Osteogenesis imperfecta: current and future treatment

Lindsay Marie-Belt Dillon

The University of Toledo

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Lindsay Marie-Belt Dillon

The University of Toledo

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Dedication

This project is dedicated to my husband Mike and our parents. Thank you for your love and encouragement which has made everything possible. To Caroline and Michelle, good thing we found each other! PA school would have been lonely without you guys.
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To my major advisor, Jay Peterson, MSBS, PA-C, thank you for your support and guidance.
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Introduction

Osteogenesis imperfecta (OI), often referred to as brittle bone disease, is one of the most common heritable connective tissue disorders affecting nearly 1 in 12,000 patients worldwide (Millington-Ward, McMahon, & Farrar, 2005). The disease is characterized by increased bone fragility and low bone mass with severity ranging widely from lethal to mildly symptomatic. Due to the wide variations in clinical presentation, many physician assistants (PAs) may not be prepared to properly diagnose, treat or council patients and their families about the disorder. This clinical review article will provide an overview of the basic pathophysiology and clinical presentations of OI and focus on the current and potential future treatment options.

OI was first documented in the medical literature by Olaus Jacob Ekman in 1788, when he described various cases of hereditary bone fragility. Ekman used the term congenital osteomalacia when referring to what is now commonly known as OI (Peltier, 1981). Through the years, osteomalacia came to mean a softening of the bone due to poor mineralization often caused by vitamin D deficiency – in children this is called rickets. Researchers realized that they were dealing with a separate disease entity that included bone fragility with easy fracture and patients that seemed to be of short stature with hypermobile ligaments. In 1849, a Dutch anatomist named Willem Vrolik was studying the embryogenesis of humans and mammals when he came upon a human fetus that had many fractures as well as the presence of wormian bones. The wormian bones, primarily in the skull, contained additional centers of ossification that resulted in irregular skull bones and an increased number of suture lines. Vrolik stated that this
condition seemed to be caused by what he termed ‘osteogenesis imperfecta’ (Weil, 1981).

OI is considered to be a disease of the osteoblasts, which are bone cells that secrete a substance called osteoid (Glorieux, 2001). This substance is made up of type 1 collagen and will mineralize to form new bone. OI is predominantly caused by mutations to genes that encode type 1 collagen (either COL1A1 or COL1A2). Type 1 collagen is a vital component of bone responsible for its strength and flexibility (Millington-Ward et al., 2005). The resultant osteoblasts produce osteoid containing either decreased amounts or poor quality collagen, depending on the mutation present (Millington-Ward et al.). The bone produced is fragile and prone to fracture. Histomorphometry was used in a study by Rauch et al to evaluate the effects of type 1 collagen mutations on bone. Transiliac biopsy was performed on 70 patients with a documented diagnosis of OI (Rauch, Travers, Parfitt, & Glorieux, 2000). The samples were compared with age-matched transiliac biopsy taken from a control group of healthy patients during various orthopedic procedures. Compared with the healthy bone from the control group, sections taken from OI patients revealed an insufficient amount of bone. Both the cortical thickness and amount of cancellous bone were diminished compared to the control group (Rauch et al.). Throughout normal growth, cortical mass is increased by the modeling process. This process is carried out by osteoblasts and osteoclasts working independently of one another at various locations to alter the shape of existing bone. This is different from remodeling which occurs at the site of fracture healing with osteoblastic and osteoclastic actions coupled (Rauch et al.) Rauch and colleagues believe that the diminished cancellous bone is caused by
trabeculae that are reduced in number and are abnormally thin. Cancellous bone functions to support red bone marrow and its production of mesenchymal stem cells as they develop into bone cells (Rauch & Glorieux, 2004). In the OI patient, bone is produced in a weakened state with the severity dependent on the type of OI present. Osteoblast and osteoclast activity is increased because of the dysfunctional bone structure. The cellular overactivity is an attempt to produce a stronger bone. However, because of the presence of the COL1A1 or COL1A2 mutation, the osteoblast will always produce defective or inadequate amounts of collagen and osteoclasts will continue to resorb all areas of injury and microfracture (Kalajzic et al., 2002).

In 1980, Sillence and colleagues developed a classification system to accommodate the spectrum of the disease. Sillence’s classification system divided OI into four categories and is still in use today (Table 1). The mildest form of OI (type I) is caused by a null mutation of the COL1A1 gene, resulting in complete loss of function and is no longer incorporated into type 1 collagen. Bone created with this defect is composed of about half the normal amount of type 1 collagen (Willing, Pruchno, Atkinson, & Byers, 1992). This bone is composed of normal type 1 collagen but in a greatly decreased amount because only one gene is functioning, yielding significantly weakened bone (quantitative defect). Patients with type I OI present with age appropriate height. A common clinical presentation of this particular type of OI is a blue sclera. Type I patients lack major bony deformities and may not receive a diagnosis of OI until later in life depending on the number of fractures incurred. This group often presents with osteoporosis early in adult life (Cheung & Glorieux, 2008; Rauch & Glorieux, 2004). OI types II-IV, which are the more severe forms of the disease, are
caused by dominant-negative mutations. Rather than inactivation of the mutated gene, as with a null mutation, a dominant-negative mutation causes the gene to have an altered function. This mutation most often affects COL1A2 and the effect on bone is that it is composed of an adequate amount, but varying degrees of poor quality type 1 collagen (qualitative defect) (Millington-Ward et al., 2005). Type II OI, the most severe form of disease, is universally lethal in the perinatal period (Rauch & Glorieux). Fatality is often caused by respiratory failure due to multiple rib fractures in utero. Type II OI is recognized in utero via 3-dimensional sonogram presentation of increased nuchal translucency and generalized decreased bone density (Aerts, Van Holsbeke, de Ravel, & Devlieger, 2006). Type III OI is the most severe form of the disease for patients who survive the neonatal period (Cheung & Glorieux). These patients will present with fracture and long bone deformity at birth. About half of these patients are wheelchair bound starting in childhood (Cheung & Glorieux). Patients in this group present with a blue/grey sclera, dentinogenesis imperfecta, and triangular facies attributed to poorly formed facial and skull bones. These patients are also extremely short in stature with height ranging from 3 – 4 feet (Cheung & Glorieux). Patients with OI type III are often afflicted with spinal deformity secondary to fracture. Because of their spinal deformity, this group tends to have respiratory difficulties; which is the leading cause of death among these patients (Rauch & Glorieux). Type IV OI is the most diverse group in terms of clinical presentation of the disease (Cheung & Glorieux). Patients with OI type IV generally have moderately severe forms of the disease, and they may present as completely mobile or wheelchair bound. These patients may or may not have blue
sclera or dentinogenesis imperfecta and may present with average or slightly short stature (Cheung & Glorieux).

