Nandrolone decanoate: new therapeutic option for telomeropathies?

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In the May issue of *Haematologica*, Diego V. Clé and co-workers[1] presented clinical trial data about the safety and activity of nandrolone decanoate in the treatment of telomeropathies (clinicaltrials.gov NCT02055456). Telomeropathies are a heterogeneous group of pathologies due to the various pathogenic germline variants in genes encoding products involved in telomere maintenance. They are characterized by multidistrict clinical impairment; these are mainly hematologic, respiratory, hepatic and cutaneous-mucosal.[2,3] Hematologic disorders such as bone marrow (BM) failure occur most often in young individuals and are often associated with organ disorders (hepatic or pulmonary) and early cancer. In adulthood, idiopathic pulmonary fibrosis is the most common symptom of telomeropathies; a significant proportion of these patients have hematologic abnormalities (macrocytosis and thrombocytopenia in particular), and a certain number will develop hematologic disease during the course of pulmonary follow-up.[4] In the case of severe organ failure, such as aplastic anemia, lung and liver dysfunction, the only potentially curative treatment is transplantation.[5]

From a hematologic point of view, patients with BM failure, high-risk myelodysplastic syndromes or leukemias should undergo allogeneic stem cell transplantation from an HLA-matched non-mutated intrafamilial donor or an HLA-matched unrelated donor. However, BM transplantation (BMT) does not correct the genetic deficiency in the extra-hematopoietic cells, and exposes the organs to infectious, toxic and immunological complications.

The prognosis of BMT in cases of telomeropathies is highly variable, often due to multi-organ impairment. In a recent review of the literature by Barbaro *et al.*,[6] overall survival in a cohort of 109 patients was estimated at 57% and 23% at 5 and 10 years, respectively, due to liver and lung complications, and graft dysfunction. To reduce organ toxicity, there is a growing trend toward alkylator- and radiation-free protocols; recently, the European Group for Blood and Marrow Transplantation recommended using the FCC regimen of fludarabine, cyclophosphamide, and alemtuzumab.[7,8]

Androgens, such as danazol, oxymetholone, and nandrolone are the main therapeutic alternative to allogeneic transplantation in cases of severe hematologic damage. In the only published prospective study, Townsley *et al.*[9] observed a hematologic response in 79% of patients at 3 months (24 patients were evaluable) and 83% of patients at 24 months (12 patients were evaluable) treated with danazol. This study also suggests a benefit in terms of a reduction in forced vital capacity loss in patients with respiratory impairment. The main side-effects reported were elevation of transaminases in 41% of cases, severe hepatic dysfunction, headaches, muscular cramps, and weight gain. In a recent *in vitro* study, Vieri *et al.*[10] did not observe any significant differences in the efficacy of danazol, oxymetholone and nandrolone to improve telomerase activity. The choice of the compound should be based on the patient's individual co-morbidities, e.g., pre-existing liver disease and expected side-effects.

In the context of this scientific background, Clé and co-workers presented a phase I/II single-center prospective trial with the aim of evaluating the reduction in telomere attrition over time compared to known rates of telomere erosion in normal individuals, and in those who carry a mutation in the telomerase genes, treated with nandrolone decanoate. Hematologic response, pulmonary function, incidence of clonal evolution, safety, and survival were all assessed as secondary endpoints. The sample consisted of 17 patients with a median age of 36 years (range, 4-59 years) with age-adjusted mean telomere length under the 1st percentile and/or identified germline pathogenic variants in telomere-biology genes associated with at least one cytopenia and/or radiologic diagnosis of interstitial lung disease (ILD). All patients were diagnosed with BM failure, seven patients were also diagnosed with ILD, and four patients also had liver involvement. Five patients had skin features of dyskeratosis congenita.

The patients received 5 mg/kg of intramuscular nandrolone decanoate every 15 days for two years.

Of the 17 patients enrolled, 13 were evaluable for the primary end point at 12 months and ten at 24 months. Consistent telomere elongation, evaluated by flow-FISH, was achieved by 77% (10/13) of patients at 12 months and by all evaluable patients (10/10) at 24 months; the average increase in intelomere length was 0.87 kb (95%CI: 0.20-1.55 kb; *P*=0.01) at 12 months and 0.49 kb (95%CI: 0.24-1.23 kb; *P*=0.18) at 24 months.

Hematologic response, assessed as improvement in cytopenia or transfusion independence or 50% reduction from baseline, was achieved in 50% of patients with BM failure at 12 months, and in 63% at 24 months. The best response was observed in hemoglobin levels, while no significant differences were observed in neutrophil or platelet values.

In patients diagnosed with ILD at baseline, there was no significant change in pulmonary function as evaluated by clinical, spirometric and radiological parameters: 2/7 died of respiratory failure during nandrolone treatment, a mild improvement in lung function was observed in 3/7, while lung function remained stable in 2/7. One of the most intriguing findings was the comprehensive analysis of the effect of nandrolone on clonal hematopoiesis; clones carrying mutations in genes associated with myeloid neoplasms remained stable or decreased.

These are interesting data and lay the groundwork for expanding our knowledge about the role of androgens in telomeropathies. However, some issues remain, mainly regarding safety. Firstly, from a practical point of view, the use of an intramuscular formulation could raise some concerns, especially in patients with low platelet concentrations. This formulation was chosen to bypass hepatic metabolism and reduce toxicity, an event, however, that has not been confirmed (elevated transaminases in 88% of cases *vs*. 41% in historical reports).[9] Secondly, two deaths due to intracranial hemorrhages were observed which were not reported from previous trials or in retrospective registry reports. Formally, a correlation with the drug cannot be ruled out; however, it should be stressed that these patients had very low platelet concentrations (<10x10^9/L).

Overall, this is the second prospective study in the field of telomeropathies, rare diseases for which it is often not easy to find possible study candidates. The study confirms previous observations and adds new data on lung fibrosis, side-effects, safety, and clonal evolution during treatment. Rare diseases such as telomeropathies remain under-explored with few therapeutic alternatives, making additional information especially useful.

Disclosures

No conflicts of interest to disclose.

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