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Emerging Treatments of Osteogenesis Imperfecta

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***Abstract*: Imperfecta (OI) is a genetic disorder characterized by various clinical features including bone deformities, low bone mass, brittle bones, and connective tissue manifestations. The predominant cause of OI is due to mutations in the two genes that encode type I collagen. This paper focuses on gene therapies that can possibly cure this condition. Unlike current treatments like bisphosphonates, growth hormone, teriparatide and denosumab that focuses only on the management of OI. Researchers believe that this hereditary disease can be cured at the prenatal stage also. The most promising approach still seems to be gene therapy which include-gene silencing, replacement of alleles; drugs that affect collagen and implantation in adults. The main modalities of treatment can be grouped into medications, surgical intervention, physical therapy, and experimental therapies).**

***Keywords*: Bioposphonates, Gene therapy, Collagen.**

1. Introduction

Osteogenesis Imperfecta is a genetic disorder in which the bones become extremely fragile and brittle. It is also known as brittle bone disease. Due to even mild trauma or without any apparent reason, the patient can have several fractures. It is a heritable connective tissue disorder. Mutation of Type I collagen is the main cause. [1]. This condition affects approximately 1 in 15,000–25,000 births. There are at least 19 recognized forms of osteogenesis imperfecta, designated type I through type XIX. Each type has certain symptoms but most of them are overlapping [2].

Patients with OI feature a prominent skeletal phenotype with a wide clinical spectrum of severities ranging from low bone mass (OI type I) to progressive bone deformities with an increased incidence of fractures (OI type III/IV) and prenatal lethality (OI type II). Additionally, OI patients may exhibit Dentinogenesis Imperfecta (abnormal tooth development), craniofacial abnormalities and joint hyper mobility, as well as extra-skeletal manifestations including blue sclera, hearing impairment, and intrinsic and extrinsic lung abnormalities [3]. The majority of OI cases occur as a result of autosomal dominant mutations in the genes encoding type I collagen (COL1A1 and COL1A2) [4]. In addition, approximately 15% of all OI cases are caused when genes that regulate the post-translational modifications have recessive mutations, secretion, and processing of type I collagen.

This review will summarize the current treatment available for this incurable disease and also prospects of emerging techniques that may possibly provide cure to patients at an early stage.

2. Treatment

The goals of therapy are to prevent long bone deformities, reduce fracture rate, maximize functional capacity and minimize chronic pain. To develop new treatment techniques one needs to focus on improving the bone quantity, bone quality and also correct the mutated gene. The identification of altered TGF-β signaling in both recessive and dominant OI matrix has emerged as a targetable pathway for therapy. Beginning with the identification of CRTAP, 14 new genes that cause OI have been discovered, primarily owing to significant advances in genomic technology [5].

3. Current treatments

A. Bisphosphonates

Bisphosphonates (BPs) are non-hydrolysable synthetic analogs of pyrophosphate. BPs adhere to mineralized surfaces, inhibit osteoclastic bone resorption, and have very long skeletal half-lives [6]. Intravenous BPs are currently the primary treatment of children with moderate to severe OI. BPs increase BMD and size in children with OI [7]. It improves daily physical activity. However, it has been difficult to confirm all of these benefits in randomized trials, and the optimal duration of BP treatment is unknown.

Several studies have been done on the use of intravenous or oral BPs in adults with OI, did not find definitive evidence of fracture reduction. Furthermore, a recent meta-analysis of placebo-controlled trials suggested that the effects of BPs for fracture prevention in OI were inconclusive [8].

B. Growth hormone

Growth hormone has anabolic effects on bone. A 1-year randomized trial of the BP, etidronate, with or without growth hormone showed a greater increase in BMD and growth velocity with growth hormone, but there was no fracture benefit of growth hormone [9].

C. Teriparatide

Teriparatide (PTH1-34) is an anabolic agent that stimulates bone formation (and ultimately bone resorption). This drug decreases vertebral and non-vertebral fractures in

postmenopausal women with osteoporosis [10]. Observational data in adults with OI suggest increased BMD with teriparatide. Recently, a randomized trial of teriparatide in adults with OI showed increased BMD as well as increased vertebral strength estimated by FE analysis 91. The benefits did not appear to occur in more severe OI (types III and IV) but in mild (type I) OI.

D. Denosumab

Denosumab is a monoclonal antibody to receptor activator of nuclear factor kappa B ligand that decreases bone resorption, increases bone density, and reduces fractures in women with postmenopausal osteoporosis [11]. This drug may represent future therapy in OI. In a study of four children with type VI OI, increased BMD and mobility and improved vertebral shape were reported after denosumab treatment, and the outcomes of this study indicated that this treatment appears to be safe [12]. Denosumab has been reported to cause hypophosphatemia, hypocalcaemia, and secondary hyperparathyroidism in a child with fibrous dysplasia of bone [13]. There was rebound hypocalcaemia after stopping denosumab [14]

4. Possible future therapies

Sclerostin is an inhibitor of the LRP5/WnT system that decreases bone formation. Antibodies to sclerostin are in clinical trials for the treatment of osteoporosis intending to increase bone density [15]. Sclerostin antibody appeared to be effective in a mouse model of moderately severe OI [16] but less so in a mouse model of more severe OI [17].