Recently, three additional subgroups of OI have been identified. These variations of OI are known as types V, VI, and VII (Table 1). The etiology of these newly identified forms of OI are not caused by a known collagen mutation and at present there is not a clear understanding of the underlying genetic defect (Cheung & Glorieux, 2008). Until recently, patients who currently fall into OI type V, VI, or VII were considered to be part of the general OI population (Cheung & Glorieux). While research is still in the early stages in regards to treatment of these forms of the disease, it is becoming evident that they do not respond to the same treatments as the classic OI groups (Cheung & Glorieux). As the molecular understanding of OI advances, researchers expect to find further subgroups within the general OI population (Cheung & Glorieux). Because OI types V, VI, and VII were identified recently they are not included in the original Silence classification.

This is a review of the literature regarding the treatment of OI. It is the hope of the author that this review will give PAs a clear understanding of the clinical picture of OI as well as the available treatment options. The goal of this paper is to organize and discuss current and potential future treatments of OI. For the purpose of this paper, focus will be placed on OI types I-IV. Current treatment will be divided into non-pharmacological and pharmacological therapies. Non-pharmacologic therapy will be further subdivided into a section focused on physical therapies and orthoses and another section discussing surgical forms of treatment. Pharmacological therapy will focus on the breakthrough of bisphosphonate treatment and its role in the management
of OI. Future treatment will include discussion regarding gene therapy and stem cell transplantation as potential cures for OI.
Physical Therapy

Physical therapy, rehabilitation, and orthopedic surgery are the mainstay treatments of OI. Physical therapy should be started as soon as the diagnosis of OI is established in a newborn or young child (Jaffe, 1995). Due to the significant clinical manifestation variations between the major types of OI, diagnosis may be confirmed via intrauterine imaging or may not be recognized until the patient has had several fractures and is well into childhood. It is important to note that the pathology of OI is purely a physical handicap (Bleck, 1981). This is a fact that stresses the importance of early physical therapy and rehabilitation. In general, therapy should be anticipatory of future needs of the patient as their disability changes or progresses; while at the same time working to maintain self-sufficiency and an optimum level of function (Jaffe).

In 1995, Jaffe and colleagues developed a list of six goals to assist health care workers in formulating rehabilitative plans for OI patients (see Table 2). Jaffe’s first three goals include prevention/correction of impairment, enhancement of systems not affected by disease, and increasing functionality. These statements direct therapy toward rehabbing any current injury and taking precautionary measures to prevent future disability. They also focus on taking advantage of areas not affected by OI and encouraging exercise that promotes independence and functionality. Jaffe’s next two goals of using adaptive equipment and modifying the environment complement each other. The OI patient is capable of a higher level of physical functioning when given tools such as braces or walkers to ambulate in their environment. In turn, when the environment is adapted to an OI patient’s needs via modifications and social support, they are able to reach their maximum potential. The final goal deals with psychosocial
aspects of having a debilitating disease that solely affects physical ability. There is a constant struggle for OI patients who strive for independence but are forced to be dependent if there is not appropriate support, rehabilitation, and adaptive aids. According to Jaffe, the amount of self-sufficiency achieved by the OI patient directly affects their level of self esteem (Jaffe).

Physical Therapy Exercises

When the OI patient begins physical therapy and rehabilitation, exercises need to be introduced in a developmentally appropriate sequence. Jaffe and colleagues also devised a general list of the aims of treatment for rehabilitation of children with OI (Jaffe, 1995) (see Table 3). These guidelines include developing exercises that increase bone density while preventing fracture and deformity. Also, treatment should focus on helping the child become familiar with his or her environment and how to function without causing injury. An important goal for therapists working with young OI patients is educating their family about the disease. This is an important point because it is often parents with good intentions who do too much for their child, resulting in hindrance of their autonomy and self-sufficiency (Jaffe).

One treatment aim that plays a major role in determining the patient’s physical potential is the prevention of deformities. OI patients readily develop deformities called contractures that are caused by inappropriate elasticity of muscle fibers that lead to a loss of joint motion. During infancy, the most common contractures to develop are those of hip abduction and of the neck musculature (torticollis) (Binder et al., 1993). Hip abduction contracture and torticollis are more likely to occur after patients are
placed in supine position for an extended period of time. This most commonly occurs when children are layed down on their backs in bed to sleep at night. This position allows their hips to abduct and their head to fall to one side. Healthy patients with normal muscle tone and elasticity are generally unaffected by their sleeping positions.

Early therapeutic intervention allows physical therapists to educate parents on the importance of positioning. Positioning is a technique that is used to mold bones and muscles of OI patients so that, when they are developmentally ready to attempt standing and walking, their legs are straight and muscles are without contracture. Binder and colleagues were the first to suggest maintenance of position with the use of towel rolls or light weight sand bags (Binder et al., 1993). Examples of how to utilize towel rolls to properly position children when sitting and laying down are displayed in figures 1 and 2. If the patient is most comfortable in the supine position, towel rolls can be placed along each side of the child from ear level to knee level as well as one towel roll under the child’s flexed knees. Towel rolls placed from ear to knee level ensure neck alignment as well as prevention of hip adduction. Placing one towel roll under the patient’s flexed knees further prevents hip adduction as well as reduces strain on the vertebra of the lumbar spine (see Figure 1). To maintain a side-lying position the child’s hips and knees should be flexed to 90 degrees. Towel rolls should be placed along the child’s back and buttocks forming an ‘L’ shape. Finally, one towel roll should be placed between the child’s knees to maintain proper hip alignment (see Figure 2). When putting a child with OI in a car seat or stroller, towel rolls should be placed along each side of the child from ear to hip level, similar to figure 1. This will allow the child to maintain upright posture and decrease the risk of injury if the seat is jostled.
As the patient gets older (1.5 to 2 years of age), the therapist is able to introduce exercises into the therapeutic regimen (Binder et al., 1993). These exercises will help prepare the patient for ambulation, continue to strengthen important muscle groups once he/she is able to walk, and prevent contracture formation. Contracture of the hip flexors becomes a danger as the patient with OI gets older and is sitting for longer periods of time. By two years of age, the child is ready to actively participate in exercises that strengthen hip extensors and abdominal muscles to decrease risk of contracture. These exercises include hip extension in supine position, hip adduction and abduction in prone position. Also, supine crunches to strengthen abdominal muscle, overhead reach to promote increased shoulder range of motion, and modified pushups to strengthen upper body muscles (Binder et al.) (see Table 4). Frequently, there are also limitations in shoulder flexion and abduction that develop in patients with OI (Binder et al.). This deficit in range of motion often leads to conditions such as adhesive capsulitis. Adhesive capsulitis is also referred to as frozen shoulder and occurs when there is inflammation within the glenohumeral joint. The ability to have full use of arms and upper body is important for OI patients, especially those who are unable to walk. To safeguard against this type of situation, therapists stress functional activities that involve overhead reaching. Strengthening of the upper extremities can be achieved by the use of 1-2 pound weights that should be closely attached to the shoulder or elbow. Attachment of the weights to the proximal arm is important, as it prevents the creation of a long arm lever that could cause bowing or fracture of the humerus (Binder et al.). In addition to muscle strengthening, aerobic exercises such as
swimming and stationary biking are encouraged to promote endurance and maintain or increase functional capacity (Van Brussel et al., 2008).

