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Effect of Auryxia on ESA utilization in ESRD patients with high Ferritin & low transferrin saturation: A Pilot Project: Final Report

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INTRODUCTION

Background

Iron deficiency anemia is very prevalent in end stage renal disease (ESRD) patients.[1] In patients with ESRD, iron deficiency occurs more frequently, because of increased external losses of iron, decreased availability of the body's storage of iron, and perhaps a deficit in intestinal iron absorption.[13]

ESRD patients tend to lose about 3 grams of iron every year from chronic bleeding, frequent phlebotomy and blood trapping in the dialysis apparatus.[5] Total body iron stores of about 20-25 mg are mostly maintained by recycling from senescent red blood cell (RBC) count by macrophages of the reticulo-endothelial system.[3] In addition, to true iron deficiency, many ESRD patients have functional iron deficiency, characterized by impaired iron release from body stores that is unable to meet the demand for erythropoiesis (also called reticuloendothelial cell iron blockade). These patients have low serum transferrin saturation (TSAT, a measure of circulating iron) and normal or high serum ferritin (a marker of body iron stores).[8] Dietary iron absorption under usual circumstances accounts for only 1-2 mg/day and is almost equal to daily iron losses from intestinal and skin cell shedding.[4]

For treatment of anemia caused by chronic renal disease, the United States Food and Drug Administration (FDA) has approved the use of ESA therapy.[16] There are two ESAs licensed for the treatment of anemia of CKD in the Unites States: epoetin alfa and darbopoetin alfa. Both are glycoproteins that are manufactured using recombinant DNA technology.[14] They stimulate erythropoiesis through the same mechanism of action as endogenous erythropoietin.[14] The starting dose of epoetin is 50 units/kg (3000–4000 units/dose) once or twice a week, and darbepoetin is started at 0.45 mcg/kg and can be administered every 2–4 weeks. [15] To avoid impaired erythropoiesis caused by true iron deficiency or functional iron deficiency, iron stores should be fully replenished before and during ESA therapy.[14] ESA therapy is considered safe. However, major adverse effects should be acknowledged, including an increased risk of death, thromboembolic complications, stroke, heart attack, aplastic anemia, tumor progression, and others. [14] To minimize risks of these adverse events, careful monitoring of hemoglobin levels, along with adjustment of ESA dosing, to maintain the lowest hemoglobin level clinically needed is recommended.[14]

Given that ESRD is a pro-inflammatory condition, substantial elevation in serum ferritin is very common in ESRD patients. The role of iron replacement therapy in ESRD patients with high serum ferritin but low transferrin saturation is not clear at all. [9] In fact, most anemia management protocols recommend stopping iron replacement when ferritin levels are greater than 1,200 ng/ml, even if the TSAT is below 20%. [9,10] The United States Renal Data System (USRDS) reports for that 55% of prevalent ESRD patients (2012-2014) have a ferritin >800 ng/ml and 22% had ferritin>1200 ng/ml. [11] In one of our local dialysis centers, close to 45% of patients seem to have a ferritin greater than 1,200 ng/ml and about 20% have a combination of low TSAT and high ferritin.

Patients with ESRD require phosphate binders for hyperphosphatemia and erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron for anemia.[12]

Ferric citrate (Auryxia) is a novel, iron-based phosphate binder that increases iron stores and decreases IV iron and ESA usage while maintaining hemoglobin levels, and may decrease the cost of ESRD care. [12] By binding phosphate in the GI tract and decreasing absorption, ferric citrate lowers the phosphate concentration in the serum. In addition to effects on serum phosphorus levels, Auryxia has been shown

to increase serum iron parameters, including ferritin, iron and TSAT. In dialysis patients treated with Auryxia in a 52-week study in which IV iron could also be administered, mean (SD) ferritin levels rose from 593 (293) ng/mL to 895 (482) ng/mL, mean (SD) TSAT levels rose from 31% (11) to 39% (17) and mean (SD) iron levels rose from 73 (29) mcg/dL to 88 (42) mcg/dL. In contrast, in patients treated with active control, these parameters remained relatively constant.

Research hypothesis

We hypothesized that treating ESRD subjects with high serum ferritin and low TSAT with oral ferric citrate will increase TSAT, hemoglobin, and lower clinical use of ESA's.

STUDY OBJECTIVES

Primary

To determine the average weekly dose in the clinical use of ESAs in subjects with the use of Auryxia.

To evaluate the effect of iron related parameters in subjects with the use of Auryxia.

Secondary

To determine the effectiveness of Auryxia in increasing TSAT (from less than 30% to greater than 30%) and Hemoglobin in ESRD subjects with elevated serum Ferritin (>1000 ng/ml) and low TSAT (<30%) after 90 days of treatment.

To determine improvement in quality of life (e.g. increased energy, reduced fatigue, reduced depression) as indicated by KDQOL-36 scores in ESRD subjects.

