Thalassemia is considered the most common genetic disorder worldwide. In Europe the disease is particularly prevalent in inhabitants of Italy and Greece. It is also common in South East Asia and in the Middle East, where it represents an important economic and social burden. In North America more than 800 patients are included in the Registry of the National Institutes of Health-sponsored Thalassemia Clinical Research Network. Thalassemia major used to be a rapidly fatal disease and the results obtained in terms of survival have been striking in the more industrialized parts of the world, while they remain disappointing in low-income countries.

In this issue of the journal there is one article reporting the results, in terms of survival, in the Greek Cypriot population, and two articles evaluating new approaches to the therapy of thalassemia.

Survival in Cyprus

Cyprus has represented an extraordinary example of how a country with a very high prevalence of the β-thalassemia gene can reduce the birth of affected patients to almost zero, thanks to the efforts of motivated and far-seeing people. The few recent births have been limited mainly to cases in which the father was not available for testing. In the present study, Telfer and his Cypriot colleagues take these important results one step further, reporting very good survival rates in recent years for all patients born after 1974. Following a significant increase in cardiac mortality between 1990 and 1999 despite intensive use of deferoxamine, they observed a reversal of this trend between 2000 and 2005. Improved survival has recently been reported from Italy, where mortality has been consistently and significantly decreasing, with an especially marked difference between patients born before and after 1970. This large improvement was certainly due to the introduction of chelation therapy with deferoxamine, which began in 1970 as an intramuscular injection and after 1979-1980 was generally administered as a subcutaneous infusion. The most frequent cause of death in patients with thalassemia major is heart disease, responsible for more than half of the deaths in both the Cypriot and the Italian study. Therefore, an improvement in survival should be obtained by a decrease in cardiac deaths. This was in fact documented in the Italian study and in the paper by Telfer et al., while, on the contrary, no trend was identified in non-cardiac deaths. Telfer et al. attribute their findings to improved medical expertise and use of combined chelation therapy. They underline the fact that there were no deaths among patients on combination therapy, for a total of 1000 person years of follow-up and suggest that the treatment, selected mainly for patients most at risk, is highly effective in preventing cardiac events. Their study did not, however, have the statistical power to evaluate the protective effect of combination therapy compared to deferoxamine. The concomitant use of daily deferiprone with subcutaneous deferoxamine 2-6 days each week was originally proposed by Dr. Wonke in London and was shown to produce additive effects, explained, later, by the shuttle hypothesis. Iron bound to a shuttle - an oral agent that mobilizes tissue iron - is exchanged in the bloodstream with a sink - such as parental deferoxamine - and excreted via the kidneys, while the shuttle is reutilized. In theory, combination therapy may enhance iron excretion, target specific iron compartments, minimize side effects, and improve compliance. In fact, several studies have confirmed that, during combined therapy, ferritin levels and liver iron concentration decrease more markedly and mean urinary iron excretion is higher than with deferoxamine or deferiprone monotherapy. It has also been shown that the combined therapy is associated with an improvement in heart function. The cardioprotective effect of deferiprone has been recognized in small retrospective studies, in a randomized controlled trial in a large epidemiological study of Italian patients. Unfortunately all studies are concordant in demonstrating that, against all hopes, the most feared side effect of deferiprone, agranulocytosis, is not rarer, and possibly is more prevalent, in patients treated with combined therapy than in those receiving monotherapy. Nonetheless combination therapy is now considered the best available treatment for patients with cardiac iron overload, whether symptomatic or diagnosed by magnetic resonance imaging.

Alternating regime of deferoxamine and deferiprone

When deferiprone and deferoxamine are not given concomitantly, but on different days, the chelating regime is called alternating. Such a regime should serve the purpose of decreasing the side effects of both chelators. Aydinok and her co-workers had adopted this regime in a small group of children in an attempt to improve compliance to deferoxamine, at that time considered the only chelator of proven efficacy. In this issue of Haematologica a group of Italian, Greek and German researchers compare the results of deferoxamine monotherapy, given for 5 to 7 days per week, with the alternating regime, in which deferoxamine was limited to 2 days and deferiprone administered for the remain-
The results were satisfactory in terms of efficacy, with similar reductions in ferritin levels and liver iron concentration, but the incidence of gastrointestinal symptoms in the deferiprone users and of local reactions due to deferoxamine infusion were not much different than would be expected with either drug alone. No cases of agranulocytosis or arthralgia were observed, but the size of the sample does not allow any firm conclusion to be drawn about these complications. Interestingly, the two patients who developed neutropenia were both receiving deferoxamine, confirming that this event is not rare in thalassemia, even independently of deferiprone administration. At present, alternating therapy might serve the purpose of increasing the compliance of patients who have difficulties with monotherapy. Although (to say it with the Nobel laureate Niels Bohr) predictions are very difficult, especially about the future, it is not unlikely that self management of chelation therapy will become common. Patients will be able to choose to use deferoxamine, deferiprone, and the new oral chelator deferasirox, alone or in combination, according to their needs and preferences, with or without the approval of their physicians.

