

and their physician members can reflect on their roles and responsibilities in this area and contribute to policies which are in the best interests of patients, providers and society. It is hoped that this will help to resolve the differences between physicians on this topic.

This document will be reviewed regularly and revised as times and thinking change.

NOTES

1. Field IT. Rationing in health care. *World Medical Journal* 1993; **39**: 61-66; Fuchs C. Ethical dimensions and dilemmas of rationing. *World Medical Journal* 1993; **39**: 75-78; Gillibrand M. Waiting lists. *World Medical Journal* 1994; **40**: 1-3; Mandell BB. Rationing of health care — the physician's perspective. *World Medical Journal* 1994; **40**: 3-9.
2. *WMA Declaration of Geneva* (1994): 'The health of my patient will be my first consideration.'
3. *WMA Declaration of Lisbon on the Rights of the Patient* (1981): 'The patient has the right to accept or to refuse treatment after receiving adequate information.'
4. *WMA Declaration on Physician Independence and Professional Freedom* (1986): 'Within the context of their medical practice and the care of their patients, physicians should not be expected to administer governmental or social priorities in the allocation of scarce health resources. To do so would be to create a conflict of interest with the physician's obligation to his patients, and would effectively destroy the physician's professional independence, upon which the patient relies. 'While physicians must be conscious of the cost of medical treatment and actively participate in cost-containment efforts within medicine, it is the physician's primary obligation to represent the interests of the sick and injured against demands by society for cost-containment that would endanger patients' health and perhaps patients' life.'
5. *WMA Statement on Patient Advocacy and Confidentiality* (1993).
6. *WMA Statement on Medical Ethics in the Event of Disasters* (1994): 'From the ethical standpoint, the problem of triage and the attitude to be adopted towards victims "beyond emergency care" fits within the framework of the allocation of immediately available means in exceptional circumstances beyond human control. It is unethical for a physician to persist, at all costs, at maintaining the life of a patient beyond hope, thereby wasting to no avail scarce resources needed elsewhere. 'The physician must act according to his/her conscience considering the means available. He/she should attempt to set an order of priorities for treatment which will save the greatest number of serious cases that have a chance of recovery and restrict morbidity to a minimum, while accepting the limits imposed by the circumstances.'
7. *WMA Declaration of Madrid on Professional Autonomy and Self-Regulation* (1987).

Clinical experience with Repotin, a locally produced recombinant human erythropoietin, in the treatment of anaemia of chronic renal failure in South Africa

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Objective. To evaluate the efficacy and safety of Repotin, a locally produced recombinant human erythropoietin (rHuEPO), in the treatment of the anaemia of chronic renal failure (ACRF).

Design. The study consisted of two multicentre non-randomised open stages.

Setting. Renal units at several teaching hospitals in South Africa.

Participants. Haemodialysis patients with haemoglobin (Hb) levels less than 8.0 g/dl were recruited. The first stage examined 26 patients during a 12-week period in which the dose of intravenous rHuEPO was adjusted according to haematological response. In the second stage 27 patients were stabilised with intravenous rHuEPO and then

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maintained at a Hb level above 8.0 g/dl by subcutaneous administration for up to 1 year.

Outcome measures. In both stages, outcome was measured by clinical examination, blood pressure, full haematological parameters and blood chemistry.

Results. In stage 1, all patients responded to therapy with a statistically significant increase in Hb from geometric means of 6.28 g/dl to 8.50 g/dl (geometric SDs of 1.17 and 1.20 respectively). The doses used ranged from 25 IU to 125 IU/kg (average 47.1). In the second stage, Hb levels reached a mean of 8.06 g/dl (SD 0.9) and were maintained at target range with an average dose of 55.5 IU/kg three times a week. Apart from changes in serum iron, ferritin (associated with increased haematopoiesis) and potassium, there were no significant alterations in blood chemistry. The incidence of adverse events reported during the 12-month second stage was no greater than that reported for other forms of rHuEPO therapy.

Conclusion. Repotin is a safe and effective rHuEPO preparation for the treatment of ACRF.