TGFβ is secreted by osteoblasts and increases osteoclastic bone resorption. Excessive TGFβ signaling may be important in some forms of OI, and anti-TGFβ therapy represents an interesting prospect for the future treatment of OI [18]

Cell-based therapy, such as bone marrow or mesenchymal stem cell transplantation, has also been investigated and may have promise; but these could also have significant risks. Gene therapy with allele-specific silencing may represent a future therapy

Gene Therapy: Silencing or Replacement of the Allele Containing the Causative Variant.

1. Ninety percent of OI patients have a causative variant in the COL1A1/2 genes encoding either the (pro)-α1 chain or the (pro)-α2 chain of collagen type I. OI types II-IV result from intertwining of mutated and normal collagen type I chain resulting in production of abnormal collagen type I (dominant-negative effect), whereas OI type I is mostly due to decreased or no expression of 1 COL1A1 allele (haploin sufficiency effect). It was therefore thought that the future treatment of OI should consist of so-called antisense suppression therapy, directed towards decreasing or silencing of the allele containing the causative variant. This would transform a severe type of OI into a mild OI type. Various murine models have been developed, which can be used for the purpose of investigating gene therapy in OI. However, the various antisense techniques (short oligonucleotides, ribozymes, silencing RNA all lack true specificity against the mutant transcript. Other problems are the stability of the antisense molecules apart from specific problems that each technique. As such, antisense suppression therapy is currently limited to in vitro studies.
2. Another approach is the replacement of cells harboring the causative variant with normal cells by bone marrow transplantation leading to engraftment of functional mesenchymal stem cells that differentiate into bone cells. This approach may hold promises for OI treatment as is illustrated by various in vitro and in vivo studies (children with severe OI. Further studies are warranted to evaluate whether bone marrow transplantation could be a possible treatment for patients with OI [19].
3. Gene therapy broadly involves the delivery of DNA encoding many different types of proteins. In addition to enabling the production of natural protein products as therapy, gene therapy also enables the production of engineered proteins (e.g., fusion proteins containing toxins, immune regulatory proteins, receptors or their ligands); produces cell types resistant to chemotherapy, infection, or immune rejection; delivers ribozymes, decoy DNAs, or DNA binding proteins to prevent viral infection, such as human immunodeficiency virus (HIV)-1; and immunizes patients with the introduction of genes, including the injection of naked DNA [20].

In some studies, gene therapy and stem cells have been combined to circumvent the primary defect in the patient's stem cells, thereby generating a corrected renewable cell source

5. Implant therapy for adults [21]

To account for poor bone strength, Marx et al. proposed using implants as a “tent-pole” for bone graft to be placed around to consolidate and maintain the graft’s volume [22].

Implant therapy for patients with OI type I may be a viable treatment option with appropriate planning, surgical skill, and routine care. Advancements within the fields of prosthetics, implants and bone grafting will make implants an increasingly practical treatment option for OI patients. However, dental practitioners should take great precaution in ensuring that bone quantity and quality is acceptable to make sure stability and successful osseo integration

6. Effects of drugs on collagen [23]

A. Phenytoin sodium

It is believed to stimulate the high-affinity phenotype of fibroblasts. Exposure of the gingiva fibroblast to phenytoin increases the level of translatable collagen mRNA; thus, there is an increased steady-state level of collagen mRNA and not a decrease in collagen degradation [24].

B. Cyclosporin

Bartold has reported a stimulatory effect on DNA synthesis which increases the synthesis of collagen. It also negates the inhibitory effect of lipopolysaccharides indicating a possible observed relationship between areas of prominent gingival overgrowth and dental plaque [25].

C. Calcium channel blocker

Lucas et al. have shown that nifedipine induced hyperplasia is due to an increase in the ground substance. Gingival overgrowth may also be related to calcium-dependent inhibitory effect on T-cells and subsequent immunosuppression. The blockade of intracellular calcium uptake by the fibroblast alters both their secretory properties as well as the synthesis of collagenases [26].

7. Discussion and Conclusion

The current treatment and management of OI is not sufficient as it is unable to cure the disorder. We need to look for newer aspects like gene therapies, stem cell therapies, etc. which have been discussed here for better results. There are other possible mechanisms also as collagen biosynthesis intervention, prenatal therapy, cross-breeding, CRISPR-Cas9 therapy which are still under study. However, apart from the treatment special attention should be paid at the management of OI. Moreover, the disorders currently identified to date point to important common pathophysiological mechanisms that contribute differentially to the integration of bone mass and quality. The future challenge will be to develop mechanistic therapies that will deliver on genotype-specific treatments in the form of personalized medicine.

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