TH-PO376

Significant Cost Savings in Hemodialysis Patients Converted from Intravenous Erythropoietin to Darbepoetin While Maintaining Hemoglobin in Target Range. Marisa Battistella,[1] Hina Ghazi,[1] Bassem Hamandi,[1] Micheal Wong,[1] Robert Richardson.[2] *[1]Pharmacy, University Health Network, Toronto, ON, Canada; [2]Nephrology, University Health Network, Toronto, ON, Canada.*

Beginning in April 2005, a 15-month open-label observational study of 212 hemodialysis patients was conducted in which all patients were converted from intravenous (IV) erythropoietin to IV darbepoetin. The primary outcome was to assess the efficacy of IV darbepoetin to maintain target serum hemoglobin (Hgb) compared to IV erythropoietin. Secondary outcomes were to evaluate the dose conversion of erythropoietin to darbepoetin and to assess the cost implication of darbepoetin therapy. Initial dose selection was chosen based on a sliding scale, beginning at 200:1 (erythropoietin to darbepoetin). Doses were titrated to a target Hgb of 110 – 125 g/L. Data was collected and assessed at 3 months prior to switch, time of switch (time 0), and then every 3 months thereafter for 12 months. Of the 212-hemodialysis patients who converted from erythropoietin to darbepoetin, 184 completed the 6-month evaluation and 168 completed the 12-month evaluation. Assuming 5g/L to be a clinically significant difference, there were no significant differences between Hgb values at each time point. The mean Hgb for patients on erythropoietin was 122g/L, and for patients on darbepoetin it was 117g/L at time 0, 119g/L at 6 months and 120g/L at 12 months. Both ferritin and Tsat were also similar at each time point. There was a significant difference in dose conversion ratios between time 0 (237:1) and 6 months (250:1; $p<0.001$) and time 0 and 12 months (300:1; $p<0.001$). Using the erythropoietin dose pre-conversion and the darbepoetin dose at 12 months post-conversion, the estimated yearly cost difference was determined. The mean 12 month cost saving associated with the administration of darbepoetin was estimated to be $2490/patient. Based on our experience, darbepoetin was as effective as erythropoietin at maintaining target Hgb levels at a substantially reduced cost.

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Epoetin Delta for the Treatment of Anemia in Patients with CKD Not Requiring Hemodialysis. Raymond D. Pratt. *Shire Plc, Wayne, PA.*

Epoetin delta (Dynepo®, Shire) will be the only commercially available, human cell-line derived erythropoietin: it is produced through a proprietary technology of gene activation. Efficacy and safety of different doses of epoetin delta were investigated in anemic patients with chronic kidney disease (CKD) not requiring hemodialysis.

Patients with hemoglobin (Hb) < 10g/dL, who had not previously received an epoetin were randomized to epoetin delta (15, 50, 100, or 200 IU/kg) or epoetin alfa (50 IU/kg) subcutaneously, twice per week. Patients received the allotted dose until they achieved two consecutive weekly Hb measures of ≥ 11.5 g/dL or a single measurement of ≥ 13 g/dL (correction success). On achieving correction success, dose was titrated to maintain Hb at ≥ 10.5 g/dL. Maintenance success was defined as Hb ≥ 10.5 g/dL at week 12. Total success was defined as achievement of correction and maintenance success.

In total 80 patients were randomized to epoetin delta 15, 50, 100 and 200 IU/kg (23, 14, 13 and 14 patients respectively) or epoetin alfa 50 IU/kg (16 patients). Baseline Hb levels were similar across all treatment groups. The proportion of patients achieving total success was higher in the pooled epoetin delta 100 and 200 IU/kg dose groups compared with the epoetin delta 15 IU/kg dose group (85.2% *vs* 13.0%; $P = 0.0001$). Dose trend analysis across the epoetin delta groups showed a statistically significant, increasing trend in total success (15, 50, 100, 200 IU/kg: total success 13.0, 40.0, 84.6, 85.7% respectively; $P = 0.0001$ for trend). No difference was observed in total success between the epoetin delta 50 IU/kg group and the epoetin alfa 50 IU/kg group. TEAEs occurred in similar numbers between the two treatments, with no obvious dose-related trend across the epoetin delta groups.

Epoetin delta is effective in increasing Hb levels in CKD patients with Hb <10g/dL and shows similar efficacy to epoetin alfa at an equivalent dose. Safety profiles were similar for both treatments. No patient receiving epoetin delta developed neutralizing anti-erythropoietin antibodies. An initial starting dose of 50 IU/kg would be suitable to correct anemia, with subsequent titration.

