

Spanish epidemiological study of the anaemia in predialysis patients

José Miguel Cruz* and the Spanish Group for the Study of Anaemia in Patients with Chronic Renal Failure.

*Department of Nephrology. Hospital La Fé. Valencia. Spain.

SUMMARY

Background. In order to analyse Spanish nephrologists guidelines, in late 1998, for the treatment of anaemia in predialysis patients with progressive renal failure and compare them with the recommendations of European Guidelines on this subject, published some months after, we proposed a retrospective, crossover, epidemiological study using a probabilistic sampling by conglomerates in two stages: random after stratification of centres at the first stage and random among the 282 patients of these units at the second stage.

Methods. Three observational cuts were performed (I: "Arrival at the Nephrology Unit", II: "Start of treatment with erythropoietin (r-HuEPO)"

and III: "Start of Dialysis treatment"), analysing in each of them the renal function, the degree of anaemia, the iron metabolism, iron therapy and, when present, the initial r-HuEPO dose and at two months, and method and frequency of administration.

Results. The haemoglobin and ferritin averages in each cut were as follows: I: 11.4 ± 2.4 g/dl and 174.7 ± 156 mg/l; II: 9.1 ± 1.1 g/dl and 173.5 ± 172.9 μ g/l; III: 9.8 ± 1.6 g/dl and 188 ± 168.2 μ g/l.

45% of patients in I, 92.7% of patients in II and 75.8% of patients in III had Hb less than 11 g/dl. 5.5% of patients in I, 10.9% of patients in II and 38.8% of patients in III received intravenous iron. For 98% of the patients, r-HuEPO was administered subcutaneously, the most common frequency was two doses per week (49% of patients) and the average dose (initially and at two months) was 68 and 74 UI/kg/week respectively.

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Conclusions. 1.- Treatment with r-HuEPO in predialysis began late and at excessively low haemoglobin concentration levels. 2.- Ferritin, even at "normal" levels, was lower than the level considered "optimum". 3.- The r-HuEPO dose,

method and frequency of administration was around the recommended level.

Key words: Anaemia. Erythropoietin predialysis. Progressive renal failure.

INTRODUCTION

In 1987, Eschbach had the opportunity of using, for the first time, recombinant human erythropoietin (r-HuEPO) to treat anaemia associated with chronic renal failure¹. From the time when it was first used, the efficacy, tolerability and low incidence of side effects of this substance were noted², although it took longer to define the appropriate doses, method of administration or need for iron during its use.

The "Clinical Practice Guidelines for the Treatment of Anaemia of Chronic Renal Failure" prepared by the U.S. National Kidney Foundation-Dialysis Quality Outcomes Initiative (NKF-DOQI)³ were published ten years later. The text of these guidelines was based on a critical review of 2,836 publications and included 349 entries in its bibliography. Their contents were based on and directed towards medical practice in the United States in the mid-1990s.

In October 1997, on the basis of an initial document prepared by the European Advisory Board of Janssen-Cilag after a carefully review of the DOQI to reinterpret and adapt them to European practice, a working group was set up, presided over by Dr. Cameron. The EDTA/ERA and all National Societies of the European Union, including some from central and eastern Europe, took part. The result of their work was the "European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure". The European Guide-

lines were published in 1999⁴, after a new critical review of all the publications on which the DOQI were founded, in addition to over 200 further studies published between 1996 and 1998. In the end, these Guidelines contained 575 bibliographical entries. Their recommendations or "Norms" are founded on three levels of evidence (A, B and C) following the guidelines of the US Agency for Health Policy and Research⁵.

In late 1998 there was a proposal to collate evidence of the most common stages of treatment of this illness in Spain at that time, coinciding with the appearance of the "European Guidelines" and two years after the publication of the DOQIs. The results of this "*Spanish Epidemiological Study*" were not published at the time, probably because there was also a compilation of data in progress at that time from another study, dealing with the same subject but at a European level (ESAM).

We have now decided to publish these results so that they may serve as a reference point in future controls which may show changes in the Spanish nephrologists' guidelines for the treatment of anaemia with r-HuEPO. We will also analyse other aspects of Spanish practice in the field of chronic renal failure, such as the moment when patients are referred to Nephrology Units and the moment when it is decided to begin treatment with extrarenal clearance.