**Orthotics**

It is also around two years of age that the OI patient is developmentally appropriate to prepare for walking. At this time, the patient should be fitted for orthotics to help him/her maintain a safe upright position. The most commonly used orthosis is called a hip knee ankle foot orthoses (HKAFO). This typically consists of a plastic clam shell design with a wide pelvic band to provide external support to the aforementioned joints while the patient is in the standing position (Binder et al., 1993). It is important to note, that before the use of external bracing can be initiated, the OI patient must have adequate bony alignment to fit within the confines of the bracing; this emphasizes the value of early intervention. One of the main goals of bracing is strengthening of the bones. Because bone is naturally weaker in patients with OI, and depending on severity of disease, it may not support the patient’s body weight. Orthotics may be utilized to take a certain amount of stress off the brittle bones, while at the same time stressing bones enough to increase their strength (Zeitlin, Fassier, & Glorieux, 2003; Weintrob, 1995).

Utilization of bracing devices encompasses a large portion of physical therapy for the OI patient. In 1980, Dr. Eugene Bleck proposed a system of bracing, referred to as functional bracing, which adapts to the patient’s growth and body changes from infancy through adolescence. Use of functional bracing begins when the patient learns to sit upright. The first orthotic is a molded seat insert that encourages upright posture with
spinal support (Bleck, 1981). Various orthotics assist the patient through normal stages of development. Bleck believed that treatment approaches should be designed to reduce disability and improve functionality, while at the same time ensuring normal developmental progresses such as crawling and walking in the face of the underlying pathological condition.
Surgical Intervention

Physical therapy and use of orthotics assist patients to some extent, but invasive surgical intervention is often also required to provide internal support to brittle bones. External support of bones with plates and screws is contraindicated in the OI population because of the high fracture rate above and below the plate in addition to poor screw fixation (Cole, 1995). The insertion of stainless steel or composite rods into long bones, most commonly the femur and tibia, is indicated some time after the OI patient’s first attempts at standing and prior to practicing walking. The surgery is timed strategically to help prevent deformities that may be incurred while learning to ambulate (Zeitlin, Fassier et al., 2003). For the purpose of this review article, discussion will be limited to the two major categories of intramedullary rods; non-elongating and telescoping.

Non-Elongating Rod

The non-elongating rod was introduced in 1948 by Sofield and Millar and proved to correct and stabilize deformity in patients with OI. The Sofield-Millar procedure involves fragmentation, realignment, and intramedullary rod fixation of long bones. The first step of the operation requires the subperiosteal exposure of the entire shaft of the long bone. Osteotomy, which is the surgical fragmenting of bone to change its alignment, is then performed through the proximal and distal metaphysis (Sofield & Millar, 1959). The entire shaft of the bone is then removed and evaluated to determine the number of additional osteotomies that need to be performed to achieve proper alignment. Sofield and Millar felt that it was better to err on the side of too many osteotomies to create the best results. Then each bone fragmentation is strung onto a
The rod is selected based on how closely it matches the size of the medullary canal. It is also interesting to note that bone fragments are placed on the steel rod in which ever order will yield the straightest line regardless of the original positions of the bone.

In 1959, Sofield and Millar published a ten-year appraisal of their procedure. The patients receiving the operation had conditions such as OI as well as congenital pseudoarthrosis of the tibia, osteomalacia, fibrous dysplasia of bone, and congenital shortening of the femur and tibia. In their appraisal of the operation, Sofield and Millar noted excellent results and very few complications. In regards to OI, there were eighty operations performed on 22 patients. They found that once the bone fragments were placed on the steel rod, solid bone union occurred every time with a medullary canal forming around the rod. Sofield and Millar did not note the length of time it took for the bony union to form. One major complication that is inevitable with any non-elongating rod is bone growth. Once the bone extends distally beyond the rod, the distal portion of the bone tends to deform by bending or fracture. It is then necessary to perform osteotomy of the distal deformed bone or repair the fractured bone by realigning it with a longer steel rod. It was found that the average length of time for rod replacement due to bone overgrowth was approximately 2.5 years (Sofield & Millar, 1959).

In 1995, Li and colleagues modified the classic Sofield-Millar operation. Their modifications included decreased exposure of bone and limiting the number of osteotomies performed (Li, Chow, & Leong, 2000). The procedure begins by placing the patient in supine position and elevating the operative limb with a sandbag. With the greater trochanter exposed, reaming or drilling out of the medullary canal may begin (Li
et al.). The size of the drill should be as close as possible to the same size as the canal to ensure proper fit of the non-elongating rod. As the drill is progressed through the canal it is visualized by fluoroscopy and then stopped at the first bony angulation. At this point the surgeon will perform a percutaneous osteotomy by making a small incision and remove a wedge of bone, thereby reducing the curvature. The cuts are made in a wedge shape to eliminate the angulation while retaining maximum soft tissue attachments (Stockley, Bell, & Sharrard, 1989). After each osteotomy, the rod is progressed distally until it reaches its destination where it will rest in the femoral condylar region near the epiphyseal line. The proximal end of the rod should be bent at a right angle medial to the greater trochanter. If the procedure is being performed on the tibia, the site of entry and location of the proximal rod placement is posterior to the patellar tendon. With tibial fixation, the distal end of the rod will rest near the distal epiphyseal line (Li et al.).