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A relative deficiency of erythropoietin is the most important factor contributing to the anaemia of chronic renal failure (ACRF).¹ Recombinant DNA technology has led to the production of erythropoietin which, with its use, has revolutionised the management of this anaemia.² Repotin is a version of recombinant human erythropoietin (rHuEPO) that is produced in South Africa from a cell line derived from baby hamster kidney (BHK) cells.³ Other versions of rHuEPO in use world-wide for the treatment of ACRF are based on the Chinese hamster ovary (CHO) cells.^{4,5} The two versions, although structurally identical in their amino acid sequence, show subtle differences in the fine detail of the carbohydrate chains⁶ which could influence the biological activity of the hormone.

This paper describes the clinical use of Repotin for ACRF in South Africa, performed in two stages. The first objective was to demonstrate the efficacy and safety of Repotin in overcoming ACRF and was designed to establish a Repotin dosage regimen (1st stage). The second objective was designed mainly to demonstrate long-term safety of Repotin use for ACRF patients stabilised on a maintenance dose (2nd stage). The overall aim was to determine whether, despite minor structural differences between Repotin and the CHO-derived rHuEPO, the efficacy and adverse events profiles were similar to those described by others.^{7,8}

Materials and methods

First stage

The first stage was a non-randomised, open, multicentre, single-group study of efficacy, dosage determination and safety of Repotin in ACRF patients on regular haemodialysis over a 12-week period. Criteria for inclusion were that patients had to be in a stable condition without a history of admission to hospital due to decompensation for 60 days

prior to trial inclusion. Subjects of either sex aged between 20 and 60 years, undergoing haemodialysis three times weekly and with a haemoglobin level of less than 8 g/dl, were eligible for inclusion. Subjects were required to have stable vascular access and women had to be non-pregnant with negative pregnancy tests. All subjects gave informed consent prior to inclusion. Exclusion criteria included anaemia due to factors other than chronic renal failure, uncontrolled hypertension, insulin-dependent diabetes, hepatic dysfunction, prior treatment with androgens or other rHuEPO preparations, and known hypersensitivity to human serum albumin and/or mammalian cell-derived products. Patients contemplating elective surgery during the course of the study, or those who had received a blood transfusion within 60 days of trial commencement, were also excluded.

Patients complying with the inclusion criteria entered the study and received Repotin at an initial dosage of 25 IU/kg body weight, 3 times per week post-dialysis over 1 minute by intravenous injection via the dialysis tubing. If the haemoglobin (Hb) level failed to increase by 0.5 g/dl in the first 2 weeks or by 1.0 g/dl in the first 4 weeks of therapy, the dosage was increased by 25 IU/kg three times a week until the Hb level increased by more than 1.4 g/dl in any 2-week period or until the Hb reached the range of 9.0 - 10.0 g/dl (target range). If the Hb reached or exceeded 10.0 g/dl, Repotin was withheld until the Hb fell below 10.0 g/dl whereupon the Repotin was recommenced at a dose lowered by 25 IU/kg three times a week.

Systolic and diastolic blood pressures (supine), oral temperature and pulse were recorded before and 10 minutes after every administration of Repotin. A full blood count and differential blood count were performed on each patient at baseline and twice weekly throughout the study period. A full blood chemistry profile was assessed at baseline and at 2-weekly intervals throughout the study.

Second stage

This was a non-randomised, open multicentre study to document the utilisation of Repotin and the resulting medical consequences over a 12-month period, in stable patients undergoing haemodialysis. Inclusion and exclusion criteria were the same as for the first stage. The dosage regimen followed to achieve target Hb levels was the same as in the first stage (stabilisation phase). When the target Hb range of 9.0 - 10.0 g/dl was achieved, each patient entered an individualised maintenance regimen in which administration was changed from an intravenous to a subcutaneous route. This regimen was designed to keep Hb levels in the target range of 9.0 - 10.0 g/dl. If it fell below the target range and the serum ferritin level was at least 100 ng/ml, the Repotin dose was increased by 25 IU/kg three times a week. Dose increases were restricted to no more than one per month. When Hb levels exceeded 10.0 g/dl, Repotin therapy was temporarily discontinued as in the first stage.

Systolic and diastolic blood pressures (supine), oral temperature and pulse were recorded before and 10 minutes after every administration of Repotin until the target Hb was reached. Thereafter these measurements were done fortnightly.

A full blood count (and differential count), as well as a full blood chemistry profile, were assessed at baseline and weekly until the target Hb level was achieved. Thereafter

these investigations were undertaken monthly. If there were dosage changes, weekly Hb measurements were carried out for 6 weeks.