SUBJECTS AND METHODS

A retrospective, crossover, epidemiological study was proposed, using a reference period of three months from the date of compilation of the information at each centre. In centres where very few patients are treated, making it impossible to cover the sample allocated, the reference period was extended to cover previous months until the planned sample size was reached.

Population

The population studied consisted of a group of patients with progressive renal failure in the pre-dialysis stage in public or private Nephrology Units / Departments on Spanish territory.

Predialysis patients was considered to mean all patients with a starting date for dialysis which coincided with the reference period, regardless of their situation when the information was compiled.

A probabilistic sampling by conglomerates was carried out, selecting at the first stage Nephrology Units and/or Departments by random sample, after stratifying the centres according to size and public or private ownership, arriving at an initial sample size of 38 centres. At the second stage, the patients included in each centre were selected by random sample among those being treated at that Unit, provided that they met the specific conditions for the population under study. 36 centres finally completed the study.

Design of the Study

Three observational cuts were made, according to:

1. Patient's referral to the Nephrology Unit / Department
2. Start of treatment with r-HuEPO
3. Start of dialysis

The following variables were analysed:

- Demographic characteristics
- Aetiology of the renal failure
- Origin of the patients
- Renal function (creatinine, creatinine clearance and time until start of dialysis)
- Anaemia (haematocrit, haemoglobin)
- Iron study (ferritin, transferrin saturation index, and the need for iron therapy).
- Treatment with r-HuEPO (doses, method of administration)

RESULTS

Referral to the Nephrologist

Finally data was compiled on the origin of 275 patients, grouped in 36 Nephrology Centres. 58 % were men and 42 % women. The average age was 58.7 years, ranging between 9 and 87 years. 43 % of them were over the age of 65 when they were referred to a Nephrology Unit / Department.

Diabetic nephropathy was the main cause of renal failure among the patients studied (25.6 %), followed in terms of frequency by glomerular nephropathies (14.7 %), nephroangiosclerosis (13.6 %), non-filiated nephropathies (11%), interstitial nephropathy (8,8%) and renal polycystosis (4,8%).

As far as patients' origin was concerned, we had data on 275 patients. Of these, 92 (34%) arrived at the Units from "Primary care", 133 (48%) through consultations between departments of the centre itself (the Departments of

Table I

| | Average ± DS | n |
|--------------------------------------|---------------|-----|
| Creatinine (mg/dl) | 4.2 ± 3.0 | 274 |
| Creatinine clearance (ml/min) | 25.7 ± 21.6 | 213 |
| Haemoglobin (g/dl) | 11.4 ± 2.4 | 273 |
| Haematocrit (%) | 33.9 ± 6.7 | 275 |
| Ferritin (mcg/l) | 174.7 ± 156.5 | 133 |
| TSI (%) | 24.3 ± 14.4 | 79 |

Internal Medicine, Urology, Accident and Emergency and Endocrinology providing most patients), and 50 (18%) were transferred from other centres (of unknown origin in over half of this group).

Renal function

Patients' average creatinine level upon arrival at the Nephrology Unit was 4.2 mg/dl and average creatinine clearance was 25.7 ml/min (Table I). 35.6% of patients arrived with Ccr below 15 ml/min, 37.6% with Ccr of between 15 and 29.9 ml/min and 26.8% with Ccr equal to or over 30 ml/min (Figure 1).

The average time for remaining in "predialysis" was 45 months. 30.1% of the patients (80) remained in predialysis for less than 6 months, 7.9% (21) between 6 and 12 months, 8.6% (23) between 13 and 18 months and 53.4% (142) over one and a half years. However, this time was not uniform for the various age groups. Thus, patients under the age of 45 had an average time in pre-dialysis of 59 months; for patients between the ages of 45 and 64, the average was 41 months, whereas older patients (65 or over) remained in predialysis for an average of 34 months.