Li and colleagues performed a retrospective study of 10 OI patients who had osteotomies with intramedullary fixation procedures. There were a total of 58 procedures between the 10 patients. The operations performed prior to September 1995 were the classic Solfield-Millar operation and those performed after were the modified technique by Li et al (Li et al., 2000). Li and colleagues analyzed time to union after the recent procedures and used information from medical records for past procedures. They defined time to union as the time it took for a bridging callus to form between osteotomies (Li et al.). The results were a statistically significant delay in time to union when there had been greater than three osteotomies. This clearly supports the Li modification of keeping the number of osteotomies performed to a minimum (Li et al.).
**Telescopic Rod**

Bailey and Dubow introduced a telescopic rod system in 1963. This system consists of a hollow sleeve and a central, removable core referred to as the obturator. These two pieces are held in place by T-pieces that anchor at the proximal and distal epiphyses of long bones. This design allows the bone to grow linearly without the need to replace the rod and may decrease the number of surgeries required for children with OI. However, a high complication rate associated with the Bailey-Dubow system ranging from 30-70% has been reported (Reing, 1995). The most common complication being that the rod fails to elongate, necessitating surgical intervention and rod replacement (Lang-Stevenson & Sharrard, 1984). The T-pieces in the Bailey-Dubow kit consist of two parts that are screwed together and were meant to be utilized to ream the medullary cavity. The concern is that during the rough process of clearing out a tunnel in the middle of the bone, these T-pieces could become damaged. Some surgeons felt that this played a part in the mechanical malfunction of the system, so the Sheffield telescopic rod system was introduced in 1986. This system was created to decrease the common complications by utilizing fixed and slightly larger T-pieces and separate hand drills to ream the medullary cavity (Stockley et al., 1989). Currently, Cho et al have proposed an interlocking telescopic rod system utilizing a hollow sleeve and obturator of the same dimensions as the Sheffield rod system. Contrary to the Sheffield system, the modification devised by Cho and his colleagues involves a telescopic rod without a T-piece at the distal end; instead having a small hole for an interlocking pin (Li et al., 2000).
The surgical technique for the insertion of the telescopic rod system is more complex than that of the non-elongating rod (Reing, 1995). Preoperative plain films are taken to assess the deformity and estimate the appropriate rod size needed. As with the surgical techniques used to insert the non-elongating rod, osteotomies must be performed. Depending on the degree of angulation present, the surgeon will decide to perform an open or percutaneous osteotomy. A Kirschner wire (K-wire) is threaded through the medullary canal of the bone fragments. The sleeve is then slid over the outside of the bone fragments that are currently being held in place by the K-wire. Once the sleeve is in place, the obturator replaces the K-wire in the medullary canal and is advanced distally. The small hole of the obturator is now at the distal epiphyseal line and ready to be secured by insertion of the K-wire (Cho et al., 2007).

There are a number of complications associated with the insertion of any types of surgical rods in OI patients. Intraoperative and postoperative fracture, as well as an increased incidence of osteoporosis from immobilization, have been found to occur equally with both insertion of non-elongating and telescopic rods (Cole, 1995). Non-elongating rods will require revision as the patient grows, or if the integrity of the rod becomes compromised. Telescoping rods will also need to be replaced if bending or breaking occurs but, as mentioned earlier, more commonly require replacement because of failure to elongate (Jerosch, Mazzotti, & Tomasevic, 1998). The majority of documented complications occur with the telescoping rods, but this may be explained by the popularity of using this method. Proximal migration into joints and soft tissue may occur with both forms of rodding but is noted most often with the Bailey-Dubow (original telescopic rod) telescoping rod (Cho et al., 2007; Jerosch et al., 1998). This
proximal migration is often attributed to dysfunction associated with T-pieces as previously discussed. Additional complications associated with any general surgery and use of anesthetic include risk of infection and respiratory distress (Cole).
Pharmacological Therapy

A major development in the treatment and management of OI has come in the form of pharmacological therapy. A class of agents called bisphosphonates has been known to chemists since the 19th century. The journey of bisphosphonates from industrial anti-corrosive agent to major class of medication started with inorganic pyrophosphate (PPi) (Russell, 2006). In the 1930’s, PPi was known to be an effective water softening agent with properties that prevented calcium carbonate precipitation thereby inhibiting abnormal calcification (Russell, 2007). It was not until the 1960’s that Fleisch and Bisaz were able to demonstrate that humans have an internal ‘water softener’ (1962). They hypothesized that PPi helped to prevent ectopic calcification in soft tissues. Later, Fleisch and Bisaz were able to isolate PPi in urine and serum (1962). Through many studies it was found that PPi was not an effective oral agent because of its hydrolysis or breakdown in the GI tract (Russell, 2007). Researchers began searching for a more stable analog that would not hydrolyze but would still have antimineralization properties (Russell, 2007). This led researchers to bisphosphonates which were found to have properties similar to those of PPi, such as a high affinity for hydroxyapatite crystals in bone mineral and prevention of abnormal calcification. However, bisphosphonates were able to prevent pathologic calcification even when administered orally (Halasy-Nagy, Rodan, & Reszka, 2001).

History of Bisphosphonates

Bisphosphonates are composed of a phosphorus-carbon-phosphorus backbone which is similar to the phosphorus-oxygen-phosphorus backbone of PPi (Halasy-Nagy
et al., 2001). The carbon atom is one of the keys to the efficacy of bisphosphonates because it allows for addition of side chains in the R1 and R2 positions (Halasy-Nagy et al.). As discussed previously, bisphosphonates bind easily to bone mineral, but this affinity can be enhanced when the R1 position on the carbon atom is occupied by a hydroxyl group (Russell, 2006). The remaining R2 side chain determines the pharmacological effects of the agent such as its antiresorptive potency (Russell) (Halasy-Nagy et al.). Based on chemical structure, bisphosphonates may be divided into two classes. The first class consists of nitrogen containing bisphosphonates such as pamidronate, alendronate, ibandronate, zoledronate, and risedronate. The second class is called simple or non-nitrogen containing bisphosphonates which are etidronate and clodronate. The nitrogen containing bisphosphonates possess one or more nitrogen atoms at the R2 position while the R2 side chain of simple bisphosphonates has a methyl group or a chloride atom (Halasy-Nagy et al.).

Both classes of bisphosphonates adsorb to bone mineral when administered orally or parenterally. However, this is not their sole mechanism of action. Once the bisphosphonate attaches to a resorption space, or area where the osteoclast is dissolving mineralized bone, it becomes internalized (Russell, 2007). This was confirmed in a study conducted by Sato et al., where radiolabeled alendronate bound to hydroxyapatite was ingested by the osteoclast via endocytosis (1991). Once inside the osteoclast, the two classes of bisphosphonates operate using different modes of action. The simple or non-nitrogen containing bisphosphonates are metabolized into toxic analogs of adenosine triphosphate (ATP) (Halasy-Nagy et al., 2001). The osteoclast is unable to catabolize or breakdown the toxic compound. Researchers believe that
simple bisphosphonates achieve their goal of inhibition of osteoclasts and in turn bone resorption through the accumulation of toxic ATP analog and induction of cell death (Halasy-Nagy et al.). Nitrogen containing bisphosphonates interfere with the mevalonate pathway also called the HMG-CoA reductase pathway. This biosynthetic pathway is responsible for the production of cholesterols and certain lipids. In particular, nitrogen containing bisphosphonates inhibit the production of two metabolites of the mevalonate pathway called farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP). FPP and GGPP are required for the modification of guanosine triphosphatase (GTPase) which are important signaling proteins that regulate functions of the osteoclast. Nitrogen containing bisphosphonates therefore exert their primary action on the mevalonate pathway which secondarily results in osteoclast apoptosis (Halasy-Nagy et al.).

