In the erythropoietin era, can we forget alternative or adjunctive therapies for renal anaemia management? The androgen example

Juan F. Navarra

Nephrology Service and Research Unit, University Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Tenerife, Spain

Keywords: anaemia; androgens; nandrolone; nutrition; recombinant human erythropoietin

Introduction

Anaemia is an almost-universal complication of renal insufficiency with significant consequences such as fatigue, reduced stamina, decreased cognition, sexual dysfunction, impaired immunity and diminished quality of life. It also plays a critical role in the development of the structural and functional alterations of the cardiovascular system that are associated with uraemia, and contributes to accelerated atherosclerosis [1–4]. Nowadays, it is widely recognized that anaemia bears a great responsibility for the increased morbidity and mortality of patients with end-stage renal disease (ESRD).

Recombinant human erythropoietin: a triumph of modern medicine

The advent of recombinant human erythropoietin (rHuEPO) represented a revolution in the field of nephrology, allowing: avoidance of blood transfusions, reduction in the risk of sensitization, prevention of iron overload and improved exercise tolerance, cognitive capacity, sexual function and quality of life. The treatment of anaemia was deeply transformed. Still, several questions and problems remain concerning the use of rHuEPO. For instance, switching from the intravenous (i.v.) to the subcutaneous (s.c.) route resulted in an improved response with a markedly reduced dose. However, why the improved response accompanying conversion to s.c. administration is observed in some patients and not in others remains unclear [5]. Furthermore, the optimum frequency of rHuEPO administration is a matter of debate.

In all, there are three main problems associated with the use of rHuEPO: cost, pure red cell aplasia (PRCA) and predictable side effects, such as hypertension. Its high cost impedes the generalized use of rHuEPO worldwide; rHuEPO remains expensive, and the existence of competing manufacturers has not led to price reduction. Between 1994 and 1999, spending on rHuEPO increased by 100% in the USA (where 90% of patients receive rHuEPO by the i.v. route [6]), and, in 1999, US Medicare’s total expenditure on rHuEPO exceeded a billion dollars [7]. A recent meta-analysis by Besarab et al. [8] showed substantial cost savings with s.c. administration compared with the i.v. route, an ~30% reduction due to the lower doses using the s.c. route. In spite of this reduction, the cost of rHuEPO treatment remains an important limiting factor. This explains why in many countries the use of rHuEPO is limited based purely on financial grounds. Moreover, reimbursement concerns pose as significant barriers, so that ~24% of haemodialysis (HD) patients will fail to achieve the targeted haemoglobin guidelines on any point prevalence sample [9]. Therefore, attempts to reduce the cost of anaemia therapy are of paramount importance [10]. In this setting, androgens may be of interest. Initial studies showed that the cost savings of 6 months of treatment with androgens ranged between $2450 and $3650 per patient [11]. These findings are in agreement with computerized decision making models that take into account the effectiveness and side effects of various therapeutic options to treat renal anaemia, including rHuEPO, androgens and transfusions. Analysis of the data concluded that at 5 years, for every 10000 HD patients treated with rHuEPO, net Medicare expenditures would be greater by >100 million dollars than if androgens were used instead [12].

With respect to side effects, some new concerns are emerging. Until 1998, only three patients had been fully documented as having anti-EPO antibodies following rHuEPO administration [13–15]. However, on February 2002, Casadeval et al. [16] reported the development of PRCA in 13 patients who were receiving rHuEPO, all of them having neutralizing antibodies against the protein moiety of epoetin. Since then, increasing numbers of cases have been reported [17,18]. The incidence of PRCA after the administra-
Androgens: a matter of persistence

Early investigations firmly established the stimulatory effects of androgens on erythropoiesis [26]. Diverse studies in the 1970s demonstrated that androgens therapy was associated with favourable effects on anaemia in HD patients [27–30], but after the availability of rHuEPO the use of these compounds was almost completely abandoned. Nevertheless, in spite of the success of rHuEPO and the parallel disuse of androgenic steroids, interest in the use of androgens, both alone or combined with rHuEPO, in the treatment of renal anaemia has remained alive in several circles.

The mechanism of action of androgens on erythropoiesis is not completely understood. The erythropoietic effect of androgens was initially considered to be due to an increase in EPO production [31]. In a prospective study we observed, however, that androgen administration to HD patients did not elicit an increase in serum EPO levels in all subjects; moreover, after discontinuing androgens serum EPO declined rapidly, whereas haemoglobin levels remained stable [32]. Therefore, other possible mechanisms of action have been suggested, such as a synergistic action with rHuEPO, an increase in the sensitivity of erythroid progenitors to EPO, increased red blood cell survival, or a direct effect on erythropoietic precursors at various stages of maturity [33,34]. Finally, in a recent study we observed that serum levels of insulin-like growth factor-1 (IGF-1) significantly increased in patients receiving androgens, in addition to which, there was a positive correlation between the rise in IGF-1 and increases in haemoglobin and haematocrit [35]. Therefore, it is suggested that the effects of androgens on haematological parameters may be mediated in part by IGF-1.

