New Modalities in the Management of Osteogenesis Imperfecta

Essay

Submitted For Partial Fulfillment of
Master Degree in Orthopaedic Surgery

By

Yasser Faris Hamed

M.B, B.Ch

Under supervision of

Professor / Mohammed Reda Abd El- Wahab

Professor of Orthopaedic Surgery
Faculty of Medicine - Ain Shams University

Professor/ Tarek Hassan Abdelaziz

Professor of Orthopaedic Surgery
Faculty of Medicine - Ain Shams University

Dr. Rasha Tarif Hamza

Assistant Professor of Pediatrics
Faculty of Medicine -Ain Shams University

Faculty of Medicine
Ain Shams University
2008

قال تعالى

بسم الله الرحمن الرحيم

أَوَلَمْ يَرَ الْأِنْسَانُ أَنَّا خَلَقْنَاهُ مِنْ نُطْفَةٍ فَإِذَا هُوَ خَصِيمٌ مُبِينٌ (٧٧) وَضَرَبَ لنا مَثَلاً وَنَسِيَ خَلْقَهُ قَالَ مَنْ يُحْيِي الْعِظَامَ وَهِيَ رَمِيمٌ (٧٨) قُلْ يُحْيِيهَا الَّذِي أَنْشَأَهَا أَوَّلَ مَرَّةٍ وَهُوَ بِكُلِّ خَلْقٍ عَلِيمٌ (٧٩) الَّذِي جَعَلَ لَكُمْ مِنَ الشَّجَرِ الْأَخْضَرِ نَاراً فَإِذَا أَنْتُمْ مِنْهُ تُوقِدُونَ (٨٠) أَوَلَيْسَ الَّذِي خَلَقَ السَّمَاوَاتِ وَالْأَرْضَ بِقَادِرٍ عَلَى أَنْ يَخْلُقَ مِثْلَهُمْ بَلَى وَهُوَ الْخَلَّاقُ الْعَلِيمُ (٨١) إِنَّمَا أَمْرُهُ إِذَا أَرَادَ شَيْئاً أَنْ يَقُولَ لَهُ كُنْ فَيَكُونُ (٨٢) فَسُبْحَانَ الَّذِي بِيَدِهِ مَلَكُوتُ كُلِّ شَيْءٍ وَإِلَيْهِ تُرْجَعُونَ (٨٣)

سورة يس من الآية (٧٧) إلى الآية (٨٣)

Contents

Chapter page

List of abbreviations

Symbol	**Abbreviation**
ALP	Alkaline phosphatase
AVN	Avascular necrosis
BMD	Bone mineral denisity
COL1A1	Collagen type 1alpha 1 chain
COL1A2	Collagen type 1alpha 2 chain
CVS	Chorionic villus sampling
DI	Dentinogenesis imperfecta
DXA	Dual energy x-ray absoptiometry
FDA	Food and drug association
FIO	Fibrogenesis imperfecta ossium.
HYP	Hydroxyproline
IM	Intra medullary
IUT	Inutero transplantation
MSC	Mesenchymal stem cell
MHC	Major histocompatibility complex
OI	Osteogenesis imperfecta
ONJ	Osteonecrosis of the jow
RDA	Recommended daily allowance

List of tables

List of figures

Introduction

Osteogenesis Imperfecta (OI) constitutes several genetically and clinically heterogeneous syndromes characterized by skeletal fragility. Other manifestations are dentinogenesis imperfecta, blue sclera, deafness and ligamentous hyperlaxity. Clinical features include multiple fractures, knee deformities and scoliosis.[18] Hearing function, dentinogenesis imperfecta, cardiac and respiratory function and neurological changes must be monitored. OI is caused by quantitative and qualitative defect in collagen synthesis.[17] It is difficult to distinguish the tarda form from child abuse.[15]