Pharmacokinetics of Bisphosphonates

The pharmacokinetics of bisphosphonates are well understood. However, there is not a complete picture of how these agents work in patients with OI. Rauch and colleagues conducted a histomorphologic study consisting of 45 patients with documented OI type I, III, or IV. The study examined changes in iliac biopsy after treatment with intravenous pamidronate versus placebo. Bone samples were taken at baseline and again after 2.4 years of treatment, revealing a significant improvement in cortical width averaging an 88% increase (Rauch, Travers, Plotkin, & Glorieux, 2002). Cortical thickness is thought to be increased through the process of modeling. Therefore, even though bisphosphonates selectively inhibit the actions of osteoclasts,
osteoblasts continue to produce cortical bone because in the modeling process the two cells work independently (Lindsay, 2002; Rauch et al.). Conversely, Rauch et al, found no change in the width of trabecular bone which is increased through the remodeling process. Remodeling involves the coupling of the osteoclastic and osteoblastic actions. Rauch et al, also noted an increase in the amount of cancellous bone, a finding which is consistent with inhibition of osteocytes.

Many advances have been made in the use of bisphosphonates in treatment of OI; however no medications are presently FDA approved for this use. With much uncertainty and lack of evidence to base decisions on, clinicians are left to wonder how to provide OI patients with the best care. The majority of the current literature regarding bisphosphonates and OI examines the effect of cyclical administration of intravenous (IV) bisphosphonates, pamidronate and more recently neridronate. A three year clinical study conducted in Italy by Gatti and colleagues is one of only two controlled trials. It is also the largest study, consisting of 64 prepubertal OI patients aged 6-11. Inclusion criteria included a diagnosis of OI, no signs of puberty, and no previous use of any bisphosphonate (Gatti et al., 2005). Subjects were randomized at a 2 to 1 ratio to receive IV neridronate or to be in the control group and receive no treatment. The group receiving treatment were administered neridronate intravenously at a dosage of 2mg/kg diluted in 250ml saline infused over 30 minutes every 3 months (Gatti et al.). Both the control and treatment groups were required to maintain a regulated daily intake of calcium through diet and supplementation. The amount of calcium required was 600mg if the patient was less than 7 years old, 800mg if between 7-10 years, and 1000mg if the patient was older than 10 years (Gatti et al.). Vitamin D supplementation
was also given if serum 25(OH)vitamin D levels fell below 20ng/ml. Patients were seen for clinical evaluation prior to the administration of medication every 3 months. The evaluation included bone mineral density (BMD) measurements by dual-energy x-ray absorptiometry (DXA), height and weight measurements, fasting serum and urinary studies, and chemistry panels to monitor serum calcium, phosphate, and creatinine. Radiographs of the spine were taken at baseline and again after 12 and 36 months (Gatti et al.). The results of this study included statistically significant increase in spinal BMD of 30% the first year, 20% the second year, and 15% the third year. Significant increases in BMD were also noted in the hip and lumbar spine. The mean individual height rose significantly by 2.6% in the treatment group as opposed to only 0.9% in the control group during the first year. During the first year of observation 45% of patients in the control group received at least one fracture, while in the treatment group a significantly lower 27% of patients experienced fracture. Because the results were so promising after 12 months, the control group was also given treatment. By the end of the trial all subjects, including those originally in the control group, had reached height values similar to those of healthy patients in the same age group. The authors concluded that IV neridronate when administered every 3 months significantly increases BMD while also significantly lowering the risk of fracture (Gatti et al.).

The second controlled trial regarding the use of bisphosphonates in the treatment of OI involved the use of IV neridronate in the treatment of adults with OI. The trial was composed of 23 males and 23 postmenopausal females. The study criteria included a diagnosis of OI and subjects who had never used bisphosphonates (Adami et al., 2003). Similar to the previous study design, patients were randomized to receive IV neridronate
(100mg over 30min every 3months) or to be in the control group at a ratio of 2:1. Every six months patients were evaluated with DXA, fasting serum and urinary biochemistry. Plain films of the spine were taken at baseline and again at 12 and 24 months (Adami et al.). Results revealed statistically significant increases in spine and hip bone density at 12 and 24 months compared to baseline. The incidence of fracture also significantly decreased in the treatment group as compared to the control group. Again, because of such promising results the control group began the same IV neridronate treatment at the end of the first trial year (Adami et al.)

The results of the previous two studies are consistent with smaller, observational studies involving cyclical IV pamidronate. At present, the optimal dose and treatment interval are unknown. The most commonly used dosing schedule for the administration of bisphosphonates, proposed by Rauch and colleagues is referenced in table 5. It is recommended that each dose be diluted in 0.9% saline and administered over 4 hours (Rauch et al., 2002). Many trials follow the same or similar dosing patterns. In a study by Gatti et al. (2005), a dosage of 8mg/kg/year for patients 6-11 years of age was used. If the researcher followed the recommendations of Rauch et al., the same patients would have received a similar 9mg/kg/year. Researches often utilize a dosing schedule with lower dosages and more frequent intervals for children younger than 2 years (Rauch et al.). In young patients, the ability of bisphosphonates to decrease chronic bone pain is short-lived. This may be due to the cellular overactivity of OI compounded with accelerated bone turnover seen in growing bones (Rauch, Munns, Land, & Glorieux, 2006) A prospective observational study conducted by Astrom et al. (2007), involved the treatment of 11 infants afflicted with OI aged 3-13 months with IV
pamidronate. The infants were originally treated with monthly infusions of pamidronate at dosages of 10mg/m² for 3 months and 20mg/m² for 3 months and finally 30mg/m². After 1-2 years of treatment, measurements showed that the children had not gained the expected BMD. They complained of bone pain, so the dose was increased to 40mg/m². This treatment was maintained for 3-6 years. Throughout the treatment period, the children were assessed every 6 months and were compared to a historic untreated control group. The results of the study found a statistically significant gradual increase in BMD as per DXA, decrease in serum and urine markers of bone metabolism, and increased vertebral height. Astrom et al. noted that IV pamidronate may help to prevent the development of scoliosis or kyphosis if started early (Astrom & Soderhall, 2002).