Other: Shire PLC; Employee

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Pharmacokinetics of Epoetin Delta: A New Erythropoietin Produced by Gene-Activation in a Human Cell Line. R. D. Pratt, J. Dowell. *Shire Plc, Wayne, PA.*

Unlike other recombinant erythropoietins, epoetin delta (Dynepo®, Shire) is produced in a human cell line. This leads to differences in glycosylation profile compared with other commercially available epoetins. We investigated the pharmacokinetics of epoetin delta in two studies in healthy individuals and two studies in patients with chronic kidney disease (CKD) requiring hemodialysis.

In Study 1, 21 healthy men were randomized to intravenous (i.v.) epoetin delta (15, 40 or 100 IU/kg) or placebo. In Study 2, 32 healthy volunteers were randomized in an open-label, crossover study to receive single doses of epoetin delta 75 IU/kg given i.v. or subcutaneously (s.c.). Study 3 involved 40 hemodialysis patients who were withdrawn from epoetin alfa and randomized to epoetin delta or epoetin alfa (50 or 100 IU/kg), three-times per week for 4 weeks. Study 4 was a single-dose study comparing epoetin delta 150 and 300 IU/kg given i.v. or s.c. in 28 dialysis patients.

Pharmacokinetic parameters were calculated from serum erythropoietin concentrations (determined by ELISA) by validated non-compartmental techniques using WinNonlin Professional v3.0A.

The pharmacokinetics of i.v. epoetin delta in healthy individuals were non-linear and dose-dependent, with a dose-dependent effect on serum hemoglobin. The bioavailability of s.c. epoetin delta is around 30%, and concentrations peak later and decline more slowly than with i.v. injection. In dialysis patients, pharmacokinetic parameters were similar to those in healthy individuals, although AUC and half-life were increased. Treatment with epoetin delta 100 IU/kg was associated with a trend to increased hemoglobin and hematocrit levels compared with the 50 IU/kg dose. Epoetin delta was well tolerated in all participants. Adverse events occurring in dialysis patients were those expected in that population and were similar with epoetin alfa and epoetin delta. No neutralizing anti-erythropoietin antibodies were detected in any patient.Epoetin delta has a pharmacokinetic profile and effect on hemoglobin levels suitable for the treatment of renal anemia by the s.c or i.v. routes.

Other: Shire PLC; Employee

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Subcutaneous Epoetin Delta for the Management of Anemia in Patients with CKD: Safety and Efficacy in a One Year Study. Jonathan T. C. Kwan. *S W Thames Renal & Transplantation Unit, Epsom & St Helier University Hospitals, Carshalton, Surrey, United Kingdom.*

Epoetin delta (Dynepo®, Shire) is an erythropoietin synthesized in a human cell line. Currently available epoetins are synthesized in Chinese hamster ovary cells. Differences in glycosylation profile between epoetin delta and available epoetins have been demonstrated. We report the safety and efficacy of subcutaneous (s.c.) epoetin delta in the management of anemia in patients with chronic kidney disease (CKD) over one year of therapy.

This was a US and European trial (1998–2000) treating predialysis, hemodialysis and peritoneal dialysis patients, who had been receiving s.c. epoetin for at least 30 days. All patients (baseline hemoglobin [Hb], 9.6–12.4 g/dL) received s.c. epoetin delta, administered 1, 2 or 3 times per week. The initial dose was identical to that received prior to study entry and dosing was subsequently adjusted to maintain Hb in the range of 10–12 g/dL. Treatments were planned to continue for 52 weeks.

Of the subjects treated with epoetin delta 76.6% (366/478) completed at least 24 weeks of therapy, with 66.7% (319/478) completing the study. Over weeks 12, 16, 20 and 24, average Hb was 11.31 g/dL and average hematocrit was 36.4%; meeting the primary efficacy endpoint. Long-term Hb data demonstrated that epoetin delta was effective at maintaining Hb levels in the range of 10–12 g/dL. At weeks 12, 16, 20 and 24; 83.9% of subject's Hb measurements were over 10 g/dL and 92.3% of hematocrit measurements were over 30%. Average weekly dose was 84.3 IU/kg/week. Epoetin delta was well tolerated in this study; frequency and types of AEs were as expected considering the baseline characteristics of the study population.

Epoetin delta, administered subcutaneously, was effective in maintaining hemoglobin levels in the target range of 10–12 g/dL. S.c. epoetin delta was well tolerated for treatment of up to one year and there was no evidence that it elicits a neutralizing immune response. Epoetin delta is a new erythropoietin for the management of anemia in patients with CKD.