Several types of treatment are available: non surgical management [physical therapy, rehabilitation, bracing and splinting], surgery (intramedullary rods , spinal and basilar impression surgery) and drugs to increase the strength of bone and decrease the number of fractures.[16] Good nutrition and an aggressive rehabilitative approach is indicated to optimise functional ability and walking capacity.[2] Appropriately timed surgery to insert intramedullary rods provides improved function of extremities despite high rate of complications. [8,14]

Intramedullary telescopic rodding has proven to be the most successful method of preventing and correcting factures and deformities of long bones improving walking ability and leading

to successful rehabilitation of even severely affected patients.[3] Surgery is required in patients with progressive spinal deformity, and in those with symptomatic basilar impression.[6],[7]

Pharmacological therapies aimed at strengthening bones are available, which decrease the pain and fracture rate in particular bisphosphonates which increase bone mineral density (BMD) and improve bone resistance leading to a decrease in fracture rate. [5,9,11] Combining pamidronate with surgery has good results over surgery alone.[4] Women with OI and osteoporosis should take estrogen replacement therapy.[1]

More recently stem cell replacement therapy in the child or fetus has been proposed as a therapeutic option.[10] Growth hormone is beneficial in patients with moderate forms of OI showing positive effect on bone turnover, BMD and high velocity rate of linear growth. [12]

Gene therapy may be directed towards either replacing cells carrying the mutant gene with normal cells or silencing the mutant allele using antisense suppression therapy, thus transforming a biochemically severe form of OI into a mild form. [13]

Much work is still necessary before recommending these techniques in clinical practice.[13]

Aim of the study

The aim of this study is to review the literature discussing the new modalities in the management of OI.

Contents

References

1- **Baroncelli GI, Bertelloni S, Sodini F and Saggese G**. Osteoporosis in children and adolescents: etiology and management. Paediatr Drugs 2005; 7(5):295-323.

2- **Binder H**. Rehabilitation of infants with osteogenesis imperfecta. Connect Tissue Res 1995; 31(4):S37-9.

3- **Cho TJ, Choi IH, Chung CY, Yoo WJ, Lee KS and Lee DY.** Interlocking telescopic rod for patients with osteogenesis imperfecta . J Bone Joint Surg (Am) 2007; 89 (5): 1028-35.

4- **El-Sobky MA, Hanna AA, Basha NE, Tarraf YN and Said MH.** Surgery versus surgery plus pamidronate in the management of osteogenesis imperfecta patients: a comparative study. J Pediatr Orthop B 2006; 15(3): 222-8.

5-**Glorieux FH.** Experience with bisphosphonates in osteogenesis imperfecta. Pediatrics 2007; l19 Suppl 2: 5163-5.

6- **Handerbrook MA and Lomberdo SR**. Silicate-substituted calcium phosphate as a bone void filler after Kyphoplasty in a young patient with multiple compression fractures due to osteogenesis imperfecta variant. Nerosurg focus 2006 15; 21(6):E9.

7 -**Janus GJ, Engelbert RH, Beek E, Finidori G, Pouliquen M Pruijs JE.** Osteogenesis imperfecta in childhood: MR imaging of basilar impression. Eur J Radiol 2003; 47(l): 19-24.

8- **Joseph B, Rebello G and B CK**. The choice of intramedullary devices for the femur and the tibia in osteogenesis imperfecta.J Pediatr Orthop B 2005; 14(5):311-9.

9 - **Land C, Rauch F, Montpetit K, Ruck-Gibis J and Glorieux FH.** . Effect of intravenous pamidronate therapy on functional abilities and level of ambulation in children with osteogenesis imperfecta. J Pediatr 2006 148(4):456-60.

10- **Le Blanc K, Gotherstrom C, Ringden O, Hassan M, McMahon R, Horwitz E, et al.** Fetal mesenchymal Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation 2005; 15; 79(11): 1607-14.

