tissues of the patient, due to dysregulated activity of the bone morphogenetic protein (BMP) signaling. Activin A receptor type I (ACVR1), also known as Activin-like kinase 2 (ALK2), is a key BMP type I receptor for the normal BMP signaling transduction. The heterozygous missense mutations in ALK2 are the root cause of FOP, and ALK2^{R206H} accounts for approximately 97% of all FOP cases. Cumulative studies have shown that Activin A, which normally activates TGF - β signaling, can induce the BMP signaling via ALK2 mutated receptor in FOP. In the past decade, multiple therapeutical strategies have been developed and several potential drugs are under clinical trials for FOP now. This article specifically focuses on the recent progress in understanding the molecular mechanism, potential drug development and the clinical trials for FOP treatment. (*Int J Biomed Sci* 2023; 19 (1): 18-25)

Keywords: Fibrodysplasia ossificans progressive; BMP signaling; ACVR1; TGF-β signaling; ALK2; Activin A; heterotrophic ossification; Palovarotene

INTRODUCTION

FOP is a rare genetic disorder characterized by progressive heterotopic ossification, the development of extraskeletal bone in muscle and soft tissues, affecting one in about two million people worldwide without specified ethnic, racial, or gender selectivity (1, 2). Malformed great toes at infantry are common clinical signs of this disease, and spontaneous or stimulated flare-ups heighten the degree of ossification, rendering many patient's wheelchair bound (3). A heterozygous mutation, arginine to histidine substitution at position 206 (R206H) in ACVR1 gene, was first identified in 2006, and it accounts for about 97% FOP cases (4, 5). Later approximately another nine causative mutations in ACVR1 have been found (6, 7). ACVR1, also known as ALK2, is a type I receptor of BMP. In normal condition, ALK2 only mediates the ligands-induced BMP signaling activation. However, in FOP, the mutated ALK2 can abnormally mediate the activin A-induced BMP signaling activation. This abnormal activin A-induced BMP signaling is believed to account for heterotopic ossification of connective tissues in FOP (8, 9). However, how Activin A, the ligand which normally signals the TGF-beta signal-

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ing, can cross-signal the BMP signaling remains poorly understood. In addition, significant efforts have been made in the past to develop drugs targeting activin A, ALK2 and others, and several drugs are currently under clinical trials. In 2022, Palovarotene was first approved by Health Canada for the treatment of FOP patients in Canada. In this article, I specifically focus on recent advances in understanding the disease mechanism, drug development, and current clinical trials in FOP.

HISTORY OF FOP

The first FOP case can be traced back to as early as 1692, when French physician Guy Patin described a patient as a "stone man", but the first well-documented FOP case was made by London surgeon John Freke in 1736, who described large swellings extending from the skeleton of a patient, joining together sections of the patient's back (10). Freke wrote: "April 14, 1736, there came a boy of healthy look and 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 three 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 bodice" (11).

In the centuries to follow, many physicians contributed to the knowledge of the FOP disorder. The term myositis ossificans progressiva (MOP) was assigned to this disorder by Von Dusch in 1868 for the episodic inflammatory flare-ups in skeletal muscle (10). Notably, malformation of the great toes was identified as a universal symptom to all the MOP patients by Frankel and Helferich (10). Until 1972, MOP was renamed as FOP by Victor McKusick, to account for the inflammatory events in the aponeuroses, fasciae, and tendons in addition to those in skeletal muscles (12). One of significant advances in our understanding FOP disease is the discovery of the first and the most common heterozygous missense causative mutation (617G>A; R206H) in ALK2 by Frederick Kaplan in 2006 (4). ALK2 as a type I receptor mediates the BMP signaling, an essential pathway for the skeleton formation and embryonic patterning (4). It has been thought that mutated ALK2 is constitutively active, and results in the basal leaky BMP signaling in the absence of BMP ligands or overactivation of BMP signaling in the presence of BMP ligands, leading to the ectopic endochondral ossification in FOP (3).