Consultant: Shire PLC

TH-PO380

Effectiveness of Converting from Intravenous (iv) or Subcutaneous (sc) Recombinant Human Erythropoietin (rHuEPO) to IV Darbepoetin Alfa (DA) in End Stage Renal Disease (ESRD) Patients (Pts) on Hemodialysis (HD). B. Rutkowski,[1] Z. Bitterova,[2] S. Ferenczi,[3] M. Nowicki,[4] J. Suchanova,[5] V. Tesar,[6] S. Hubbard,[7] V. Zani,[7] C. Mattin,[7] I. Kiss.[8] *[1]MedU, Poland; [2]NefroDial, Czech Republic; [3]EurCare, Hungary; [4]ULodz, Poland; [5]TadorHemdia, Czech Republic; [6]KlinNefr, Czech Republic; [7]Amgen, United Kingdom; [8]EurCare, Hungary.*

Anemia is a frequent complication in ESRD pts, with erythropoiesis stimulating agents (ESAs) being the standard treatments and iv as the preferred route of administration for HD pts. IV DA administration has been shown to be as effective as scDA dosing. However, direct conversion from sc or iv rHuEPO to ivDA administration has rarely been reported. In this study, we evaluated the therapeutic effect of switching adult HD pts with 10≤Hb≤13g/dL and adequate iron stores treated with either sc or iv rHuEPO(BIW or TIW) to ivDA(QW). Pts were converted to ivDA using a 200:1(rHuEPO unit:1µg DA) conversion ratio, per the EU package insert. The study consisted of a 20-wk titration period(TP) followed by a 4-wk evaluation period(EP). Here, we report interim results from the 1st 100 pts of 200 planned. Final data will be presented at ASN. 40 pts on sc rHuEPO and 60 pts on iv rHuEPO switched to ivDA. The mean(SD) Hb at baseline was 11.2(0.71)g/dL, with 59% of pts having Hb>11g/dL. During the EP, 84% of pts had Hb>11g/dL and the mean(SD) Hb(n=100) was 12.0(1.03)g/dL overall (table). Similar changes in Hb were observed in both sc and iv rHuEPO groups. The geometric mean % change(95%CI) [n=91] in the ESA dose from baseline to the EP was –6%(-19%,8%). These interim results suggest that

switching these pts from either sc or iv rHuEPO BIW or TIW to ivDA QW is efficacious. The increased number of pts achieving the EBPG targets for Hb suggests that DA offers greater flexibility in the route of administration without a dose penalty.

Parameter	Switched from sc rHuEPO (n=40)	Switched from iv rHuEPO (n=60)	Total (N=100)
Hemoglobin – g/dL			
Baseline			
Mean (SD)	11.1 (0.67)	11.3 (0.73)	11.2 (0.71)
% pts with Hb>11.0 g/dL	50%	65%	59%
Evaluation Period[a]			
Mean (SD)	11.8 (1.11)	12.1 (0.97)	12.0 (1.03)
% pts with Hb>11.0 g/dL	73%	92%	84%
Weekly rHuEPO Dose Before Conversion – IU/wk			
Mean (SD)	6663 (3159)	6683 (2902)	6675 (299;
Weekly DA Dose After Conversion (200 rHuEPO units:1 µg DA) – µg/wk Geometric mean (95% CI)			
Baseline[b]	29.4 (25.2, 34.4)	29.6 (26.2, 33.3)	29.5 (26.9, 32.4
Evaluation period[c]	29.6 (21.7, 40.3)	26.9 (21.3, 34.0)	28.0 (23.3, 33.6
% change from baseline to evaluation period[c]	3.3% (-21.3%, 35.7%)	-12.4% (-25.7%, 3.3%)	-6.3% (-19.0%, 8.4

[a] Hb imputed as last available weekly Hb value for patients with no Hb values during the evaluation period.
[b] The first DA dose administered in study week 1.
[c] Total patients=91 (sc rHuEPO=37; iv rHuEPO=54).

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Price Should Be the Principal Determinant of Choice of Erythropoiesis Stimulating Agent in Chronic Haemodialysis Patients. Aisling E. Courtney, Peter T. McNamee, Alexander P. Maxwell. *Regional Nephrology Unit, Belfast City Hospital, Belfast, United Kingdom.*

Erythropoiesis stimulating agents (ESAs) are effective in the treatment of the anaemia of chronic kidney disease. Within Northern Ireland the prescription of ESAs is at the discretion of the individual nephrologist. We performed a comparison cross-sectional analysis of ESA prescribing and haemoglobin (Hb) concentration in established haemodialysis (HD) patients in four dialysis centres in Northern Ireland.