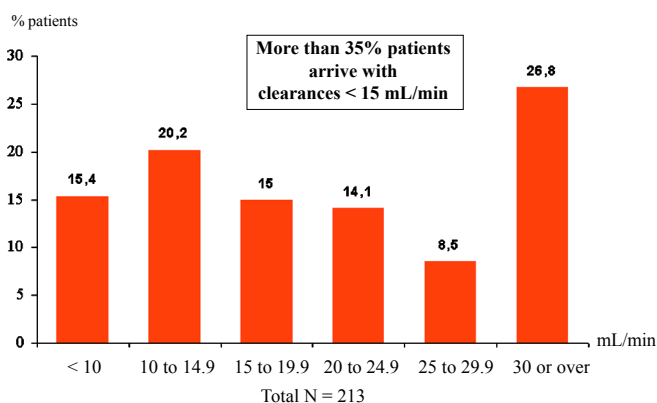


Figure 1: Creatinine clearances when entering the Nephrology Unit

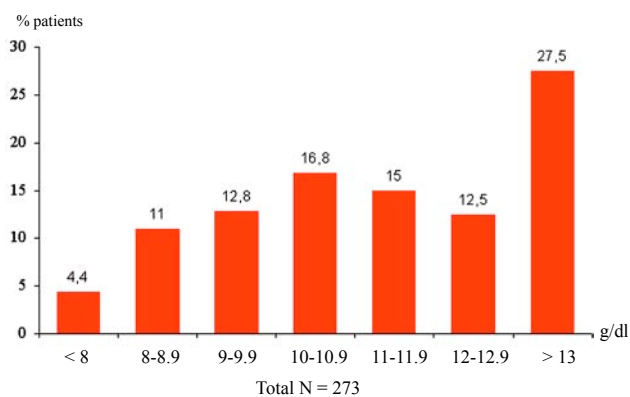


Figure 2: Haemoglobin values when entering the Nephrology Unit

Anaemia

Average haemoglobin upon arrival at the Unit was 11.4 g/dl and average haematocrit was 33.9% (Table I). 27.5% of the patients had haemoglobin equal to or higher than 13 g/dl; 27.5% had between 12.9 and 11 g/dl and 45% had haemoglobin below 11 g/dl. It must also be pointed out that around 30% of the patients in this latter group were referred with haemoglobin below 10 g/dl (Figure 2).