BMP SIGNALING IN FOP

BMP ligands are a class of signaling molecules that play important roles in a diverse range of cellular activities including apoptosis, embryonic development, and differentiation (13). When binding to an extracellular domain of the BMP receptors, the ligands trigger a sequential phosphorylation pathway, in which BMP type II receptors activate the type I receptors through phosphorylating the glycine-serine-rich intracellular domain of the type I receptors (Figure 1). Subsequently, the phosphorated type I receptors further phosphorylate intracellular Smad1/5/9 proteins, which then form a proteins complex with Smad4 protein, and migrate into the nucleus to regulate the transcription process of BMP target genes. BMP type I receptors have four members including ALK1, ALK2, ALK3 and ALK6, and mutated ALK2 (such as $ALK2^{R206H}$) can abnormally induce basal leaky BMP signaling in the absence of BMP ligands and hyper-responsiveness in the presence of BMP ligands, which have been thought to lead to heterotopic ossification in FOP. Nevertheless, new studies have demonstrated that activin A abnormally mediates the Smad1/5/9-dependent BMP signaling via mutated ALK2 receptor in FOP whereas activin A normally only transduces the TGF-β signaling by using ALK4 and ALK7 as type I receptors through Smad2/3 phosphorylation (14, 15). Understating of FOP mechanism has greatly advanced drug development for FOP the treatment.

DRUG DEVELOPMENT FOR FOP

Potential Drugs targeting activin A

As aforementioned, activin A typically signals the TGF-β pathway by using ALK4 or ALK7 as type I receptors and Smad2/3 as intracellular signal transducers under physiological condition. But in FOP pathological condition, activin A can abnormally activate the BMP signaling via the mutated ALK2 receptor-mediating Smad1/5/9. This discovery represents an important breakthrough in the understanding of FOP mechanism and offers a critical basis for developing drugs by targeting activin A activity for FOP treatment (9). REGN2477 (also known as Garetosmab) is a humanized anti-activin A-neutralizing antibody which is effective to block heterotopic ossification in a FOP mouse model (8). Clinical trial of REGN2477 has indicated that there is no dose-limiting toxicity in a phase I study (16). In this study, most adverse effects were mild, with one serious case of hospitalization forhyperthyroidism which was later ruled out as being unre-