The ESA, dose and method of administration, and current Hb concentration for all haemodialysis patients in the four units was extracted from the renal data information system. Patients maintained on HD for less than 3 months were excluded.

415 HD patients receiving ESA therapy were analysed. Epoetin beta was prescribed for 184 (46%) and darbepoetin alpha for 219 (54%). There was no significant difference in the mean Hb concentration between the two groups (Hb=11.4 g/dL and Hb=11.7 g/dL respectively, p=0.13).

The mean Hb concentrations were comparable for subcutaneous (SC) and intravenous (IV) administration for both agents: 11.5 g/dL (n=119) and 11.4 g/dL (n=65) respectively with epoetin beta (p=0.70), and 11.8 g/dL (n=39) and 11.6 g/dL (n=180) with darbepoetin alpha (p=0.49).

The mean weekly dose of epoetin beta was 7941 units with SC and 9200 units with IV administration (p=0.10). The mean dose of darbepoetin alpha was 45 µg in the SC group and 46 µg in the IV group (p=0.94).

The weekly cost per patient of achieving equivalent Hb levels was £61.86 ($114.86) with SC and £71.67 ($133.07) with IV epoetin beta, and £70.16 ($130.26) with SC and £71.71 ($133.30) with IV darbepoetin alpha.

Epoetin beta and darbepoetin alpha are equally effective in the treatment of anaemia in HD patients but there is an economically significant difference in cost. It is our opinion that the choice of ESA prescribed should be determined by price and in our dialysis facilities SC epoetin beta is the most cost effective ESA, with a total weekly cost saving in our HD population of approximately £4000 ($7500).

TH-PO382

Epoetin Alfa (EPO) Responsiveness Predicts Survival in the Normal Hematocrit Study (NHS). R. Kilpatrick,[1] C. Critchlow,[2] A. Besarab,[3] S. Fishbane,[4] C. Stehman-Breen,[2] M. Krishnan,[2] B. Bradbury.[2] *[1]UCLA, CA; [2]Amgen Inc, CA; [3]Winthrop-University Hospital, NY; [4]Henry Ford Hospital, MI.*

Observational studies of the association of EPO responsiveness with mortality are limited by the fact that dosing is titrated to Hb and current dose may correlate with EPO response history, and thus, may be confounded by patient disease severity. Analysis of data in which a uniform dose increase was applied would reduce this bias. We used data from the normalization arm of the NHS, a randomized clinical trial evaluating the effect of increasing hematocrit (Hct) to 42±3% from 30±3% in hemodialysis (HD) patients with pre-existing cardiac disease, to examine mortality in relation to EPO responsiveness.

In the NHS, following randomization, subjects in the normalization arm were targeted to receive an initial 50% dose increase, irrespective of baseline characteristics. We analyzed the response of patients who actually received a 40-70% first on-study dose increase. Responsiveness was defined as the Hct slope (from linear regression) over the first 3 study weeks divided by the absolute dose change in units from baseline to the first on-study weekly dose (the [modeled] change in Hct per week per unit increase in weekly EPO dose). Subjects were followed until death, censoring or 365 days. Cox regression estimated the association between responsiveness and mortality, adjusting for potential confounders.

319 of 619 patients (52%) contributed data: mean age 65±12, 52% female, 47% white. 1-year survival increased from 62% to 85% (p=0.009) through increasing quartiles of responsiveness. A higher pre-randomization EPO dose (a potential marker of coexistent disease), showed a trend towards lower survival (hazard ratio [HR]=1.02 per 1000U, p=0.14) in crude analyses. Adjustment for the baseline EPO dose and other confounding variables resulted in increased survival with increased EPO responsiveness (HR=0.44 highest vs. lowest, 95% CI: 0.21, 0.90).

In the normalization arm of the NHS, subjects with greater responsiveness to EPO had significantly higher 1-year survival. Controlling for underlying disease severity (confounding) strengthened the observed protective effect.

