

Facts about Osteogenesis Imperfecta

A Recommendation from OI Experts- Treating the Adult with Osteogenesis Imperfecta

Selection of pharmacological therapies for fracture prevention in adults with OI

On July 27-28, 2017, a meeting was held in Baltimore, Maryland under the auspices of the Osteogenesis Imperfecta Foundation to consider general recommendations for the treatment, both pharmacologic and orthopedic, of adults with osteogenesis imperfecta (OI). In attendance were physicians from different institutions in the US with knowledge of the current treatment patterns for adults with OI in their respective areas.

The following recommendations are intended to assist in formulating pharmacological treatment plans when indicated. These are not intended to replace a physician's best judgement when advising adult patients with OI about treatment options.

1. **Team Management** is essential for adequate care. This is particularly important in the transition from pediatric to adult medical supervision. Involved disciplines should include: Primary care physician, Geneticist, Endocrinology re: ongoing assessment of bone health, Orthopedics, Dentists and Physical therapy and Rehabilitation particularly following orthopedic surgery. Initial Genetic consultation periodic pulmonary assessment, and hearing evaluation are important components of continuing care.
2. **Diagnosis:** A confident diagnosis of OI is essential for subsequent treatment planning. Factors to be considered in the diagnosis of osteogenesis imperfecta in adults include: age of onset of fractures, fracture history, and clinical findings including scleral color, low bone density for age and body size, and skeletal deformities. Supportive findings include family history, hearing loss and dentinogenesis imperfecta.
3. Limited and somewhat arbitrary criteria (height, skeletal deformity, fracture history and ambulatory status) are used in the assignment of specific "OI type" to adults. The designations mild, moderate or severe may reflect ambulatory status, height, and fracture history for clinical purposes.
4. **Genetic Evaluation:** DNA analysis is useful for assisting in the diagnosis of OI and in family planning decisions. Testing uses DNA that can be derived from blood, saliva, or in some cases, from fixed tissue. Usually about 3-5ml of blood in a lavender top tube, 1ml of saliva in a special collection tube or fixed tissue from paraffin blocks is useful. Discuss the materials to be obtained and the precise amount with the laboratory chosen to do the testing. Genetic analysis is not required for the selection of pharmacological therapy of OI in adults except:
 - 1) when a patient presents with low BMD and/or fractures and the diagnosis of OI is not clear then the use of genetic testing can make the diagnosis of OI more confidently. If OI is present, the use of pharmacological therapy might be undertaken at an earlier stage because the risk of future fractures may be proportionately higher than in someone without OI. This is particularly germane for younger adults who might otherwise not be considered as candidates for pharmacological therapy.
 - 2) when the diagnosis of OI has been made but the type of OI is in question. This may be important when an anabolic agent is being considered (e.g. teriparatide) since type III/IV patients have been noted not to respond to that agent.
 - 3) Skin biopsies for protein electrophoresis are not routine but may be indicated when DNA analysis is not diagnostic.
5. **History and Physical.** A thorough H&P is useful to identify medical conditions that might affect the rate of bone loss or the risk of fractures. Such conditions may affect the decisions about pharmacological therapy or the therapeutic agent selected.

6. **Laboratory Biochemical testing** is recommended at an initial evaluation to evaluate for co-morbidities or other diagnoses in addition to OI that may 1) further increase the risk of bone loss or fracture and thus prompt more serious consideration of pharmacological therapy or 2) require specific therapy (e.g. thyrotoxicosis). The approach for laboratory testing in OI adults being evaluated for potential pharmacological therapy should be similar to that suggested in osteoporosis. There is no clear rationale for testing of bone biomarkers to determine the usefulness of pharmacological therapy or the specific agent to be used. Bone turnover markers can be helpful in specific situations for assessing responses and changes in therapy.
7. **Fracture Risk Assessment:** Determining the patient's risk of future fracture is essential for making the decision about whether pharmacological therapy may be appropriate. The predictors of increased fracture risk in adults with OI has not been adequately examined, but several factors are probably important:
 - a. **Fracture history.** Patients with a history of recent fractures (within 5 years) are probably at increased risk of additional fractures, especially if the fractures have been of long bones or vertebrae. The number of recent fractures should also be considered. Skull and finger/toe fractures are less important.
 - b. **Bone Density measurements:** Although it is likely that in OI fracture risk is higher at any BMD than in the normal population, there is limited data concerning the relationship between BMD and fracture risk in OI. In the absence of adequate evidence, it's reasonable to assume that fracture risk is increased when BMD is significantly low (T-score- 2.5 or less). Therefore, BMD testing can provide useful information to evaluate the need for pharmacological therapy. BMD measurements should include L1-L4 spine, total hip and femur neck. Skeletal deformity may limit obtaining DXA scans at the spine and hip, and BMD at the radius may be useful in those situations. Trabecular bone score (TBS) and distal radius HRpQCT may be useful where available.
 - c. Bone density should be periodically measured in adults with OI. Initially, measurements at 1-2 year intervals are reasonable until it's clear that BMD is stable, and at 2-5 year intervals thereafter. Patients with declining BMD should be considered at higher risk of future fracture. They should undergo a diagnostic evaluation to identify potentially remediable causes of the decline. If none are found, pharmacological therapy should be considered to prevent further declines.
 - d. **Vertebral Fracture Assessment:** Vertebral imaging is advised in view of unrecognized vertebral fracture in this population.
 - e. **Additional Risk Factors:** Other factors may increase the risk of fracture and lower the threshold for beginning pharmacological therapy. They include menopause without estrogen replacement therapy, increased age (>65 yrs), and other active medical conditions (e.g. rheumatoid arthritis, diabetes) or medications (e.g. glucocorticoids) that increase the risk of fracture. Patients who have an increased risk of trauma (e.g. increased fall risk) are at higher risk of fracture and may benefit from pharmacological therapy to increase bone strength.
 - f. **FRAX:** Currently, FRAX does not include risk assessment for adults with OI and probably should not be used.
8. **Orthopedic Care:** There are many issues that influence the orthopedic management of adults with osteogenesis imperfecta. These include the severity of bony deformity, ligamentous laxity, low

bone mass, previous surgery and surgical hardware. It is essential that the complete history of orthopedic care including pediatric care be brought to the attention to the orthopedist.

In the specific treatment of fractures in adults with OI, it is important to note that very few fractures may need to be managed emergently. In less severe cases, fractures may be managed by most orthopedic surgeons. For patients with complex fractures, severe disease or deformity, transfer of care to an orthopedic trauma surgeon or a tertiary referral center may be indicated. Patients with severe disease should also have a pneumology consultation before anesthesia.

9. **Pharmacologic Treatments Available for Adults:** Calcium and vitamin D supplementation should be consistent with recommendations appropriate for adults in general, with adjustment for size and weight in the adult with OI.

Drugs currently used in age- related osteoporosis may be considered for treatment in adults with OI including bisphosphonates (oral alendronate, or IV pamidronate and zoledronic acid), denosumab and teriparatide. These drugs are likely to increase bone density. In addition, teriparatide is shown to increase parameters of bone strength. However, in contrast to fracture protection in children with OI, there is limited evidence regarding fracture protection by bisphosphonates, denosumab or teriparatide in adults with OI. Thus, information about the use of a specific drug should be a matter of discussion between patient and physician prior to treatment.

a. **Follow-up during treatment:**

1. Annual physician evaluation as indicated
2. BMD measurements q 1-2 yrs until stable
3. No specific lab evaluations are usually required

- b. **Treatment duration** should be similar to the recommendations in osteoporosis.