Statistical methods

The change in the haematological variables from baseline to end-point (week 12) was analysed by calculation of point estimates and 95% confidence intervals for the 'week 12/baseline' mean ratio of the variable in question. The confidence intervals were obtained by calculation of a conventional paired *t*-test-based confidence interval for the 'week 12/baseline' on the logarithmic scale, and then taking the antilog of the confidence limits.

The point estimate for the 'week 12/baseline' ratio was obtained as the geometric mean of the individual ratios of the week 12 and baseline data, respectively.

Results

First stage

Thirty-four patients were enrolled at this stage. Eight patients were withdrawn: 1 patient was a protocol violator, who should have been excluded due to iron deficiency; 3 patients were lost to follow-up; 1 died; 1 developed dizziness; and 2 required blood transfusions (1 following surgery and the other following extensive burn wounds). Thus 26 patients — 15 males and 11 females, mean ages 41.1 (range 19 - 60) and 39.3 (range 23 - 56) years respectively — were included in the main efficacy analysis and 31 patients who received study treatment were included in the safety analysis. Apart from the events mentioned above, no patient was withdrawn because of the adverse effects of treatment. Dose levels used throughout this stage all commenced at 25 IU/kg three times a week and were increased according to the schedule where necessary. The maximum dose needed was 125 IU/kg three times a week and the average throughout the stage was 47.1 IU/kg three times a week.

Twenty-five of the 26 patients' Hb levels at endpoint were not lower than at baseline and for 15 patients the target level of 9.0 g/dl was reached during the study period. Table I shows some important features of the efficacy analysis. Haemoglobin, the primary efficacy variable, and haematocrit increased significantly during the 12-week period and the serum ferritin level fell. White cell and platelet counts were not significantly affected. Other haematological variables that increased significantly were red blood cells, monocytes and reticulocytes. Significant increases were observed in total iron-binding capacity and iron levels. These changes should be seen in the light of the fact that supplementary iron was taken by all subjects included in the main efficacy analysis.

Second stage

Twenty-seven subjects (17 male, 10 female) were successfully enrolled and followed up during the course of the study for up to 12 months. Twenty-three were initially started on a regimen to improve Hb levels up to 9.0 g/dl (stabilisation phase); the remaining 4 in whom a Hb level of

Table I. The effect of Repotin treatment on haematological and blood chemistry parameters (Geometric means (and geometric standard deviations) on values from 26 subjects)

	Baseline	After 12 weeks	Mean ratio (%) [†]	95% CI (%) [‡]
Haemoglobin (g/dl)	6.28 (1.17)	8.50 (1.20)	135	124 - 147*
Haematocrit (%)	18.6 (1.21)	26.2 (1.19)	141	129 - 153*
White cells (x 10 ⁹ /l)	5.30 (1.31)	5.93 (1.42)	112	100 - 125
Platelets (x 10 ⁹ /l)	201 (1.51)	230 (1.45)	114	102 - 128
Red blood cells (x 10 ¹² /l)	2.20 (1.19)	3.00 (1.18)	136	126 - 148*
Monocytes (x 10 ⁹ /l)	0.27 (2.06)	0.41 (1.54)	155	126 - 192*
Reticulocytes (x 10 ⁹ /l)	19.8 (3.19)	47.3 (2.57)	239	177 - 323*
Iron (µmol/l)	11.0 (2.57)	16.9 (2.15)	153	102 - 230*
Ferritin (µg/l)	148 (3.80)	86.0 (3.33)	58	41.4 - 81.2 ^{††}
Total iron-binding capacity (µmol/l)	42.4 (1.18)	49.9 (1.14)	118	107 - 130*

* A statistically significant increase.

† Geometric mean of individual week 12/baseline ratios.

‡ 95% conventional confidence interval for the mean ratio.

†† A statistically significant decrease.