**Oral Bisphosphonates**

There are only two studies regarding the efficacy of oral bisphosphonates in patients with OI. Sakkers et al. (2004) conducted a two-year randomized double-blind placebo-controlled study that consisted of 34 children with a documented diagnosis of OI, who had not previously used bisphosphonates, and had restricted ambulation. The criteria for restricted ambulation was that the patient could not walk more than 250m without the aid of crutches. The 34 subjects were randomly assigned to the treatment (16) or control group (18). The treatment group received olpadronate orally in the dosage of 10mg/m2 for 2 years. Primary endpoints of the study consisted of incident fractures of long bones, change in DXA outcome, or change in functional outcome. Measurements obtained during this study included measurement of bone mineral
density and bone mineral content by DXA of the lumbar spine and os calcis or calcaneus at baseline, after one year, and at the conclusion of the trial (Sakkers et al.). Sakkers et al also measured changes in functional outcome according to the modified Bleck scale (Engelbert, Uiterwaal, Gulmans, Pruijs, & Helders, 2000). The criteria on the modified Bleck scale of 1-9 are defined as: 1) non-walker, 2) therapy walker with crutches, 3) therapy walker without crutches, 4) household walker with crutches, 5) household walker without crutches, 6) neighborhood walker with crutches, 7) neighborhood walker without crutches, 8) community walker with crutches, or 9) community walker without crutches. An improvement of one positive score on the modified Bleck scale as compared with baseline was considered a significant finding (Sakkers et al.). The results of this study revealed an increase in one level on the modified Bleck scale in 3 patients in the treatment group and 3 patients in the control group. Therefore, Sakkers et al. concluded that olpandronate had no statistically significant effect on functional outcome. However, results did reveal a significant 31% decrease in the relative risk of fracture rate per year in the treatment group and also a significant increase in spinal BMD with a between group difference of 0.054g/cm2 (p=0.01). Sakkers et al. denied that patients had any complaints of gastrointestinal side effects during the trial. However patients and caregivers did report occasionally forgetting to take the study medication.

In a clinical trial conducted by DiMeglio et al., oral alendronate was compared with IV pamidronate in a two-year prospective trial. The trial was composed of 18 OI patients with half of the subjects randomly assigned to receive alendronate in the dose of 1mg/kg/day tablet (taken daily) or IV pamidronate in the dose of 1mg/kg for 3 days
every 4 months (DiMeglio & Peacock, 2006). After one year, both groups exhibited a significant increase versus placebo in total BMD. Statistically significant increases in BMD were observed in both the IV and oral pamidronate groups of 48% and 42%, respectively. The subjects in both groups experienced statistically significant improvement in their linear growth rate to a level similar to healthy patients in the same age group. DiMeglio et al. concluded that both oral and IV bisphosphonate therapies are effective treatments in children with OI.

At present, all clinical trials involving bisphosphonates as a treatment for OI have shown positive results. However, there seems to be great variation in the results of these trials. One cause of the variability could be due to the types of OI being treated in each study. A trial composed mainly of subjects with the more severe forms of OI, such as types III and IV, may show greater improvement because their condition is so much worse. Conversely, a study whose subjects are afflicted with a milder type of OI, such as type I, may have less improvement compared to placebo because of their better functional status and lower fracture rate (Rauch & Glorieux, 2005). Another potential cause of variable results among studies could be due to the availability and use of many different bisphosphonates. Each bisphosphonate has slightly different properties in regards to efficacy, duration of action, and potential side effects.

There are many clear advantages to the use of oral bisphosphonates for patients with OI. It is more convenient for patients to have their medication at home; whereas frequent hospitalizations are required for IV treatment. These visits are time consuming and may become costly (Rauch & Glorieux, 2005). There are also disadvantages to oral agents such as compliance issues of forgetting to take medication or difficulty
swallowing pills. Also, with oral bisphosphonates, there are specific instructions regarding taking pills on an empty stomach, not eating for a certain amount of time, and remaining upright after ingesting the medication. Non-compliance with any of the instructions could decrease the efficacy of the drug.

At present, there are still many uncertainties regarding the use of bisphosphonates to treat OI. Researchers have accepted bisphosphonates as a safe short-term therapy for children with OI (Astrom et al., 2007; DiMeglio, Ford, McClintock, & Peacock, 2004; Rauch & Glorieux, 2005), but the long-term safety of these agents is unknown. It is also unknown when, if ever, to cease bisphosphonate treatment (Rauch & Glorieux). Peripheral quantitative computed tomography (pQCT) was used to assess BMD in 23 OI patients who were discontinuing IV pamidronate treatment after at least 3 years (Rauch, Cornibert, Cheung, & Glorieux, 2007). The subjects ranged in age from 5.9 to 21.3 years of age at treatment discontinuation. pQCT was performed on the radius at the distal metaphysis and at the diaphysis. Measurements were taken when treatment was stopped and again at an average of 1.9 years later (Rauch et al.). The first set of pQCT measurements revealed all subjects to have close to normal BMD and BMC at the distal radial metaphysis most likely due to use of IV pamidronate. The second measurement revealed that subjects who were still growing when they discontinued IV pamidronate experienced a rapid decrease in BMD at the distal radial metaphysis. Conversely, subjects whose growth plates had closed prior to stopping treatment retained near normal levels of BMC and BMD at the distal radial metaphysis (Rauch et al.). Researchers found that while growth plates are open and bone is still growing longitudinally, each cycle of IV pamidronate results in the accumulation of a
band of mineralized tissue between the growth plate and the metaphysis (Rauch et al.). These bands are visible radiographically as metaphyseal lines. Animal studies suggest that these metaphyseal lines eventually remodel into secondary bone (Rauch et al.). When bisphosphonates are given after growth plate closure, there is no evidence of additional metaphyseal lines and the effect on bone mass is much smaller (Rauch et al.). Patients who had stopped IV pamidronate prior to growth plate closure experienced a significantly higher risk of fracture. Researchers found that the interface between the dense bone created during treatment and the less dense 'untreated' bone were common fracture sites. The authors concluded that continuing IV pamidronate treatment may be beneficial as long as growth continues (Rauch et al.).

While the use of bisphosphonates has brought clear improvements to the lives of OI patients there are also potential adverse effects. The extent of the side effects is currently unknown because bisphosphonates have only recently been used as a treatment for OI. There is concern that prolonged bisphosphonate use resulting in decreased remodeling may have harmful future effects for OI patients (Rauch & Glorieux, 2005). The decrease in remodeling through inhibition of osteoclastic activity is one of the actions of bisphosphonates. Researchers hypothesize that this may result in accumulation of calcified cartilage as opposed to mature bone formation. Calcified cartilage results when, in the process of bone formation, growth plate cartilage is not fully removed by the osteoclasts. Because osteoclasts are inhibited by the bisphosphonates and the growth plate cartilage is not resorbed, mature bone may be unable to form. The formed calcified cartilage would be less resistant to fracture than mature bone (Rauch & Glorieux, 2005; Zeitlin, Rauch, Plotkin, & Glorieux, 2003).
Another concern is that bisphosphonates are known to remain in the bone for several years even after discontinuation of therapy and the long-term effects of this phenomenon are unknown. One population in particular that this may affect are females of child-bearing age (Rauch & Glorieux). General side effects associated with bisphosphonates that are not OI specific include stomach irritation, osteonecrosis of the jaw, and electrolyte disturbance.