STUDY PLAN AND PROCEDURES

Overall study design and flow chart

This is an un-blinded open label trial of Auryxia in ESRD subjects to determine the effect of this oral therapy on Iron parameters and to estimate the change in the clinical use of ESAs. Subjects meeting the inclusion/exclusion criteria and following informed consent had their current phosphate binder replaced with Auryxia. Initially dosed at 2 tablets of 210 mg each three times daily with meals.

The investigator caring for the subjects allowed increasing or decreasing the Auryxia dose once a month solely based on its role as a phosphate binder. Additional phosphate binder therapy added at the discretion of treating investigator only after a maximum dose of 12 Auryxia tablets a day found to be insufficient for at least 1-month therapy. The study staff recorded all dosage changes made by the investigator.

Intravenous (IV) iron therapy held for enrolled subjects as per clinical care/site protocol and KDIGO guidelines as their ferritin levels are greater than 1000 ng/ml.

Rescue IV iron therapy was allowed only if ferritin levels fall below 1000 ng/ml and TSAT is less than 20%, as per site anemia management protocol.

ESA dosing as per standard clinical/site protocol.

Baseline average weekly ESA dose for these patients 3 months prior to the switch was determined from their EMR.

Monthly monitoring of serum iron parameters as per standard protocol for the HD unit protocol. IV iron on hold for the duration of the study with the exception of needed rescue therapy, as described above.

Labeling

Auryxia supplied to subjects in labelled containers with one-month supply (180 tablets) at a time. Auryxia 210 mg ferric iron tablets equivalent to 1 g of ferric citrate supplied as 200 tablets in 400-cc high-density polyethylene bottles. The 210 mg ferric iron tablets are film-coated, peach-colored, and oval-shaped tablets embossed with "KX52."

Concomitant and post-study treatment(s)

All medications (prescriptions and/or over-the-counter medications) continued at the start of the study or started during the study and different from the study drug reported to the study team.

Treatment compliance

Subjects trained on study medication dosing. Subjects encouraged to bring ALL medication bottles to each visit. Compliance with visits and treatment monitored, and study drug compliance defined as 80% or above.

Discontinuation of investigational product

In subjects who could not be followed up for primary outcome, it wass aimed to at least determine the vital status of the subjects at the final visit.

Withdrawal from study

The subject had the right to withdraw from the study at any time for any reason. The investigator could also decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion. If a subject was withdrawn from the study, they were not replaced.

Reasons for removal from the study may include any of the following:

- subject request
- safety concern (e.g., due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria, pregnancy)
- decision by drug manufacturer (other than subject request or safety concern)
- death
- lost to follow-up

Results:

Baseline Demographics of the Cohort: Table 1

Thirty subjects signed informed consent and enrolled in the trial. Two subjects dropped out, one after 1 day and the second one after 1 month due to hospitalization. All subjects were included in the analysis.

16 subjects were male (453.3%), 18 (60%) were African American and 11(36%) white. 19 (63%) were non- Hispanic ethnicity. Mean age of the cohort was 55 years.

60% patients had DM2, 100 % had HTN and 15 % had Coronary Artery Disease and 80% hyperparathyroidism.

75 % patients were on beta-blockers, 10 % on anticoagulants at the start of the study.

Baseline Anemia and Iron Parameters of Cohort: Table 2

At the baseline visit, the mean Iron was 55 (±5.2) mcg/dl , the mean Ferritin was 1497 (±687) ng/ml, mean Transferrin Saturation was 23.54 (± 1.9) %, Mean Hemoglobin was 10.2 (± 0.3)g/dL, mean phosphorus was 5.98 (±0.7) mg/dl, mean PTH was 663.73 (±375.9) pg/ml and mean serum albumin was 3.82 (± 0.2) mg/dl

Baseline KDQOL parameters of the Cohort and effect on intervention: Table 3

At baseline, the cohort had a mean KDQOL 36 total score of 90.47 with the domains of Health scoring 31.5, domain of Kidney disease scoring 41 and domain of effect of kidney disease on daily life scoring 18

During the course of the trial, the scores for the domain of health improved by 9.44 points and there were reductions in the burdens of kidney disease and effect of kidney disease by 1.7 and 1.6 points resulting in a mean reduction in KDQOL score by 4.5 point. This represent a 30% improvement in self-reported health of ESRD patients and 10% reduction in the effect of kidney disease on daily life suggesting an improvement in quality of life of ESRD patients.

Effect of Intervention on Iron Profile: Table 2

Mean serum Iron increased from 55 mcg/dl to 82 mcg/dl over the 4 month period (p= 0.0007) with peak mean serum iron of 109 mcg/dl noted at visit 2 (after 2 months on study drug).

Serum Ferritin: did not increase during the course of the trial starting at 1497.87 and ending at 1119.2 at the end of 4 months

Transferrin Saturation increased from 24% to 37% (p= 0.0001).

Hemoglobin levels increased from 10g/dL to 11 g/dL

Effect of Intervention on ESA use:

Mean ESA dose at baseline was 66 units/week and this was reduced to 39 units/week at visit 4 (p= 0.012) representing a 36% reduction in ESA use over the 4 month period.