9.0 g/dl had been reached were enrolled directly into a maintenance phase. Fourteen subjects were entered and monitored by the Renal Unit, Department of Medicine, University of Cape Town, and the remainder by the corresponding unit, University of Stellenbosch. As in the first stage, dosage was adjusted according to Hb response with the overall average doses being 63.4 IU/kg three times a week (range 25 - 100) during stabilisation and 55.5 IU/kg three times a week during the maintenance phase. The main haematological efficacy variables showed the same response during stabilisation as in the first study with a statistically significant rise in both Hb and haematocrit from week 6 of therapy. By week 12, the Hb had reached a mean of 8.06 g/dl (SD 0.93). This significant rise was maintained throughout therapy, although a slight dip in mean Hb levels was evident during months 3 and 7 of the maintenance period due to concomitant systemic infections in 2 patients and/or a reduction in Repotin dose.

This second stage enabled the safety of Repotin to be evaluated over 12.5 patient-years. A total of 46 adverse events were recorded in 21 subjects receiving Repotin. Of these, only 7 events were thought to be in any way causally associated with Repotin (Table II).

Table II. Adverse events recorded during the second stage of Repotin use in ACRF

Event	No.	Relationship	Incidence per patient-year
Flu-like symptoms	1	Possibly	0.08
Fever, lightheadedness	1	Possibly	0.08
Clotted fistula	3	Possibly	0.24
Headache	1	Probably	0.08
Pruritus	1	Probably	0.08

Two deaths were reported during the study period, both of which were thought to be unrelated to drug therapy (haematemesis and bleeding duodenal ulcer). Apart from a rise in mean potassium levels at months 6 and 9, no other changes in blood chemistry variables were observed throughout the study period.

Discussion

This report on the clinical use of Repotin in South Africa has shown it to be a safe and effective form of rHuEPO in the treatment of ACRF. Although the number of patients treated is small in comparison with clinical trials of similar erythropoietins elsewhere, it appears that the product behaves in a manner that is indistinguishable from similar products, resulting in a specific dose-related increase in red cells. This is an important finding, since Repotin is produced in culture from a different mammalian cell line (BHK) from that of rHuEPO preparations in current clinical use (CHO). This is significant because there are minor differences between the carbohydrate structures of BHK- and CHO-derived rHuEPO^{9,11} and it has been shown that the carbohydrate structure of a glycoprotein such as rHuEPO can influence its stability and biological activity *in vitro* and *in vivo*.^{12,13}

Of equal importance to the finding of similar efficacy is the demonstration that administration of Repotin is not associated with any more serious side-effects than those of the widely used CHO-derived products.^{7,8} By monitoring the safety of patients on maintenance therapy over several months during the second phase, we were able to evaluate 12.5 patient-years and demonstrate an incidence of adverse events per patient-year that is comparable to that reported for other products.⁷ The causal relationship between the adverse events reported and administration of Repotin is speculative. The most dramatic of these is the clotting of the fistulas, but in other reported instances where this has happened, it has generally occurred through rapid increases in haematocrit and changes in the bleeding time;¹⁴ bleeding times were not formally assessed in this study. The protocol was specifically designed to ensure that the rate of rise in both haemoglobin and haematocrit was kept slow and no significant increases in blood pressure were observed. This slow and gradual increase in haematocrit obtained by careful dosing according to haematological response is a mode of rHuEPO therapy now widely accepted. It is also noteworthy that there were no significant effects on platelet or white cell counts, reinforcing the knowledge that erythropoietin acts specifically at the erythroid progenitor level.¹⁵

In keeping with the increase in erythropoiesis there was a dramatic increase in iron demand, as illustrated by the significant fall in serum ferritin levels. This fall occurred despite the patients' being on oral iron supplements. It has, however, been shown that in patients with ACRF on rHuEPO therapy, the absorption of iron from the gastro-intestinal tract is insufficient to meet the demands of an activated bone marrow.¹⁶

The rise observed in serum potassium levels was not unexpected in patients with chronic renal failure and probably related to Repotin therapy in an indirect way, since

the increase in patient well-being leads to dietary indiscretions with the consequent increased intake of potassium-containing foods.⁷

An important aspect of this study is the question of long-term benefits of rHuEPO therapy in relation to cost of haemodialysis in general. The economics of this type of intervention have been the subject of several publications,¹⁷⁻¹⁹ which have perceived it as costly even in developed countries. The advent of a locally produced version, which will be available at a lower price, is therefore an important step forward for South African health care.

This report provides evidence that this locally produced product will be a safe and effective alternative to imported preparations and, consequent on lower pricing, will become available to a broader spectrum of the population.

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