Other Pharmacological Agents

Other pharmacologic treatments for OI include calcitonin, vitamin D, and calcium. Calcitonin is a human hormone produced in the parafollicular cells of the thyroid glands (Inzerillo, Zaidi, & Huang, 2004). Calcitonin acts primarily on osteoclasts to inhibit bone resorption thereby decreasing the level of calcium in blood. Because of its antiresorptive properties calcitonin was thought to be a potential treatment for OI. However, through research it was found that calcitonin only has a half life of 10-15 minutes and has fallen out of favor since the advent of bisphosphonates and their half lives ranging from 10-60 hours (Inzerillo et al.). Calcium and vitamin D supplementation are both recommended for OI patients. In most clinical studies, OI patients are required to ingest 500-1000mg of calcium and 200-400IU/day of vitamin D in conjunction with the treatment being studied in the clinical trial (Rauch, Travers, & Glorieux, 2006 ; Sakkers et al., 2004 ; Zeitlin, Rauch, Travers, Munns, & Glorieux, 2006).
Future Treatments

Gene therapy is actively being researched by scientists and genetic engineers as a potential therapy or cure for OI. Basic gene therapy involves insertion of a wild type or corrected copy of the mutated gene into the genome. The goal of providing the corrected copy is to decrease the amount of dysfunction caused by the mutated gene. This could benefit the OI patient by reducing the degree to which abnormal bone is formed, in turn decreasing the severity of OI. The OI patient may still have some OI symptoms such as bone fragility, but this treatment could potentially decrease the number of fractures. The process of inserting the corrected copy of the gene into the genome requires the use of vectors. Viruses naturally have the ability to deliver their own genes into the human genome because this is how they replicate and infect their host. Genetic engineers have altered this feature and created viruses that serve as vehicles (vectors) to deliver wild type genes to the genome.

Gene therapy is complicated by the variations in mutations causing OI. With such a wide range in pathogenesis it may be unreasonable to expect one treatment to cure or treat all forms of the disease (Niyibizi, Wang, Mi, & Robbins, 2004; Rauch & Glorieux, 2006). To date, there have been no human clinical trials involving gene therapy. Researchers hypothesize that basic gene therapy might be effective in treating OI caused by null mutations (OI type I). However, OI caused by dominant negative mutations, the more severe types III and IV, may require another step (Millington-Ward et al., 2005; Rauch & Glorieux). The extra step to silence the dominant negative mutation is called antisense gene therapy. Antisense is a strand of DNA or RNA manipulated by scientists to be complementary to mRNA for the mutant gene. Without
the presence of antisense, the mRNA for the mutant gene is normally translated, and the mutated gene continues to be expressed (Millington-Ward et al.; Niyibizi et al.). The goal of the antisense stand is to bind tightly to the mRNA for the mutant gene, discontinuing its translation, and resulting in silencing of the gene. By silencing the gene, the degree of OI could be down-regulated from a severe to a mild form. Essentially, the patient may have a null mutation expressed as OI type I and if the patient pursues the hypothetical next treatment step of basic gene therapy, their condition may be further improved (Millington-Ward et al.).

Another treatment, termed cellular therapy, involves the transplantation of adult bone marrow from matched donors to OI patients. Adult bone marrow is used because it contains mesenchymal stem cells (MSC) that have the ability to differentiate into a variety of tissue types including cartilage, muscle, fat, and, most importantly for OI patients, bone (Niyibizi et al., 2004; Rauch & Glorieux, 2006). Researchers have hypothesized that through the transplantation of MSC containing bone marrow, the formation of normal osteoblasts would occur. The other importance of initially having normal osteoblasts is that they do not proliferate and have a definite life span (Chevrel & Cimaz, 2006). In 2001, Horwitz and colleagues, spurred on by positive murine trials, conducted the first human clinical trial of MSC transplantation in OI patients. The trial was conducted using five patients with a diagnosis of OI type III (Horwitz et al., 1999). The patients were divided into a control consisting of two patients and the remaining three patients in the experiment group. The study design required that each of the trial participants have a bone biopsy taken from one of their iliac crests before and then again 6 months after transplantation. Prior to MSC transplantation the patients had to
be irradiated to essentially destroy the existing bone marrow and in turn the mutant stem cells. MSCs were transplanted via an IV catheter into the patient’s blood stream. The stem cells circulated throughout the patient’s blood, eventually finding their way to the hollow marrow cavity. The goal was for the MSCs to engraft within the bone marrow cavity and re-establish normal levels of cells. In this clinical trial engraftment was associated with improvements in bone histology (Horwitz et al., 2001). Comparison of the histologic composition of the pre- and post-transplant bone biopsies revealed that the 3 patients of the experimental group had engraftment of donor cells. From the biopsies, through the use of high powered microscopy, it was determined that the engraftment was partial – only 1.5-2% of the cells in the biopsy were found to be of donor origin (Horwitz et al., 2001). Horwitz and colleagues reported that the participants exhibited significant increases in their total body bone mineral content of 45-77 percent above baseline (Horwitz et al., 1999). This increase placed the experimental group at the lower limit of normal for age-matched healthy patients. However, with extended follow up, bone mineral content decreased to pre-transplantation levels (Horwitz et al., 1999). The transplantation of MSCs as a cure or even a treatment for OI is still in early stages of development. It is important to note that since the trial conducted by Horwitz et al., there have been no further human trials published regarding the treatment of OI with MSCs. Many researchers question the risk to benefit ratio of conducting MSC trials involving irradiation and uncertain outcomes on OI patients (Horwitz et al., 2001; Niyibizi et al., 2004; Rauch & Glorieux, 2006).
Conclusion

Osteogenesis imperfecta is a disease for which there is currently no cure. At present, modern medicine is able to offer various treatment options to OI patients, including physical therapy and orthotics, surgical intervention and pharmacological therapy. Physical therapy consists of exercises and positioning that aim to prevent contracture, strengthen muscle, and decrease fracture. Use of orthotics and other walking devices allow many OI patients to function independently. This independence tends to have a positive effect on the patient's self-esteem and encourages goal setting.

Surgical intervention includes the placement of steel rods to correct deformity. The benefit of these types of surgeries is that many patients who were previously wheelchair bound due to bony deformity may be able to walk. The use of bisphosphonates to increase bone mineral density is becoming common practice but is still considered off label use. Many published studies discuss the use of IV bisphosphonates. However, it seems more practical to give OI patients daily oral bisphosphonates. The studies performed by Sakkers et al. and DiMeglio and Peacock measured the effects of oral versus IV bisphosphonate and found no statistically significant differences.