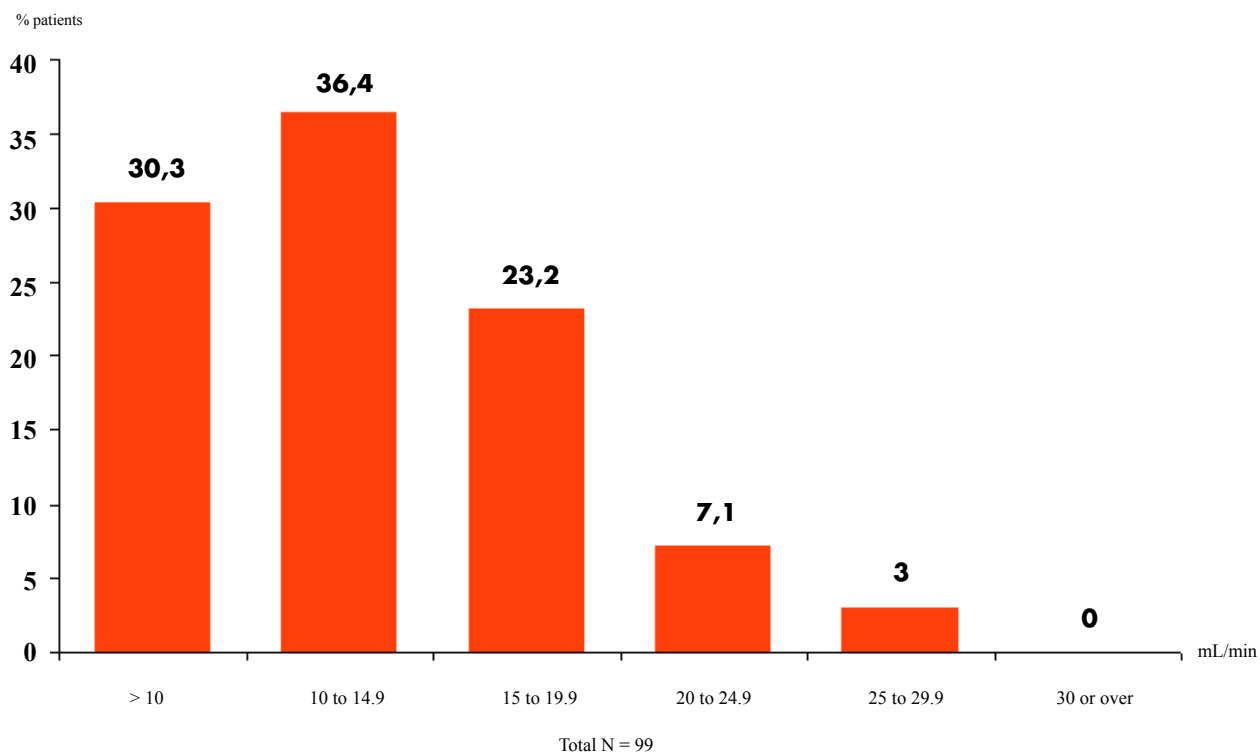


Figure 3: Creatinine clearances at the onset of treatment with r-HuEPO

Iron study

The average ferritin on arrival at the Unit was 174.7 mg/l and the transferrin saturation index was 24.3%. (Table I)

A total of 168 patients stated whether they were receiving any form of iron therapy. 64.2% of these (108 patients) were not receiving any treatment with iron when they were referred to the nephrologist; 30.3% (51 patients) were receiving iron orally and 5.5% (9 patients) intravenously.

Treatment with r-HuEPO

36.5% (113 patients) in predialysis were receiving treatment with r-HuEPO. The average

time between referral to the nephrologist and the start of treatment was 39 months. The average initial dose of r-HuEPO was 68 ± 31 UI/kg/week and the maintenance dose (at two months from the start of the treatment) was 74 ± 31 UI/kg/week. The r-HuEPO was administered subcutaneously in all patients in which this data was recorded, most commonly 2 times a week (49%). 29% of cases received one dose per week and 22% received three doses per week.

The average creatinine when starting treatment with r-HuEPO was 6.2 mg/dl, while the average creatinine clearance was 12.5 ml/min (Table II). Two thirds of these patients began treatment when their clearance was below 15 ml/min, and the remainder began with CCr between 15 and 30 ml/min (Figure 3).

Table II

| | Media ± DS | n |
|-------------------------------|---------------|-----|
| Creatinine (mg/dl) | 6.2 ± 3.1 | 113 |
| Creatinine clearance (ml/min) | 12.5 ± 5.0 | 99 |
| Haemoglobin (g/dl) | 9.1 ± 1.1 | 110 |
| Haematocrit (%) | 27.3 ± 3.2 | 111 |
| Ferritin (mcg/l) | 173.5 ± 172.9 | 83 |
| TSI (%) | 24.8 ± 14.5 | 51 |

Patients' average haemoglobin when starting r-HuEPO treatment was 9.1 g/dl, with haematocrit at 27.3 %, ferritin at 173.5 mg/l and the TSI at 24.8% (Table II). 92.7% of patients started EPO treatment with Hb below 11 g/dl and 7.3% started with Hb between 11 and 12.9 g/dl (Figure 4).

A quarter of the patients began r-HuEPO treatment without receiving iron treatment (42 patients). 63.6% (107 patients) received iron treatment orally and 10.9% (19 patients) intravenously.

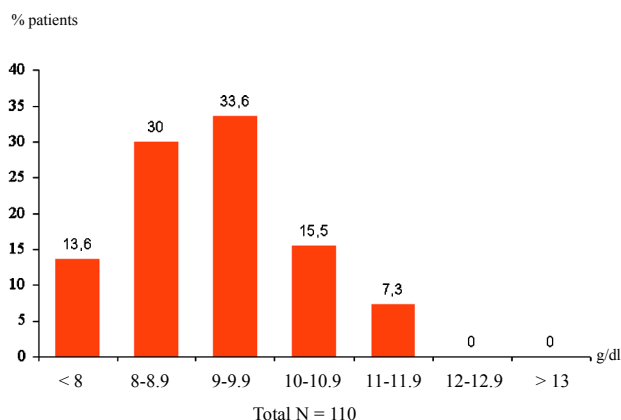


Figure 4: Haemoglobin values at the onset of treatment with r-HuEPO

Start of dialysis

Patients' average creatinine at the start of dialysis was 7.9 mg/dl and the average creatinine clearance was 77 ml/min. 74.7% of patients started dialysis with Ccr below 10 ml/min; 20.6% between 10 and 14.9 ml/min; 4.2% between 15 and 19.9 ml/min and 0.5% with 20 ml/min or over.