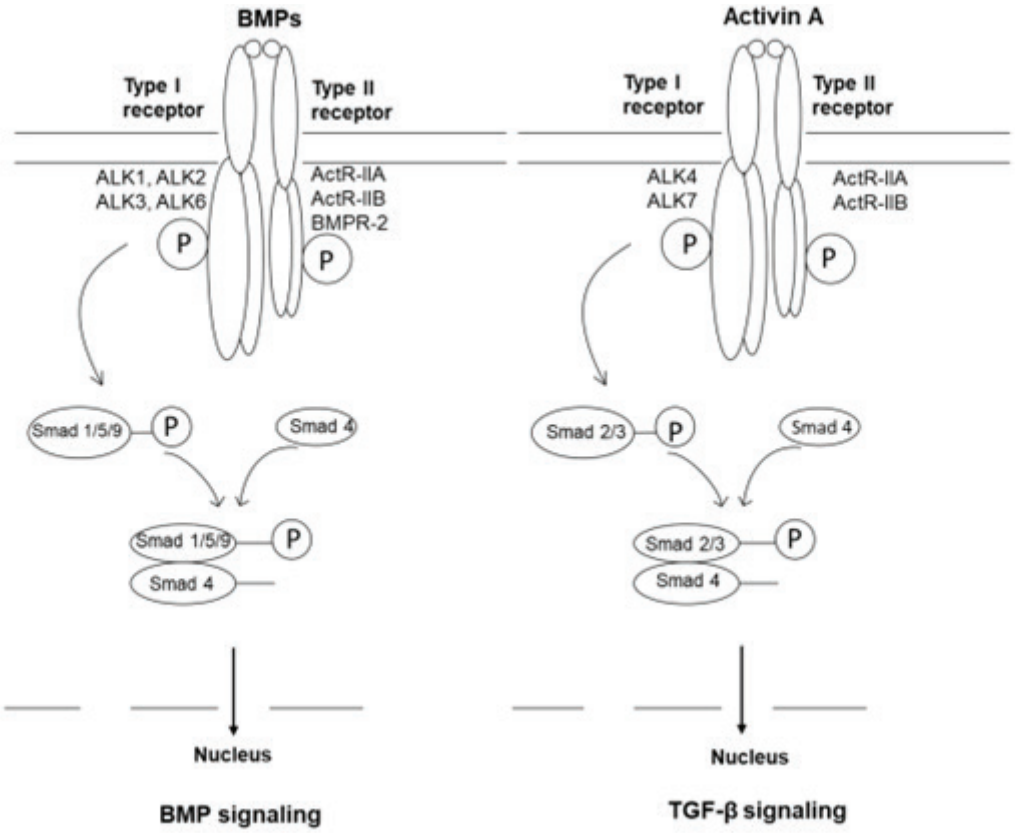

Figure 1. The BMP and Activin A signaling pathways. When BMP or activin A ligands bind to a heterotetramer complex f type II receptors and type I receptors (ALK1/ALK2/ALK3/ALK6 for BMP and ALK4/7 for activin A). The type II receptor phosphorylates the type I receptor. Subsequently, the phosphorated type I receptors further phosphorylate intracellular transcription factors (Smad1/5/9 proteins for BMP, and Smad2/3 for activin A) which then form a complex with Smad4 protein and migrate into the nucleus to regulate the transcription process of BMP or TGF β target genes.

lated to REGN2477 (17). In 2017, phase II clinical trial of REGN2477 was initiated and patient enrollment was completed. However, the study result has not published to date. Interestingly, a recent phase III clinical trial has been approved by FDA, suggesting that REGN2477 may have worked well in the clinical phase II study. Nevertheless, Activin A-induced TGF-β signaling plays important roles in normal cell proliferation and apoptosis as well as in regulation of tissue homeostasis, organ development and inflammation. (3). REGN2477 may raise safety concerns, as Activin A is expressed in many organ systems, and plays important roles in the development and maturation ovarian follicles, spermatogenesis, and steroidogenesis in the testes, and inhibiting Activin A could affect the proceedings of these processes (17). Many of the currently devised approaches are unselective towards activin A, and go to affect other signaling molecules, such as BMPs and TGF-β (18).

Potential Drugs targeting ALK2

As ALK2 mutant which abnormally mediates BMP signaling is the root of FOP disease, developing potential drugs to targ*et al*K2 for the signaling inhibition is a promising therapy for FOP treatment. Dorsomorphin, the first small-molecule ALK2 inhibitor, was discovered in a zebrafish embryos-based screening for small-molecule inhibitors of the BMP signaling (16). Dorsomorphin inhibits ALK2 activity by directly binding to the ALK2-ATP interaction site through forming a hydrogen bond to the main chain amine in the ATP hinge region (19). Unfortunately, dorsomorphin displays significant off-target activities against a variety of other kinase receptors including vas-

cular endothelial growth factor receptor 2 (VEGFR2) and AMP-activated protein kinases (20). Following the discovery of Dorsomorphin, efforts have been made to study the structure and activity relationship of Dorsomorphin analogues, and several more selective and potent ALK2 inhibitors have been identified. For instance, LDN-193189 is an optimized Dorsormorphin analogue and exhibits higher selectivity and potency against ALK2 (IC_{50} = 0.67 nM for LDN-193189 vs IC_{50}=9.76 for Dorsormorphin. Note: IC_{50} is the concentration of a drug or inhibitor needed to inhibit enzyme activity by 50%) (2, 21, 22). Meanwhile, LDN-193189 displays increased inhibitory activities against ALK4 and ALK5 but decreased activities against AMPK and VEGFR2 in comparison to Dorsomorphin (Figure 2). Later, Mohedas *et al* developed LDN-212854 by a further modification of the binding position to quinoline in LDN-193189, which was more selective towards ALK2 than LDN-193189 (Figure 2). In addition, Hao *et al* developed DMH1, a highly selective ALK2 inhibitor, which does not show detectable activities against the closely related kinases such as AMPK, ALK5 and VEGFR2 (Table 1). Nevertheless, Neither LDN-212854 nor DMH1 can effectively distinguish ALK2 from the other three BMP type I receptor ALK1, ALK3 and ALK6. As each of BMP type I receptor member plays different biological roles in cellular activities, it is essential to develop exclusively selec-