11- **Madenci E, Yilmaz K., Yilmaz M and Coskun Y**. Alendronate treatment in osteogenesis imperfecta. J Clin Rheumatol 2006; 12(2): 53-6.
12- **Marini JC, Bordenick S, Heavner G, Hopkins E, Glorieux FH, Chrousos GP**, **et al.** The growth Positive linear growth and bone responses to growth hormone treatment in children with types III and IV osteogenesis imperfecta: high predictive value of the carboxyterminal propeptide of type I procollagen. J Bone Miner Res 2003; 18(2):237-43.

13-**Niyibizi C, Wang S, Mi Z and Robbins PD**. Gene therapy approaches for osteogenesis imperfecta. Gene Ther 2004; 11(4): 408-16.
14- **Ozturk IT, Oztemur Z, Bulut O and Unsaldi T** . Complication following intramedullary fixation with a fixion nail in a patient with osteogenesis imperfecta: a case report. Acta Orthop Belg 2005; 71 (2): 227-9.
15- **Paterson CR , McAllion SJ**. Classical osteogenesis imperfecta and allegations of nonaccidental injury. Clin Orthop Relat Res 2006; 452: 260-4.

16-**Russell RG.**Bisphosphonates: mode of action and pharmacology. Pediatrics 2007; l 19 Suppl 2: 5150-62.
17- **Tedeschi E, Antoniazzi F, Venturi G, Zamboni G and Taty L.** Osteogenesis imperfecta and its molecular diagnosis by determination of mutations of type I collagen genes. Pediatr Endocrinol Rev 2006; 4(l): 40-6.
18- **Venturi G, Tedeschi E, Mottes M, Valli M, Camilot M, Viglio S , et al.** Osteogenesis imperfecta: clinical, biochemical and molecular findings. Clin Genet. 2006; 70(2): 131-9.

Protocol

Introduction

Osteogenesis Imperfecta (OI) is an autosomal dominantly or recessively inherited disorder primarily caused by mutations of type I collagen genes, COL1A1 on chromosome 17 and COL1A2 on chromosome 7.[87]

OI is characterized by osteopenia , multiple bone fractures , dentinogenesis imperfecta , kyphoscoliosis , joint hyperlaxity , easily bruis ed skin , bule sclera, conductive hearing loss , inguinal hernia , mitral valve prolapse, and aortic insufficiency .[82]

Therefore, a thorough evaluation of the ear, skin, teeth, cardiovascular and orthopaedic systems is needed. Bone deformities and recurrent bone fractures are the major concerns for patients with OI. [87]

The disease is classified into seven types by phenotype and mode of inheritance .[87]

Table 1.Clinical classification of OI.[87]

Classification	Clinical severity	Clinical picture
Type I OI	Classical mild OI	Complete non-functional COL1A1 usually minimal bone deformities, occasional fractures before puberty, blue sclera, dentinogenesis imperfecta and normal height.
Type II	Perinatal. lethal	Inutero and perinatal death occur.
Type III	Progressive, deforming	High frequency of fractures and severe progressive deformities

Type I V	Moderately deforming	Normal sclera, dentinogenesis imperfecta and less severe deformities are present.
Type V	Moderately deforming	Bone fragility,dislocation of radial head , mineralized interosseous membrane, hyperplastic callus, short stature and white sclera.
Type VI OI	Moderate to severe deforming	Disordered mineralization of bone tissue, white sclera, and scoliosis.
Type VII	Moderate to severe deforming	Bone fragility, rhizomelia and-coxa vara.

The treatment of OI requires a multidisciplinary team to maximize function and comfort, and decrease fracture incidence.[15]

Medical treatment with bisphosphonates has allowed for safer, more effective surgical management of children with OI.

indications and choices of surgical techniques based on recent clinical studies5 .[15]

Several new intramedullary rodding surgical techniques and modifications of older techniques have been developed to correct deformities of the long bones.

These techniques decrease the trauma associated with surgical treatment .[73]

The newer techniques limit postoperative immobilization, enabling earlier rehabilitation, and allowing for treatment of multiple bones simultaneously .[15]

Recent medical and surgical advances have allowed improved safety, function and comfort in treating children with OI.[45].