**Osteoporosis**

As a consequence of longer survival, the thalassemic patient’s quality of life is becoming more important and more attention is being given to new complications. Some of these complications did not have the time to appear when patients died at a younger age, while others were not considered important when the patients were dealing with life-threatening heart disease or other serious complications. Osteoporosis, which has been found to affect 51% of the patients with an additional 45% affected by osteopenia, probably pertains to both groups. In the first description of thalassemia major, Dr Cooley mentioned the peculiar bone changes due to leukoblastic hyperplasia. More recently, reduced mineral density and consequent susceptibility to fractures in older patients have been attributed not only to hyperactivity of the bone marrow but also to iron overload, endocrine dysfunction, adverse effects of deferoxamine, and lack of physical exercise. In one study, male gender, lack of spontaneous puberty in female patients, active hepatitis, heart disease, and diabetes represented significant risk factors, while transfusional history, chelation and erythropoietic activity did not. The role of genetic predisposition is controversial. Analysis of genetic polymorphisms for the collagen type I gene, vitamin D, estrogen, and calcitonin receptors has not given conclusive results so far. Fractures, often secondary to mild or moderate trauma, are more frequent in thalassemic patients than in the general population. In addition to decreased bone formation, characterized by decreased levels of osteocalcin, an increase in bone resorption through the RANK/RANKL/osteoprotegerin pathway, has been demonstrated. Conventional therapy for osteoporosis of thalassemia has included - until recently - a rather bland regimen of sex hormone-replacement therapy, regular exercise, and calcium and vitamin D supplements. However, reports on the treatment of male and menopausal osteoporosis have demonstrated the efficacy of several therapeutic agents, opening the way for a more effective treatment also in patients with thalassemia. Bisphosphonates, which are potent inhibitors of osteoclast activation, represent a logical choice in the management of these patients. Alendronate and pamidronate have been shown to be effective, while clodronate was unable to increase bone mineral density. A large prospective, placebo-controlled, randomized trial on the use of zoledronic acid, the most potent third generation bisphosphonate to date, is reported in this issue of *Haematologica* by Voskaridou et al. Following a first encouraging report by Peritanis et al., they here compare zoledronic acid, given twice a year or four times a year, to placebo. All the patients were also receiving daily supplementation with a low dose (500 mg) of calcium. The majority of the patients enrolled had suffered one or more pathological fractures before entering the study. The primary end point should have been the reduction in incidence of osteoporotic fractures, but the size of the sample was not sufficient to demonstrate this. In fact, no fractures occurred during the study period, and the authors therefore report the efficacy in terms of improvement in bone mineral density, modification in the biochemical markers of bone formation and resorption, and pain reduction evaluated by two different scoring systems. This last parameter is particularly important because the majority of patients complain that bone pain of varying severity affects their quality of life.

The study demonstrated a significant increase in bone mineral density of the vertebrae but not of the femoral neck, a reduction of markers of bone resorption, and a reduction of bone pain, in patients receiving zoledronic acid every 3 months. When the drug was given twice a year, bone mineral density did not improve, but bone pain was favorably affected, as were the biochemical markers of improved balance between bone formation and resorption. Patients on placebo did not experience any change in bone mineral density nor in pain and showed an aggravation in the markers of bone resorption. The results are encouraging, but before we can accept the drug as effective in the treatment of osteoporosis in thalassemia, larger studies are needed in order to clarify its efficacy in preventing fractures. Also, the description of several cases of jaw necrosis in people treated with pamidronate and zoledronic acid is disturbing. A further note on the use of calcium and vitamin D, the most widely used prophylaxis and treatment for osteoporosis in post-menopausal women and in tha-
lassesm, is important. We all feel virtuous and safe in prescribing this therapy, but recent results from the Women’s Health Initiative study on the risk of fractures during daily supplementation with 1000 mg of elemental calcium as calcium carbonate and 400 IU of vitamin D3 failed to demonstrate a reduction in hip fractures, while the risk of kidney stones increased by 17%.32 Similar data have not been reported for the thalassemia population. Although several factors could have contributed to the lack of effectiveness, including too low a dose of vitamin D, additional therapy is probably necessary in patients at risk of fractures. Particular attention should also be given to monitoring urinary calcium excretion in thalassemia patients who probably have an increased risk of kidney stones. It has been suggested that the risk could be decreased if calcium citrate were used instead of calcium carbonate.

Although other treatments for osteoporosis, including teriparatide33 or strontium ranelate,34 are capable of reducing the risk of fractures in the population at large, no formal trials of these drugs have been conducted in thalassemia. It is likely that in the treatment of osteoporosis, as in iron chelation, combined or sequential regimens will be useful. The relative merits of starting teriparatide in thalassemia major die untreated, or 87% of children born with thalassemia major die untreated, while at least 15% of those who start on regular transfusions have no access to iron chelation therapy. It is important that we unite our voices to help the rest of the world to obtain what we have obtained in the past 30 years.35 In addition, new waves of immigration have increased the prevalence of hemoglobinopathies in areas where they were previously rare. There is a strong rationale for pan-European collaboration to enable countries to benefit from the experience of others, to share methodologies, and to develop standardized preventive and therapeutic approaches.36

Conclusions

In conclusion, patients with thalassemia are living longer, the once dreaded parenteral chelation therapy is now easier as new regimens and new chelators have become available, and we can pay more attention to the best management of previously untreated complications such as osteoporosis. The temptation is strong to congratulate ourselves, as a scientific community, for the results obtained thus far, but this should be tempered by the knowledge that worldwide, around 87% of children born with thalassemia major die untreated, while at least 60% of those who start on regular transfusions have no access to iron chelation therapy.36 It is important that we unite our voices to help the rest of the world to obtain what we have obtained in the past 30 years.35 In addition, new waves of immigration have increased the prevalence of hemoglobinopathies in areas where they were previously rare. There is a strong rationale for pan-European collaboration to enable countries to benefit from the experience of others, to share methodologies, and to develop standardized preventive and therapeutic approaches.36

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