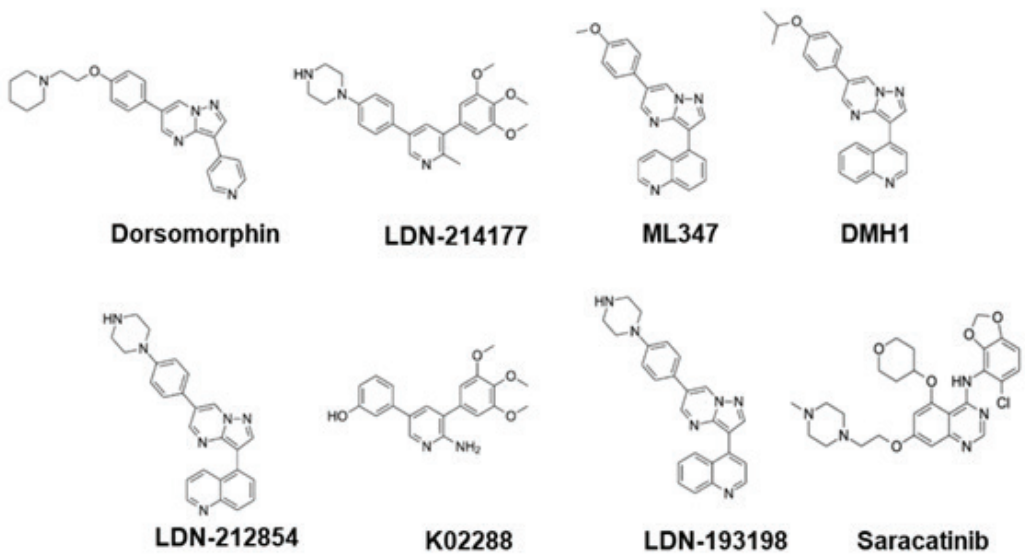

Figure 2. Chemical structures of ALK2 inhibitors.

Table 1. IC_{50} of the reported small molecule BMP inhibitors against ALK2 and related kinases

Molecule	ALK1 (nM)	ALK2 (nM)	ALK3 (nM)	ALK4 (nM)	ALK5 (nM)	ALK6 (nM)	AMPK (nM)	VEGFR2 (nM)
DM	19.5	9.76	222	3,080	7,829	235	234.6	21.8
DMH1	77.9	12.62	241	11,023	5971	47.6	>100,000	>100,000
LDN193189	1.48	0.67	14.3	108	117	60	1,122	214.7
LDN212854	2.4	1.3	86.8	2,133	9,276	N/A	N/A	2,800
ML347	46	32	10800	>100, 000	>100,000	9,830	>100,000	19,700
LDN214117	27	27	1,171	N/A	3,000	N/A	N/A	N/A
K02288	1.8	1.1	34.4	302	321	6.4	N/A	N/A
Saracatinib	19	6.7	621	3900	6890	6130	N/A	N/A

tive ALK2 inhibitors that show no or little activity against other three BMP type I receptor members, ALK1, ALK3 and ALK6 (23, 24, 25, 26, 27).