There was no difference between the levels of haemoglobin and haematocrit in patients starting dialysis treatment according to whether or not they had been treated previously with r-HuEPO (10 vs 9.8 g/dl and 30 vs 29.2% respectively).

The average time between the start of EPO treatment and onset of dialysis was 6 ± 8 months.

75.8% of patients had haemoglobin below 11 g/dl when starting dialysis; 21.2% had between 11 and 12.9 g/dl and 3% had 13 g/dl or over (Figure 5).

As far as the study of iron was concerned, the average ferritin level when patients started dialysis treatment was 169.6 mg/l, with no significant differences between those who had received EPO (169.6 mg/l) and those who had not received it (200.3 mg/l). The TSI was 24.8% and there was also no difference between those who had received r-HuEPO (24.8%) and those who had not received it (25%).

A third of the patients who started dialysis were not treated with iron (55 patients); 28.4% received iron orally (48 patients) and 33.8% intravenously (65 patients).

DISCUSSION

Anaemia is one of the most common and significant problems in patients with CRF. It is caused by inadequate production of erythro-

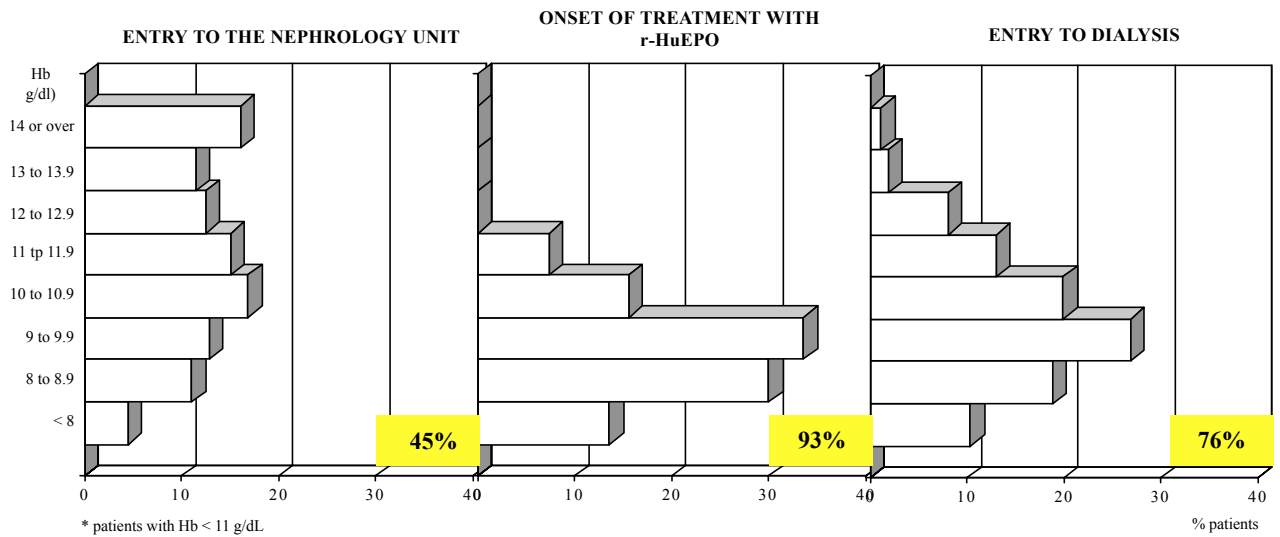


Figure 5: Haemoglobin values (percentages by intervals)

poietin, with low haematocrit levels therefore not producing an appropriate increase in the production of that hormone. There is progressive reduction in haemoglobin levels as the deterioration in renal function advances⁶. Anaemia almost invariably appears when the creatinine clearance is below 30 ml/min, although there are pathologies such as polycystic kidney disease in adults where it may appear later, or even not at all.

Since anaemia in CRF appears progressively, its chronic nature allows compensating mechanisms to be started up in order to maintain adequate tissue oxygenation. This translates to a hyperdynamic state characterised by a reduction in peripheral resistances which will determine the heart overload and the consequent development of left ventricle hypertrophy⁷.