The potential role of androgens as adjuvant therapy in enhancing the effectiveness and reducing the required doses of rHuEPO has been demonstrated in HD patients. Ballal et al. [36] observed a much greater haematocrit increase in patients receiving rHuEPO plus nandrolone decanoate (NAND) than in those receiving rHuEPO alone (from 24.4 to 32.9% vs 25.3 to 27.4%, respectively). The data have been recently confirmed in a long-term prospective randomized trial by Gaughan et al. [37]. The authors found that the use of a combination of low-dose rHuEPO and NAND was associated with a significantly greater increase in haematocrit than the use of rHuEPO alone (8.2 vs 3.5%, respectively).

More relevant is that other investigations have shown that androgens alone are also effective in the treatment of renal anaemia. Some studies were retrospective or included a small numbers of patients [11,38], but three prospective studies need to be highlighted. In 1996, Teruel et al. [39] found that after 6 months of therapy, the increase of haemoglobin concentration in 18 HD patients treated with NAND was similar to that observed in 22 persons receiving rHuEPO. Similar results were reported by Gascón et al. [40]. In that
effects, and of greater concern, are related to liver rhoea and increasing libido. Other classical adverse actions, hirsutism, changes in voice, masculinization, amenorrhea, and 60 years or older seem to be the optimal candidates for androgens therapy. The maintenance of a good nutritional status is critical in patients with ESRD. In this setting, androgens may play the important role of nutritional therapy. These compounds possess distinct anabolic properties that increase nitrogen retention, body weight and lean body mass, and they are therefore used in treating wasting in chronic diseases, including acquired immunodeficiency syndrome, pulmonary and liver disorders, burns and cancer. In the context of renal failure, the high prevalence of malnutrition, the impact of this complication on morbidity and mortality, and the characteristics of the patients, are reasons to highlight the importance of nutritional therapy in this population. Early indications that nutritional markers improve after androgens therapy in dialysis patients [47,48] have been clearly confirmed by recent studies. Johansen et al. [42] in a randomized, double-blind, placebo-controlled trial found that lean body mass increased significantly in patients given NAND compared with subjects given placebo. Teruel et al. [39] found that patients treated with NAND had an increase in dry weight and serum albumin, whereas these parameters did not change in subjects receiving rHuEPO. Gascón et al. [40] observed that HD subjects on NAND had a significant increase in serum creatinine, total protein and transferrin, along with an improvement of anthropometric parameters. Finally, in a prospective randomized study in peritoneal dialysis patients, we found that subjects receiving NAND...
showed a significant improvement of anthropometric and biochemical nutritional variables when compared with subjects treated with rHuEPO [35].

Conclusions

In spite of the availability of rHuEPO, several groups have continued using androgens to treat renal anaemia, getting results similar to those observed with the use of rHuEPO. Moreover, some benefits have been found when NAND is compared with rHuEPO, i.e. the effect on nutritional parameters. There is more to chronic renal failure than anaemia, and therefore, androgenic steroids have the potential to be valuable as adjuvants or substitutes for rHuEPO in the treatment of renal anaemia in select patients. Several key aspects, such as the class of androgen being used and the characteristics of the patient, must be kept in mind, however.

Overall, the data suggest that androgens may be an option for the treatment of renal anaemia in the EPO era—at a time when not all problems related to rHuEPO are resolved. Results of prospective randomized studies show that androgens are useful, and not only as adjunctive therapy in combination with rHuEPO. These investigations indicate also that androgens can be used alone as treatment of renal anaemia in select patients. Currently, based on available data it can be suggested that NAND is the androgen of choice for administration to uraemic individuals. Anaemic male patients older than 50 years seem to be the ideal candidates for this therapy, especially if they are malnourished. Along with its age-related efficacy, other aspects concerning side effects—including testicular atrophy, infertility, longer-term hepatic concerns and those mentioned in the previous section, justify the recommendation that androgen therapy be avoided in young males and all females. In spite of the good tolerance of NAND, its potential side effects must be watched for. Monitoring lipid profiles, hepatic function and prostatic markers is mandatory.

Finally, it is necessary to continue investigating several aspects related to androgens use, including their optimal schedule of administration and dosage, their potential role in pre-dialysis patients, their long-term efficacy and safety, and the potential impact of androgens-induced nutritional benefits on morbidity and mortality. In order to obtain solid evidence and definitive responses to questions, multicentric, prospective, randomized, double-blind trials comparing androgens and rHuEPO would need to be developed. Economic aspects, however, seem to be powerful limitations. As of now, androgens seem to offer a partial solution for the treatment of renal anaemia in the rHuEPO era. The question is: Are we ready to revive androgens?

Conflicts of interest statement. None declared.

References