It is evident that patients with OI benefit from early diagnosis and treatment initiation. However, OI is a heterogeneous disease with many different presentations. For PAs this means including OI in the differential diagnosis when presented with a variety of clinical pictures. It is well-established that when a young child presents with a long-bone fracture, abuse should remain high on the differential and must be ruled out. However, when a young child with an acute fracture of any bone is found to have a history of multiple fractures, the diagnosis of OI should also be entertained. An astute
PA may further investigate the potential diagnosis particularly if the child is of short stature for his/her age, has blue sclera or subtle limb deformities. Another situation in which OI must be included in the differential diagnosis occurs when a young adult (less than approximately 45) presents with atraumatic low back pain and is found to have radiographic evidence of compression deformities in the spine. The PA should then probe further into the past medical history for previous fracture history as this patient may have type I OI.

When a patient is suspected to have OI it is vitally important to refer them to the proper medical professionals for early management and treatment of the disease. PAs should utilize resources in their area to find the medical personnel nearby that specialize in OI management. A referral needs to be made to one of the many medical specialties that diagnose and/or treat OI patients. Endocrinology and neurology are two such specialties that have experience in the requisite testing and diagnosis of OI and related disorders. An orthopedist, particularly one in subspecialty pediatric orthopedics, should be consulted to determine if/when surgical intervention is necessary in a patient newly diagnosed with OI. Physiatrists often coordinate all aspects of the necessary rehabilitation and the use of orthotics that is standard of care in OI. In adulthood, it is important to remember that many patients with OI may seek the services of a geneticist if they wish to have children. PAs should also be aware that the future treatment of OI will likely be composed of standard dosing regimens for oral and IV bisphosphonates and in the distant future may include genetic or mesenchymal stem cell therapy.

Finally, it is the hope of the author that this review article will provide PAs with a general ability to recognize the signs and symptoms of OI. In the situation of a child
who incurs multiple fractures it may be the PA who plays the vital role of suspicion and recognition of the disease process. The PA may have the responsibility of being the first health care worker to discuss OI with the patient’s parents. It is important to reassure the patient and their parents that the effects of the disease are completely physical. The patient’s mental capabilities will not be affected by OI. The PA should also assist the patient by referring them to the proper health care professionals. While there is no definitive cure for OI, the most effective treatment is provided by an interdisciplinary health care team.


Table 1

Types of Osteogenesis Imperfecta

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Severity</th>
<th>Typical Features</th>
<th>Mutations</th>
<th>Severity</th>
</tr>
</thead>
</table>
| I    | Mild non-deforming                 | Normal height or mild short stature  
Blue sclera present                                                                           | COL1A1            | Least      |
| II   | Perinatal lethal                   | Multiple rib and long bone fractures at birth  
Low density of skull bone on radiograph  
Grey sclera  
Dentinogenesis imperfecta                                                                 | COL1A1 Or COL1A2 | Most       |
| III  | Severely deforming                 | Very short stature with triangular face  
Severe scoliosis  
Grey sclera  
Dentinogenesis imperfecta                                                                  | COL1A1 Or COL1A2 | Moderate to Severe |
| IV   | Moderately deforming               | Moderate short stature  
Mild to moderate scoliosis  
Grey/white sclera  
Dentinogenesis imperfecta                                                                  | COL1A1 Or COL1A2 | Moderate   |
| V    | Moderately deforming               | Mild to moderate short stature  
Mineralized interosseous membranes  
White sclera                                                                                   | unknown           | Moderate   |
| VI   | Moderately to severely deforming   | Moderate short stature  
Accumulation of osteoid bone in soft tissues  
White sclera                                                                                   | unknown           | Moderate   |
| VII  | Moderately deforming               | Mild short stature  
Short humeri and femora  
Coxa vara; hip deformity caused by a decreased angle between the ball and shaft of the femur  
White sclera                                                                           | unknown           | Moderate   |

Table 2

Goal Oriented Treatment Strategies to Lessen or Eradicate Disability

| Prevention or correction of additional impairment or disability |
| Enhancement of systems unaffected by the pathological process |
| Enhancement of functional capacity of affected systems |
| Use of adaptive equipment and aids to promote function |
| Modification of the social, educational, and vocational environment |
| Psychological techniques to enhance patient performance |


Table 3

General Aims of Treatment and Care for Children with OI

| Increase in bone mineral density |
| Decrease in fracture rate |
| Prevent the development of deformities |
| Manage the child’s movement and allow maximal function and environmental interaction |
| Enhance family and child adaptation to the disability and their ability to cope with its associated stresses (promote resilience) |
| Promote the child’s self-esteem and sense of competence |
| Enhance parent-child interaction and the child’s overall social adjustment |

## Table 4

### OI Exercise Descriptions

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Action/ Muscle group strengthened</th>
</tr>
</thead>
</table>
| **Prone and supine lying exercises** | - Pt lies in supine position on a bed or padded mat while extending the hip, elevating the leg into air, and strengthening the hip extensors  
- Pt lies in prone position on bed and abducts hips to strengthen hip abductors and adductors; pt is encouraged to reach legs beyond edge of bed                                                                                                                                                                      |
| **Supine crunch**                 | - Pt lies supine on supportive surface with knees bent to support the lumbosacral spine and performs crunches to strengthen the abdominal muscles                                                                                                                                                                         |
| **Overhead reach**                | - Pt uses non weighted ball or light weights attached at shoulder to perform shoulder flexion and abduction exercises. This will strengthen the anterior and lateral deltoid as well as prevent shoulder contractures                                                                                                                                 |
| **Pushups**                       | - Pt performs pushups on elbows or extended arms as tolerated. These will strengthen chest muscles as well as the triceps and prevent elbow contractures.                                                                                                                                                                                                                   |


## Table 5

### Dosing Guide for Bisphosphonates in OI

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Dose(mg/kg/day) x number of days</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2</td>
<td>0.5mg/kg/day x 3 days</td>
<td>Every 4 months</td>
</tr>
<tr>
<td>2-3</td>
<td>0.75mg/kg/day x 3 days</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>&gt;3</td>
<td>1.0mg/kg/day x 3 days</td>
<td>Every 4 months</td>
</tr>
</tbody>
</table>

Figures

Figure 1
Figure 2
Abstract

Objective: The purpose of this review is to educate physician assistants (PAs) in the recognition and treatment of osteogenesis imperfecta (OI). OI is an incurable genetic disease that causes strictly physical limitations such as decreased bone mass and increased fracture occurrence.

Methods: Databases were searched including MEDLINE, CINAHL, and EBSCO.

Results: Review of the literature revealed that current treatments for OI include physical therapy, use of orthotics, and surgery. Bisphosphonates are used off label to treat OI, however there is still controversy regarding the correct dosage and long-term effects of these drugs. Stem cell and gene therapies are being studied as potential future treatments.

Conclusion: OI is best managed via an interdisciplinary team approach consisting of orthopedists, endocrinologists, psychologists, neurologists, and physical therapists. PAs who are aware of the signs and symptoms of OI may be able to more quickly initiate early intervention and treatment of the disease.