Anaemia is important in patients with CRF due to the high morbidity and mortality with which it is associated, as is proved in various studies on patients in dialysis^{8,9}.

With the use of r-HuEPO in CRF patients, the treatment of anaemia in this population has changed considerably in recent years. There are many well-known benefits of treatment with r-HuEPO in dialysis patients. This substance began to be used in 1988 in advanced CRF in predialysis stages. Since then, there are more and more studies showing the benefits of this treatment in pre-dialysis patients. However, despite that, r-HuEPO is still clearly under-used at this stage.

If we bear in mind that most of the disorders induced by anaemia become irreversible over time, it is clear that treatment with r-HuEPO must begin at earlier stages of CRF. In an ideal situation, the patient would never even develop anaemia. However, this is very far from the day-to-day reality, partly because most patients with CRF are referred to a nephrologist at very late stages of the illness.

This study included a random sample of patients from different units with demographic characteristics representing the current Euro-

pean situation in the field of CRF¹⁰. Diabetic nephropathy was the primary cause of renal failure and this has started to become constant in European series in recent years, as it has been for some time in the United States¹¹.

With the results of this study we were able to show how a high percentage of patients are referred to a nephrologist at a late stage. In our series, the average CCr when patients first came into contact with the Nephrology Unit was only 25 ml/min, emphasising that in almost 30 % of these patients it was even lower than 15 ml/min. Also, up to a third of patients needed to begin a programme of extrarenal clearance within less than 6 months from their referral to the Nephrology Unit. This percentage is still higher in more elderly patients. There is little more data needed to conclude that the policy of later referral to a nephrologist, as has already been stated by other authors, has harmful consequences for patients^{12,13}. These consequences include the low possibility of any measures being taken to halt the progression of CRF, the absence of early treatment for anaemia with r-HuEPO and even failure to plan vascular or peritoneal access to begin extrarenal clearance. In our series, almost half of the patients studied had haemoglobin values below 11 g/dl when they were referred to Nephrology Units. On the basis of this reality, this study aimed to analyse the Spanish nephrologists' guidelines for the treatment of anaemia in late 1998 and compare them to the recommendations of the European Guidelines published at that same time⁴.

The first topic to be studied is the moment when treatment with r-HuEPO should begin. According to the European Guidelines, treatment with this substance must begin when haemoglobin concentrations are persistently below 11 g/dl (*Norm 4*)⁴. There is sufficient evidence to show that the increased Hb concentration for values above 10-11 g/dl (haematocrits above

30-33%) induces significant improvements in quality of life, cardiovascular morbidity, the capacity for physical exercise and sexual, immune and endocrine functions¹⁴⁻²⁰ both in predialysis and dialysis patients. In our study, the patients' average haemoglobin when they began r-HuEPO treatment was 9.1 g/dl and the haematocrit was 27.3 %, which already gives us some idea of the late start of this treatment. This is proved by the fact that in almost 80 % of patients the r-HuEPO began with significant levels of anaemia (haemoglobin below 10 g/dl). As we state above, this fact was partly conditioned by the late referral to Nephrology Units. However, another factor associated with this late start is to do with the nephrologists themselves, since we observed that the average time between referral to the nephrologist and the start of treatment with r-HuEPO was 39 months. Thus, the time between the start of r-HuEPO and entry to dialysis was only 6 months and, as we have seen, up to 76 % of patients began extrarenal clearance with haemoglobin values below those recommended by the European Guidelines. One of the main consequences of this fact is the development of injuries which are difficult to reverse in subsequent stages, despite correcting the anaemia, as occurs with left ventricle hypertrophy (LVH). This develops initially as a mechanism to compensate for heart volume overload induced by anaemia. At the preliminary stages, which recent studies has shown to take place in the first stages of CRF²¹, these disorders are of a reversible nature. Nevertheless, if the conditions which gave rise to the development of LVH, such as anaemia, continue to be present or even progress, a number of irreversible changes begin to take place at a myocardial level -principally the increase in the fibrous setting²². For that reason, it appears that treatment with r-HuEPO should begin in early stages of CRF. Nevertheless, future studies are

needed to confirm this.