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Effect of HCV Status on Epoetin Dose Requirement in Chronic Hemodialysis Patients. Benjamin J. Wilcox, Rasib M. Raja. *Nephrology, Albert Einstein Medical Center, Philadelphia, PA.*

Purpose: The purpose of this study is to determine the effect of chronic Hepatitis C (HCV) infection on epoetin dose requirement and serum ferritin level in chronic hemodialysis patients. Because Hepatitis C is an inflammatory disease, we expected that infection with HCV may induce functional iron deficiency and epoetin resistance, and that serum ferritin levels may be elevated in HCV positive patients. Methods: The outpatient laboratory values of 115 chronic hemodialysis patients were reviewed. The mean serum ferritin, hemoglobin, and per treatment epoetin dose were calculated. These values were then analyzed to determine the relationship between chronic HCV infection, erythropoetin dose requirement, and serum ferritin levels. All patients were on thrice weekly dialysis with high flux polysulfone dialyzers with single use. Epoetin dosage and iron administration were carried out according to set unit protocols. Results: The mean hemoglobin level for Hepatitis C positive patients was 11.85g/dL, and the mean hemoglobin level for Hepatitis C negative patients was 11.83g/dL (p=NS). The mean serum ferritin level was 662ng/mL in Hepatitis C positive patients and 925ng/mL in hepatitis C negative patients (p<0.01). The mean per treatment epo dose required in HCV positive patients was 10400 units per treatment, as compared to 8300 units per treatment for HCV negative patients (p=NS). Values for serum Tsat, Retic count, MCV, UIBC, and serum iron were similar between groups. Conclusions: Patients with chronic HCV infection in this analysis required a higher epoetin dose to achieve the same hemoglobin level, indicating a trend toward epoetin resistance in HCV positive patients. However, the difference in dose requirement was not significant. Additionally, serum ferritin levels were not related to epoetin dose in our analysis; those patients with higher levels actually required less epoetin to achieve the same hemoglobin level. There was no relationship between HCV infection and serum ferritin level. Interestingly, transaminase levels, serum albumin were not significantly different between HCV positive and negative patients.

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Erythropoietin (Epo)-Responsiveness Decreases over Time. Claudia Barth,[1] Andrej Woehrmann,[1] Mathias Schaller,[2] Conrad A. Baldamus.[3] *[1]KfH, Kuratorium für Dialyse und Nierentransplantation, Neu-Isenburg, Germany; [2]Department of Public Health; [3]Department of Nephrology, University of Cologne, Cologne, Germany.*

Epo-responsiveness is described by ERI (Epo/week/kg bodyweight/Hb). To analyze whether and why ERI increases over time HD-vintage (V) was analyzed cross sectionally in a large cohort of 15,388 patients. In addition a subgroup of 2,135 patients (male 53,9 %; age 62,4 y) was formed which was on stable HD at least since January 2003. Data of the first quarters from 2003 to 2006 were compared.

Cross sectional analysis resulted in a significant correlation: ERI = 0,285 · V + 7,05. In risk adjusted analysis vintage remained an independent risk factor. In longitudinal intra individual analysis ERI increases with V. Possible explanations like non linearity of EPO response in Hb range of 11,5 – 12,0 g/dl or increased blood loss during HD (sloppy HD) cannot be excluded.

	1/03	1/04	1/05	1/06	p-value 03/06
Hb (g/dl)	11.6	11.7	11.8	11.9	<0.01
Epo (U/kg/w)	76.5	82.4	84.9	90.6	<0.01
ERI	6.8	7.3	7.4	7.9	<0.01
Kt/V	1.5	1.5	1.6	1.6	<0.09
Tsat (%)	30.2	29.8	28.6	29.3	0.23
CRP (mg/l)	14.4	15.6	13.5	14.2	0.8
Morbidity (d/quarter in Hospital)	8.6	8.9	9.1	9.1	0.34
Albumin (g/l)	40.9	40.1	39.3	39.7	0.43

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Why Do We Need Relatively More Erythropoietin (Epo) in 2006 Than 2003. Claudia Barth,[1] Andrej Woehrmann,[1] Conrad A. Baldamus,[2] Mathias Schaller.[2] *[1]Kuratorium fuer Dialyse und Nierentransplantation, KfH, Neu-Isenburg, Germany; [2]Department of Nephrology; [3]Department of Public Health, University of Cologne, Cologne, Germany.*

Although the Epo effect on correcting renal anemia in hemodialysis patients is a non linear relationship the Epo response is frequently described by the Epo resistance index (ERI= U-Epo/kg/week/Hb) assuming a linear relationship for the observation range (10 – 12,5 g/dl). Since in a large cohort study an unproportionally increased i.v. Epo dosage was observed between first quarter of 2003 and 2006 ERI was cross sectional analyzed for the first quarters of 2003 to 2006 and correlated to the parameters in the table below.