SPECIAL COMMUNICATION

The first approved drug for abnormal bone formation: palovarotene challenges and way forward

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Abstract

The current communication was planned to assess the validity of a potential cure for two disorders of bone formation that have traditionally been limited to symptomatic treatment in orthopaedic medicine. Heterotopic ossification and fibrodysplasia ossificans progressive, also known as Stoneman Syndrome, are rare conditions that result in abnormal bone formation within soft tissues, causing immense suffering and high mortality rate due to limited treatment options. Several studies have supported the promising outcomes associated with palovarotene, a novel drug, in terms of reducing lesion volumes induced by heterotopic ossification, alleviating inflammation and pain and doing so with minimal side effects. Given its novelty, research on palovarotene is still in its infancy. Consequently, challenges surrounding the introduction of palovarotene needs to be studied along with its potential indications and advantages in the disorders characterised by abnormal bone formation.

Key Words: Palovarotene, Myositis ossificans, Bone morphogenetic proteins.

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Introduction

An exciting breakthrough in the field of bone and mineral research has attracted the attention of the scientific community. Recently, a novel drug, called palovarotene, has been approved for medical use in Canada and the United States for the treatment of heterotopic ossification (HO) and fibrodysplasia ossificans progressive (FOP), which are rare and debilitating conditions that cause abnormal bone formation in soft tissues.[1] Patients of these diseases suffer immensely because of few treatment options that are available.

HO and FOP are characterised by progressive ossification of muscles, tendons and ligaments, leading to severe pain, reduced mobility, joint fusion and decreased quality of life.[2] HO can occur after trauma, surgery or neurological disorders, while FOP is a genetic disease that affects children right from birth.[3] Both the conditions have no effective treatment or cure, and the current management options are limited to symptomatic relief by painkillers, surgical removal of ectopic bone, or prevention of flare-ups.[2,4] Before palovarotene, patients with HO and FOP had a poor prognosis and a high risk of mortality due to complications, such as respiratory failure, infections and malignancies.[5,6]

Palovarotene is a selective retinoic acid receptor gamma (RARγ) agonist that works by inhibiting the activity of bone morphogenetic proteins (BMPs), which are key mediators of endochondral ossification. Palovarotene has been shown to reduce the formation and severity of HO and FOP lesions in animal models[4,5] as well as human clinical trials.[6]

The current communication was planned to highlight the significance of palovarotene as a groundbreaking treatment for HO and FOP, and to discuss the drug's potential to transform patient outcomes, the hurdles in ensuring its accessibility and affordability, and the areas where further research is required to optimise its use.

Discussion

In a phase 2 multicentre, randomized, placebo-controlled clinical trial conducted across the US, France, and the United Kingdom, a total of 40 patients with FOP were enrolled: 21 received palovarotene 10/5 mg, 9 received palovarotene 5/2.5 mg, and 10 received placebo. Palovarotene was administered at a dose of 5 mg/day for 14 days, followed by 2.5 mg/day for 28 days, starting at the first sign of a flare-up. The primary endpoint was the change in volume of new HO lesions at 12 weeks, measured by low-dose whole-body computed tomography (CT). The results demonstrated that palovarotene reduced the least-squares mean (LSmean) volume of new HO lesions by 79% in the 10/5 mg group

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and 92.7% in the 5/2.5 mg group compared to placebo (placebo LSmean: 18.0×10^3 mm^3; palovarotene 10/5 mg: 3.8×10^3 mm^3; palovarotene 5/2.5 mg: 1.3×10^3 mm^3) ($p = 0.11$ and $p = 0.12$, respectively). Palovarotene also improved the range of motion (ROM) of major joints and reduced the pain and swelling associated with flare-ups. The most common adverse events included headache, fatigue, nausea, and diarrhoea, which were generally mild to moderate in severity and resolved without intervention.[6]

Based on these findings, palovarotene was granted conditional approval by Health Canada in December 2022 and by the US Food and Drug Administration in January 2023 for the treatment of FOP.[1] Palovarotene is the first drug to be approved for this indication and the first RARγ agonist to be approved for any indication. It is also being investigated for the prevention of HO in patients undergoing hip or knee replacement surgery or spinal cord injury.[7] However, palovarotene also poses some challenges that need to be addressed to make this breakthrough discovery more beneficial for the common folk.

One of the main challenges is the high cost of palovarotene, which may limit its accessibility and affordability for many patients who need it. According to a recent report by the Canadian Agency for Drugs and Technologies in Health, palovarotene costs about $1,022,894 per year per patient in the US market.[8] Another challenge is the optimal dosing regimen and duration of treatment for palovarotene, which are still unclear and may vary depending on the type and severity of HO or FOP. Palovarotene has been tested in different doses and schedules in animal models[4,5] as well as human trials[6], but the results are not consistent or conclusive. For example, some studies suggest that palovarotene is more effective when given before or during the early stages of HO or FOP.[9] Also, with regard to dosage, the biggest trial of palovarotene experimented with both intermittent and continuous dosage regimen with mixed results. While continuous dosage helped with the symptoms, the incidence of side effects was more debilitating than with the intermittent dosing schedule. Thus, no conclusive dosage regimen has been agreed upon[10]. More research is needed to determine the optimal dose and schedule of palovarotene for different patients and scenarios. Also, in regards to the side effects, although the common side effects, as mentioned above, were mild and resolved without intervention but as with many long-term treatments, the possibility of long-term severe side effects cannot be entirely ruled out without specific longitudinal studies focussing on tolerance development as well as its effects on pregnant women. Thus, long-term follow-up studies are needed to monitor the safety and efficacy of palovarotene in different populations and settings.

Finally, palovarotene may not be effective for all patients, or prevent all HO or FOP episodes, as some patients may have different genetic mutations or environmental triggers that affect their response to palovarotene. For example, rarely patients with FOP have different mutations besides activin A receptor type I (ACVR1)[11], which encodes the BMP receptor that is targetted by palovarotene. Some patients with HO may have other factors that promote ectopic bone formation, such as inflammation, infection, or hypoxia. Therefore, palovarotene may not be sufficient to inhibit all the pathways involved in HO or FOP, and may need to be combined with other drugs or interventions to achieve better outcomes.

Conclusion

The scientific community should continue to explore the potential of palovarotene as a novel therapeutic option for HO and FOP, as well as other diseases involving aberrant bone formation. The policymakers need to make sure that discoveries like palovarotene should be more available to the common people so that maximum benefit may be extracted. Overall, it is a breakthrough discovery that is going to help people a lot.

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HNKA: Concept, literature investigation, preparing the original draft, reviewing, editing and administrating the project.

AP: Concept, review, editing and supervision.

PKA: Literature investigation, drafting, review and editing.

NZ: Data visualization, drafting, review and editing.