Osteogenesis imperfecta – where next?

In the last 20 years knowledge of osteogenesis imperfecta (OI; the brittle bone syndrome) has been transformed.\(^1,2\) Virtually every patient with OI carries a mutation for one of the two genes controlling type-I collagen synthesis, and most fit into one of four clinical types. Research on OI has illuminated dark corners of collagen chemistry, cell biology and genetics, and has provided insights into the mutational analysis of many skeletal dysplasias.\(^3\) The Sixth International OI Conference in Holland, September 1996\(^4\) was the time to take stock; how much do we know, does this help, and where should we go from here?

How much do we know? Osteogenesis imperfecta is the body’s response to mutations in the type-I collagen genes (Byers, Seattle)\(^5\); it comes at the end of a complex cascade from defects in the genetic code to bone fragility. There is an overall relationship between collagen mutation and type of OI.\(^6\) In the least severe form, type-I OI, mutations prematurely terminate the message for one half of type-I collagen synthesis. The remaining collagen is structurally normal, and the phenotype is mild.

In stark contrast, replacement of a helical glycine with a larger amino acid can be a catastrophe. The mutant chain wrecks helix formation and normal collagen may fall to 20%, incompatible with life (type-II OI). In type-III (the progressively deforming variety) and type-IV OI the mutational results are less severe. Such mutations may disturb mineralisation (Kadler, Manchester)\(^7\) and possibly the interactions between collagen and non-collagen proteins. The relationship between genotype (mutation) and phenotype (syndrome) is greatly modified by tissue expression, by mosaicism, and by clinical and genetic background (Mottes, Verona).\(^8\)

Long-term follow-up studies provide useful clinical information. In 37 Australian adults from an original study of 85 (Sillence, Sydney)\(^9\) bone fragility, judged by fractures, continued throughout life, and in women with OI, pregnancy was a major cause of height loss and back pain. Symptoms from basilar impression were significant in young adults, especially in type-IV OI, as were problems of gait in later life. Deafness which was common, often from adolescence, was troublesome both domestically and at work. Most patients with type-I, type-III and type-IV OI were fully employed, especially those who were better educated, and almost all live independently (Ault, Sydney).\(^6,7\)

Excess early mortality in those with type-III OI was due to respiratory illness, injury and basilar invagination. Minor injury, especially with intracranial bleeding, can rapidly cause death; OI children in wheelchairs should wear a seat belt.\(^6,7\)

How does this help the patient? Knowledge of the biochemistry helps with diagnosis and assessment of the potential outcome after appropriate clinical care.

The management of OI begins in utero, and its early detection is important. In a series of 129 pregnancies at risk for OI studied over 15 years (Pepin, Seattle)\(^5\) prenatal diagnosis in most was based on the analysis of collagen synthesis by cells cultured from biopsies of chorionic villus. If the exact mutation was known from a previous affected pregnancy, or when the haplotype linked to OI had been identified from a family study as in type-I OI, prenatal diagnosis could also be performed directly on chorionic villus DNA. For type-II (lethal) OI, diagnosis by specialised ultrasound can now be made at about the same time as by biochemistry at 14 to 15 weeks of gestation, but is later for type-III and type-IV OI. The usefulness and necessity of biopsy of chorionic villus in lethal OI may therefore be questioned.

The infant severely affected with OI requires specialised help from many disciplines. In many of his 248 patients (followed for more than 20 years) Finidori (Paris)\(^5\) used extensible intramedullary rods for the lower limbs. Surgery aimed to reduce fractures, pain and immobility to allow rehabilitation and to avoid deformity. ‘Rodding’ requires training and experience and the complications are considerable. Brunelli (Brescia, Italy)\(^5\) found that 127 operations for primary rodding in 47 severely affected patients reduced the annual period of immobilisation from 12 weeks to less than one and improved walking. The surgical options available for OI, however, are not ideal.
In type-III OI spinal deformity can be very severe. Finidori (Paris) regards spinal fusion as mandatory, often preceded by halocranial traction. No form of surgery corrects the severe shortening, including that of the upper segment, in type-III and type-IV OI. Growth hormone produced a sustained increase in linear growth rate in some children with type-IV OI (Marini, NIH, Bethesda), but it is too early to draw any conclusions from this study and work from Australia (Sillence) and Italy.

Since sodium fluoride stimulates osteoblasts it is an obvious therapeutic candidate in OI; however, in a double-blind placebo-controlled randomised study pulsed sodium fluoride was found to be ineffective in children with OI (Whyte, St Louis).

In contrast, bisphosphonates selectively reduce bone resorption. Intermittent pamidronate (APD; an amino bisphosphonate) produces dense lines in the growing skeleton. In eight children with type-III or type-IV OI intravenous APD given at four- to six-month intervals increased bone mineral content and density, reduced bone resorption (assessed biochemically) and improved symptoms (Glorieux, Montreal).

Potentially, the most dramatic form of treatment in OI is gene replacement (Prockop, Philadelphia). In type-I OI this could involve stimulation of type-I collagen synthesis and in types II, III and IV replacement of the gene. The ethical and technical problems of correcting type-II OI mutations in utero are, at present, too great. In normal mice, injected stromal cells containing a human type-I collagen gene may survive for a significant period but previous irradiation causes significant mortality. Replacement of the defective gene in human OI would also necessarily begin with destruction of the mutant stromal cells. Horwitz (Memphis) described the infusion of normal bone marrow into infants with severe type-III OI after previous ablation chemotherapy. If such normal stromal cells do engraft in the marrow, it is not known whether they will alter the phenotype.

Where should we go from here? The excitement of mutation discovery has declined and gene therapy seems far ahead. Many new osteotropic agents are now being developed, some as a spin-off from research on osteoporosis, and these may increase bone mass and possibly strength. We can no longer delay in assessing their effectiveness in OI by properly conducted clinical trials. Since OI is so phenotypically variable this is not easy and never will be.

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REFERENCES

Bone allograft: a cause for concern?

Skeletal allograft is now widely used to restore bone stock especially during joint reconstruction and for limb salvage after tumour resection. Many patients have benefited and there is now a shortage of allograft in parts of the UK. Despite this popularity, a number of issues regarding its biology, processing and safety remain unresolved. Reports of graft-related failure and of complications such as infection, fracture and nonunion are relatively common.

Deep infection in an allograft is usually disastrous. Its occurrence has been shown to increase with the size of the graft and may be seen in over 10% of massive allografts. It appears to be unrelated to preoperative contamination of the graft, and probably results from the complexity of the procedure and poor incorporation with dead bone behaving like a sequestrum. The incorporation process also appears to weaken the bone, predisposing to fracture. In a large series of massive allografts, Mankin and his co-workers reported an overall fracture rate of 19%. Without incorporation, allografts are essentially bony endoprostheses. The aim is peripheral union, but radiological nonunion can be expected in about 17%. Union is difficult to assess reliably on radiographs; postmortem analyses of acetabular structural grafts have shown little evidence of histological