By modifying the chemical groups at pyrazolo[1.5-a]pyrimidine scaffold of Dorsomorphin, Engers, *et al*., identified ML347, which displays much higher selectivity against ALK2 (IC_{50} =32 nM) in contrast to ALK3 (IC_{50} =10,800 nM), ALK6 (IC_{50} =9,830 nM) and other kinases (VEGFR2, IC50 =19,700 nM: AMPK, IC50>100,000nM). However, ML347 lacks selectivity between ALK1 (IC_{50} =46 nM) and ALK2. In parallel, Mohedas and colleagues reported a new pyrazolo[1.5-a]pyrimidine derivative LDN-212854 which exhibits substantially improved selectivity for BMP versus the TGF-β type I receptors and other kinases (28) (Table 1). However, like ML347, LDN-212854 fails to display distinct inhibitory activities against ALK2 and ALK1 (28). Recently, Sanvitale *et al* screened a kinase-directed library consisting of 2000 compounds against a panel of 80 purified human kinases, they identified K02288, a new class ALK2 inhibitor with a 2-aminopyridine scaffold (Figure 2). The kinase selectivity assay indicated that K02288 has favorable selectivity toward ALK2 without detectable inhibitory activities against AMPK and VEGFR2 (29), The selectivity of K02288 against ALK2 was further improved by Mohedas and colleagues (22). K02288 binds directly to the ALK2-ATP site through two hydrogen bonds to the aminopyridine group. By studying the structure activity relationship of 2-aminopyridine, they found that LDN-214117 exhibits 100 times greater selectivity i for ALK2 in comparison to K02288, and LDN-214117 does not show any detectable inhibitory activities against ALK4, ALK6, AMPK and VEGFR2 (13). Presently, none of these ALK2 kinase inhibitors are in clinical trials.

Very recently, Williams *et al*. reported that Saracatinib, a drug developed by AstraZeneca to treat ovarian adenocarcinoma, is a potent and selective ALK2 inhibitor, and Saracatinib can effectively suppress heterotopic ossification in two FOP animal models, an inducible $ACVR1^{Q207D}$- transgenic mouse model and an inducible $ACVR1R^{206H}$-knockin mouse model. As it displays excellent pharmacokinetic parameters and safety, the clinical trial of Saracatinib is underway for FOP treatment (30).

Potential Drugs Targeting Others

In a high-throughput screening system using FOP patient–derived induced pluripotent stem cells (FOP-iPSCs), Hino *et al* identified mTOR as a critical downstream signaling of the Activin-A/FOP ALK2 cascade for the aberrant chondrogenesis in FOP (30). As rapamycin, an immunosuppressive drug used for transplant rejection and the lung disease lymphangioleiomyomatosis, is an FDA approved drug of mTOR inhibitor, Hino *et al* examined rapamycin in two FOP mouse models, and found that rapamycin effectively blocked heterotopic ossification in both mouse models (30). In addition, the study by Agarwal *et al* has further confirmed that rapamycin decreased heterotopic ossification in both traumatic and genetic mouse models of heterotopic ossification (31).

Nuclear retinoic acid signaling plays a critical role in chondrogenesis and normal skeleton formation, and attenuation of retinoic acid signaling induces the formation of ectopic cartilage during chondrogenesis, a critical early step prior to heterotopic ossification. (2). Therefore, nuclear retinoic acid signaling induction could effectively block chondrogenesis and subsequent heterotopic ossification in FOP. In 2011, Shimono *et al* first reported that agonists of nuclear retinoic acid receptor γ (RARγ) dramatically inhibited heterotopic ossification in three mouse models likely via inhibiting the BMP signaling by blocking the differentiation of the progenitor cells into a skeletogenic lineage (32). Palovarotene, a RARγ agonist drug approved by FDA for emphysema treatment, was studied as a therapy for FOP. In the inducible $ALK2^{Q207D}$ transgenic mouse model of FOP, palovarotene dramatically blocked the heterotopic bone formation (32, 33). Furthermore, palovarotene was examined in an inducible $ACVR1^{R206H}$-knockin mouse model, and the result demonstrated that palovarotene significantly reduced the heterotopic bone formation in the knockin mouse model as well (30, 32). Through targeting nuclear RARγ, palovarotene successfully inhibited heterotopic ossification in a mouse model, blocking both trauma-induced and spontaneous ossification, without altering limb mobility or growth (22, 34).