One of the most controversial points in treatment with r-HuEPO, particularly in dialysis patients, is currently the "target" haemoglobin value²³⁻²⁵. For that reason, the recommendations of the "norm" are minimum values based on the available evidence²⁶⁻³⁰. Norm 5 of the European Guides state that the target to be attained and maintained, in over 85% of the population, is a concentration of haemoglobin over 11 g/dl, which means that the average for the total population is between 12-12.5 g/dl. In our study, as we stated above, only 24 % of patients began extrarenal clearance with haemoglobin concentrations above 11 g/dl, the average Hb being 3 points lower than the value recommended by the Norm.

A consensus has been reached on the method of administration of r-HuEPO in pre-dialysis. There are sufficient arguments contained in the literature³¹ to make subcutaneous administration advisable in these patients. In this respect, the conduct demonstrated in our study conforms to the indications contained in the Norm, with this method being used in all patients for whom this data is recorded.

The dose and frequency of administration also conformed to the recommendations of the European Guidelines, which were strongly supported by a number of recent studies³²⁻³⁴. In our environment at that time the most common frequency of administration was twice a week (49% of patients), followed by weekly administration (29%) and the least common was 3 times per week (22%). With regard to the average dose administered, we were at the low levels recommended both at the start (50 - 150 U/kg/week according to Norm 10) and at the maintenance stage (< 125 U/kg/week according to Norm 12). The use of these doses below the recommended levels probably allows to reduce undesirable effects of r-HuEPO treatment. This

mainly applies to the rises in blood pressure associated with high doses. Another of the great theoretical disadvantages of treatment with r-HuEPO in predialysis is the possible acceleration in the progressive renal failure. This has been proved in experimental studies, although it has not been confirmed in humans. Studies recently published have even shown slower CRF progression in these patients^{35,36}. The doubts on the r-HuEPO role in the progression of CRF is another reason for under-use of this substance in predialysis, although, as mentioned above, there is an increasing amount of evidence that it is not harmful. However, this is not a matter for this study and more works are still needed to allow this aspect to become clearer.

Another consideration is the iron requirements to reach and maintain adequate levels of haemoglobin. Thus, Norm 6 recommends that sufficient iron must be administered to achieve serum ferritin above 100 µg/l and a transferrin saturation index of over 20%. Levels of serum ferritin between 200 y 500 µg/l and an TSI of between 30 and 40% are established as optimum.

There are currently sufficient data confirming that the need for iron increases with the use of r-HuEPO³⁷, with both absolute and functional deficits of this substance being common among patients with CRF³⁸. Our patients, at that date, had average values for ferritin within the range recommended by the Norm (174.7 upon arrival at the Unit, 173.5 at the start of r-HuEPO treatment and 188 at the start of dialysis), although they were considerably below the figures that the Norm considers optimal (between 200 and 500 µg/l).

Although there are no data to compare methods for administering iron in pre-dialysis patients with progressive renal failure, in recent years there has been a tendency to use iron

intravenously more often and at an earlier stage in these patients³⁹. Despite this, it is recommended that the use of oral iron should continue as a first attempt in predialysis patients despite that its low intestinal absorption and its inability to maintain the balance of iron reserves in the long term^{40,41} has been proved.

There was a clear conservative attitude towards treatment with iron in our environment at that time. Only 5.5% of patients received iron intravenously upon arrival at the Unit; this figure was slightly higher (10.9%) at the start of r-HuEPO treatment and only one third (38.8%) received it intravenously when they began dialysis treatment.

CONCLUSIONS

In the light of the data supplied by the *Spanish Epidemiological Study on the Treatment of Anaemia in Predialysis Patients* carried out in late 1998, three basic conclusions could be drawn:

1. - The treatment of anaemia with r-HuEPO began late and at excessively low haemoglobin concentration levels, considering the evidence already existing at that time.

2. - The doses of r-HuEPO and the method and frequency of administration were close to recommended levels in the light of the existing evidence.

3. - Patients' iron balance, although within "normal" levels, were below what was considered optimal for the evidence found.

Subsequent studies along these same lines should confirm whether there has been any change in the treatment guidelines of anaemia in patients with chronic renal failure on the basis of personal experience and the experience

gained from working with the available guidelines.

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