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

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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-
tion rHuEPO is not known, although for the period from July 1997 through December 2001, 82 cases were reported by the Food and Drug Administration [18]. Most of those patients were treated with epoetin alpha, but several individuals had received epoetin beta. To date, about 200 suspected cases of PRCA occurring in patients with chronic kidney disease have been reported to health authorities. Antibodies against erythropoietin have been demonstrated in about 120 of them [19]. Most of these patients were treated with epoetin alpha. However, five patients with PRCA and anti-erythropoietin antibodies have been reported who had been treated exclusively with epoetin beta; and there are three additional cases in whom an association between PRCA and the use of epoetin beta cannot be excluded. Finally, there have been reports of skin and systemic allergic reactions associated with darbepoetin; and in one patient, anti-erythropoietin antibodies cross-reactive with this new molecule have been demonstrated [20]. To date, however, there are no reported cases of antibody-mediated PRCA caused by darbepoetin [19]. This new concern has caused the creation of specific registries in several countries in order to ascertain the incidence and prevalence of this complication.

If anti-EPO antibodies are found in a patient, rHuEPO should be discontinued immediately; and challenging these patients with another erythropoietic protein is not recommended, for the antibodies have been shown to cross-react with all available recombinant erythropoietic products [17,20]. Withdrawal of rHuEPO therapy is associated with a decrease in antibody titers concomitant with an increase in reticulocyte count [17,21]. Most patients with PRCA associated with rHuEPO have received different immunosuppressive treatments, including immunoglobulin, steroids, cyclophosphamide, cyclosporine and plasmapheresis [17,22]. In most cases, antibodies were not detectable after these therapies, and erythropoiesis recovered, with the patient’s transfusion requirements becoming similar to those prior to rHuEPO treatment. Transplantation in these patients is not contraindicated; moreover, patients who received a kidney transplant after unsuccessful immunosuppressive therapy have achieved haemoglobin levels in the normal range during follow-up.

Finally, the development or aggravation of arterial hypertension has traditionally been considered as the main adverse effect of rHuEPO. This complication may occur in up to 30% of patients in the first months of treatment [23], less frequently after conversion to s.c. administration [24]. Furthermore, some patients in early trials developed hypertensive encephalopathy and seizures, although this encephalopathy was not the same as the classical hypertensive one, lacking fundal changes [25]. Many of its clinical features were consistent with defective cerebral autoregulation; however, there currently is considerable lack of information concerning the effects of rHuEPO on cerebral blood flow.

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 [1,38], 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
study, 33 HD patients receiving rHuEPO were randomized to either continue this therapy \( (n = 19) \) or to stop 15 days before the start of NAND \( (n = 14) \). After 6 months, there were no significant differences in the haematological parameters between the two groups. Finally, a 6-month randomized prospective comparison between rHuEPO and androgens in continuous ambulatory peritoneal dialysis patients has been published recently [35]. In this study, we observed that haemoglobin and haematocrit concentrations underwent similar increases in patients treated with NAND or with rHuEPO.

There are different androgenic compounds, with specific properties that determine their beneficial effects as well as their adverse actions. In the past years, NAND has been the most extensively used of the compounds, and currently available data strongly suggest that this agent is the androgen of choice for ESRD patients. The characteristics of patients determine the amount of benefit obtained from androgen therapy. The response of haematologic parameters is not dependent on primary renal disease or sex. A clear association has been found, however, between favourable therapeutic responses and patients’ age. In this study [11] the authors observed that, after NAND administration, haemoglobin increased by 0.8 g/dl in subjects younger than 46 years, by 1.8 g/dl in patients between 46 and 55 years and by 2.7 g/dl in patients older than 55 years. Moreover, whereas in 62% of patients younger than 46 years the increase in haemoglobin was minimal, 70% of subjects older than 55 years showed an increase > 2 g/dl. Therefore, subjects aged between 50 and 60 years or older seem to be the optimal candidates for androgens therapy.

Androgens are not without adverse effects, which are essentially due to their androgenic properties, and depend on the class of agent used, the dosage and the route of administration. The common side effects have been reported mainly in adolescents and young men and women, and include flushing of skin, acne, hirsutism, changes in voice, masculinization, amenorrhoea and increasing libido. Other classical adverse effects, and of greater concern, are related to liver function.

Hepatic side effects were more frequently reported in initial studies due to the use of testosterone esters (propionate, enanthate) or 17α-alkylated agents (oxymetholone, fluoxymesterone) [33,34]. Treatment with 17α-alkylated androgens has consistently been associated with disturbances in liver function, ranging from a mild increase in sulfobromophthalein retention to a cholestatic picture that may end in hepatic failure. Hepatic and splenic peliosis as well as hepatocellular adenoma and carcinoma also have been described following therapy with alkylated compounds. However, the main androgen used in the last two decades is NAND. This is a 19-nortestosterone non-alkylated compound, and is much better tolerated.

Available data show that non-alkylated compounds, such as NAND, rarely cause liver disorders [37,39–41]. In three patients with antibodies to hepatitis C, Teruel et al. [11] found elevations in liver enzymes that returned to normal when androgen treatment was stopped. However, none of 13 patients with biochemical indicators of liver disease experienced worsening of the disease during therapy. Other studies have not observed any cases of hepatotoxicity during androgen treatment [35,37,39,40,42].

The effects of NAND on lipid profiles have been evaluated recently [43,44]. Administration of NAND produces a significant increase in triglycerides and apolipoprotein B levels and a decrease in apolipoprotein A and high-density lipoprotein cholesterol (HDL), due exclusively to a decline of the HDL3 subfraction. Usually these changes are transient and resolve after discontinuation of therapy. Finally, therapy with NAND in HD subjects has not been associated with changes in serum concentrations of prostatic markers (prostatic acid phosphatase and prostate-specific antigen), suggesting that in these patients this compound has no significant side effects on the prostate [45].

In different studies, androgens have been shown to have significant actions apart from their effects on erythropoiesis, mainly on lipoprotein(a) (Lp(a)) and nutritional status. A significant reduction of Lp(a) levels, an independent cardiovascular risk factor in dialysis patients, has been reported by Teruel et al. [43]. Compared with baseline values, median Lp(a) decreased by 64%. After this initial observation, similar results have been reported both in HD [40] and CAPD [44] patients, and interestingly, the reduction of Lp(a) has been observed in patients receiving NAND, but not in subjects treated with rHuEPO [35,40].

The maintenance of a good nutritional status is critical in patients with ESRD. In this setting, androgens may play the important role of nutritional treatment. 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 [46]. 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?

Conflict of interest statement. None declared.

References