CLINICAL TRIALS FOR FOP

REGN2477

For its excellent ability to block heterotopic ossification in preclinical studies, REGN2477, the anti-activin A-neutralizing antibody, has been examined in a double-blind, placebo-controlled phase I clinical study for its safety, tolerability and pharmacokinetics (15). 40 healthy women of nonchildbearing potential were randomized to receive a single dose of intravenous REGN2477 at 0.3, 1, 3, or 10 mg/kg; subcutaneous REGN2477 at 300 mg/kg; or placebo. It was demonstrated that REGN2477 exhibits an acceptable safety profile with good pharmacokinetics and no

dose limiting toxicities, supporting a further investigation of REGN2477 in FOP patients. Next, Phase II clinical trial of REGN2477 was initiated in 2019 to examine its safety, tolerability and efficacy in FOP patients who were administered 10 mg/kg REGN2477 intravenously every 4 weeks for 6 months (NCT03188666). This Phase II clinical study was completed recently, but no result has been published yet. However, a Phase III trial of REGN2477 in FOP adult patients was recently announced by Regeneron Pharmaceuticals in 2022, suggesting promising outcomes in the previous Phase II clinical trial (NCT05394116). Nevertheless, activin A plays important roles in multiple biological functions including development of body tissues, and cell proliferation and differentiation. Blocking activin A by REGN2477 in FOP patients raises concerns for its side effects, which must be closely monitored in FOP patients (Table 2).

Rapamycin

Rapamycin, a FDA approved immunosuppressive drug, has been shown to lessen the degree of heterotopic ossification in mouse models (30). With a proved safety profile, Kaplan *et al* recently reported a case study of rapamycin treatment in two FOP patients with the classic $ALK2^{R206H}$ mutant (35). One patient was treated with rapamycin for persistent, acute flare-up of her neck and back for four months while the other patient received rapamycin for 18 years for chronic immunosuppression following liver transplantation (36, 37). Unfortunately, heterotopic ossification progressed in both patients, and they did not show clear responses to pharmacological doses of rapamycin. Nevertheless, it is difficult to evaluate therapeutic efficacy of rapamycin without a well-controlled clinical trial, particularly for a lack of therapeutic dose optimization. Recently, Phase II/III clinical trials of Rapamycin were initiated at Kyoto University Hospital in Japan (UMIN000028429) in 2017, and the clinical results have not been publicly released yet.

Palovarotene

With a characterized safety profile, Phase II clinical trial of palovarotene was launched in 2014 by Clementia Pharmaceuticals to evaluate whether palovarotene can attenuate heterotopic ossification during and following flare-ups in FOP patients (NCT02190747). In 2016, the clinical trial was completed, and results have shown that palovarotene reduces the percentage of patients developing heterotopic ossification, and the recovery time and pain from flare-ups (31, 33, 38). In 2017, a Phase III study of Palovarotene was initiated to assess its efficacy for the treatment of FOP (NCT03312634), and about 110 patients with age 4 years and older have been recruited

Table 2. Drug clinical trials for FOP treatment

Drug Name	Title	Phase	Sponsor
Palovarotene	A Rollover Study to Further Evaluate the Safety and Efficacy of Palovarotene Capsules in Male and Female Participants Aged ≥14 Years with Fibrodysplasia Ossificans Progressiva (FOP) Who Have Completed the Relevant Parent Studies.	III Rollover (NCT05027802)	Ipsen
REGN2477	A Study to Examine the Safety, Tolerability and Effects on Abnormal Bone Formation of REGN2477 in Patients with Fibrodysplasia Ossificans Progressiva	II (NCT03188666)	Regeneron Pharmaceuticals
Rapamycin	Multicenter randomized double-blind comparison test followed by open-label continuous administration test of NPC-12T for Fibrodysplasia Ossificans Progressiva	II, III (UMIN000028429)	Institute for Frontier Life and Medical Sciences, Kyoto University
Garetosmab	Study to Assess the Efficacy and Safety of Garetosmab in Japanese Adult Patients with Fibrodysplasia Ossificans Progressiva (FOP)	III (NCT04577820)	Regeneron Pharmaceuticals
INCB000928	To Assess the Efficacy, Safety, and Tolerability of INCB000928 in Participants with Fibrodysplasia Ossificans Progressiva (Progress)	II (NCT05090891)	Incyte Corporation
DS-6016a	Single-Ascending Dose Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of DS-6016a After Subcutaneous Injection in Healthy Japanese Subjects	I (NCT04818398)	Daiichi Sankyo Co., Ltd.

in this study. Currently no result from this clinical trial has been reported. In November 2021, the rollover Phase III study started to further evaluate the efficacy of palovarotene in FOP patients who have previously received palovarotene treatment (NCT05027802), and the FOP patient recruitment is ongoing. In January 2022, Health Canada first approved palovarotene (Sohonos™) for the treatment of patients with FOP for both chronic use and for flare-ups in these patient populations. Nevertheless, palovarotene has not currently approved outside of Canada. Interestingly, in June, 2022, the French pharmaceutical company Ipsen announced in a press release that FDA is currently conducting a priority review for palovarotene application in FOP patients, marking a significant milestone for FOP patients living in US and worldwide, assessed on October 23, 2022 (40).

Saracatinib, INCB000928 and DS-6016a

Saracatinib, previously approved by FDA to treat ovarian adenocarcinoma has been repurposed for FOP treatment as it can inhibit ALK2 (39). Phase II clinical trial of Saracatinib for FOP was initiated in August 2020 (NCT04307953) in Amsterdam. It is a six-month, double-blind, randomized trial, followed by a 12-month trial comparing open-label extended Saracatinib treatment with historical control data. This study is estimated to complete in 2024 (Table 2).

Recently, one small molecule ALK2 inhibitor, INCB000928, developed by Incyte corporation and one anti-ALK2 monoclonal antibody, DS-6016a, developed by Daiichi Sankyo and Saitama Medical University in Japan, have been subjected to phase 1 clinical trial for their safety, tolerability, and pharmacokinetics in healthy participants and the study results have not been released to date (NCT05090891 and NCT04818398) [53] (Table 2).

CONCLUSION

FOP is a rare genetic disorder with causative heterozygous mutations identified in ALK2 which therefore has become a hot druggable target for FOP. To date, multiple small molecules, and antibody targeting ALK2 have been developed including DMH1, LDN193189, LDN212854 ML347, LDN214117, K02288, etc. Among them, Saracatinib, INCB000928 and DS-6016a have entered clinical trials for FOP treatment recently. Nevertheless, all these ALK2 inhibitors cannot distinguish the normal wild type ALK2 allele from the mutated FOP allele, raising significant safety concerns since they also block important physiologic BMP signaling required for normal cellular functions. The future research to develop FOP disease-specific ALK2 inhibitors with no or minimal interference to the wild type ALK2 is warranted.

In addition, the discovery of activin A, which normally transduces the TGF-β signaling under physiological condition, but aberrantly activates the BMP signaling in FOP, has made Activin A an ideal drug target for FOP. REGN2477, a humanized anti-activin A-neutralizing antibody, has been developed and it is effective to block heterotopic ossification in FOP mouse models (8). Currently, REGN2477 is under phase 3 clinical trial for FOP treatment. Moreover, drugs that target other transcriptional effectors associated with the early heterotopic ossification are also evaluated in preclinical and clinical studies. Rapamycin, a FDA approved immunosuppressive drug, can significantly block heterotopic ossification in FOP mouse models (36), and a phase 2 clinical trial for Rapamycin is ongoing. Palovarotene, a RARγ agonist that has been studied in phase 3 clinical study, was approved in Canada in 2022 to treat FOP patients for chronic use and acute flare-ups. Currently, Palovarotene is under a priority review by FDA for the treatment of FOP patients, offering tremendous hope for the FOP patients worldwide.

CONFLICT OF INTEREST

The authors declare that no conflicting interests exist.

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