Maximal reduction in ESA dose occurred between visit 2 and visit 3 from mean dose of 64 u/week to 52 u/week at visit 2 and from 52u/week to 41 u/week at visit 3.

The reduction in ESA dose appears to lag behind the improvement in serum iron parameters by 30 days possibly due to the monthly lab draws for testing anemia and iron parameters at the study site.

Side Effects and discontinuations:

Most subjects tolerated Ferric Citrate well with no major side effects

The most commonly reported side effect was diarrhea (16.6 %), followed by GI upset and headaches

Three subjects hospitalized during the trial. All hospitalizations adjudicated to be unrelated to the trial procedure. Two subjects discontinued the IP and dropped out of the trial.

Discussion

We conducted a pilot pragmatic trial of oral Ferric Citrate phosphate binder therapy in ESRD patients on hemodialysis that have low transferrin saturation suggesting Iron deficiency but High serum Ferritin that made them ineligible to receive IV Iron therapy as per current Anemia management protocols endorsed by the KDIGO and all the large and medium dialysis organizations.

These patients presumably have “functional Iron deficiency “where the elevated Ferritin from inflammation reduces the body`s incorporate IV Iron into RBC`s. In this specific setting, we chose to explore the role of orally absorbed Iron in the form of Ferric Citrate currently used as a phosphate binder to examine its efficacy in improving Iron parameters in these ESRD patients and on the cumulative dose of ESA needed to treat anemia in ESRD.

Given the “pragmatic” nature of the clinical trial, the only intervention allowed was to change the patient`s phosphate binder to Ferric Citrate tablets, dosed as per FDA label.

During the course of the trial, a definite, statistically significant increase was noted in both mean serum Iron and mean Transferrin saturation without any dramatic changes in mean serum Ferritin suggesting absorption of the oral Iron and its incorporation into RBC`s.

This seemed to result in a statistically significant 40% reduction in mean ESA dose/week over the 4-month period of the trial. The reduction in ESA dose was most dramatic between day 30 – day 60 and day 60- day 90 of the trial, whereas the improvement in mean serum Iron and TSAT were largest

between baseline –day 30 and day 30 – day 60 suggesting a lag between repletion of iron stores and reduction in need for ESA.

We also collected data on the effect of oral Ferric Citrate therapy on KDQOL 36 scores in ESRD patients with high Ferritin and low Transferrin saturation. The mean baseline KDQOL 36 score for the cohort was 90 with the domain of “health” at 31.5, “kidney disease” 41 and “effect of kidney disease on daily life” 18. Over the course of the trial, these scores changed with a decrease in the domain “Health” to 30.3, a reduction in “kidney disease” to 39.3 and reduction in “effect of kidney disease on daily life” to 16.3

This resulted in a statistically significant and clinically meaningful reduction in the Total KDQOL 36 score from 90.5 to 85.5. Given the paucity of studies showing interventions that have a meaningful impact on patient’s quality of life, we believe that the role of oral Ferric Citrate in improving quality of life in ESRD patients merits further investigation.

In conclusion:

Oral Ferric Citrate, a phosphate binder used in ESRD patients with low transferrin saturation but high serum Ferritin is efficacious in improving Iron parameters and reducing weekly ESA dose by 40 % in this pilot pragmatic clinical trial. In addition, oral Ferric Citrate may have a role in improving ESRD patients’ quality of life.

Table 1: Baseline Characteristics of the Cohort

Co-morbid Condition	**Percentage**
Hypertension	100
Anemia	90
Hyperparathyroidism	80
DM	60
Hyperlipidemia	50
GERD	40
Coronary Artery Disease	15

Table 2: Changes in Iron Parameters and ESA use from baseline to visit 4

	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	p
Mean Iron(mcg/dL)	55	82	109	77	82	0.0007
Mean TSAT (%)	24	39	34	36	37	0.0001
Mean Hb(g/dL)	10	11	11	11	11	0.1040
Mean ESA (units/week)	66	64	52	41	39	0.0117
Mean Ferritin	1497.87	1163.54	1112.84	1070.96	1119.22	0.249207

Table 3: Changes in KDQOL 36 scores

	Baseline	Visit 3	Change	% change	p
KDQOL H	31.50	30.3	9.44	-4%	0.56
KDQOL K	41.00	39.30	-1.70	-4%	0.08
KDQOL E	17.97	16.35	-1.62	-9%	0.46
KDQOL total	90.47	85.96	-4.51	-5%	0.04

Table 4: Side Effects and SAE`s:

Adverse Events	Number of subjects
Diarrhea	5
Black stool	4
Hyperkalemia	4
Hyperphosphatemia	4
Tachycardia	2
Stomach Cramps	2
Constipation	2
Vomiting	1
Shortness of breath	2

Severe Adverse Events

S.A.E.	Number of subjects
Stroke	1
Access clotting	1
LE amputation	1
Severe Hypocalcemia	1

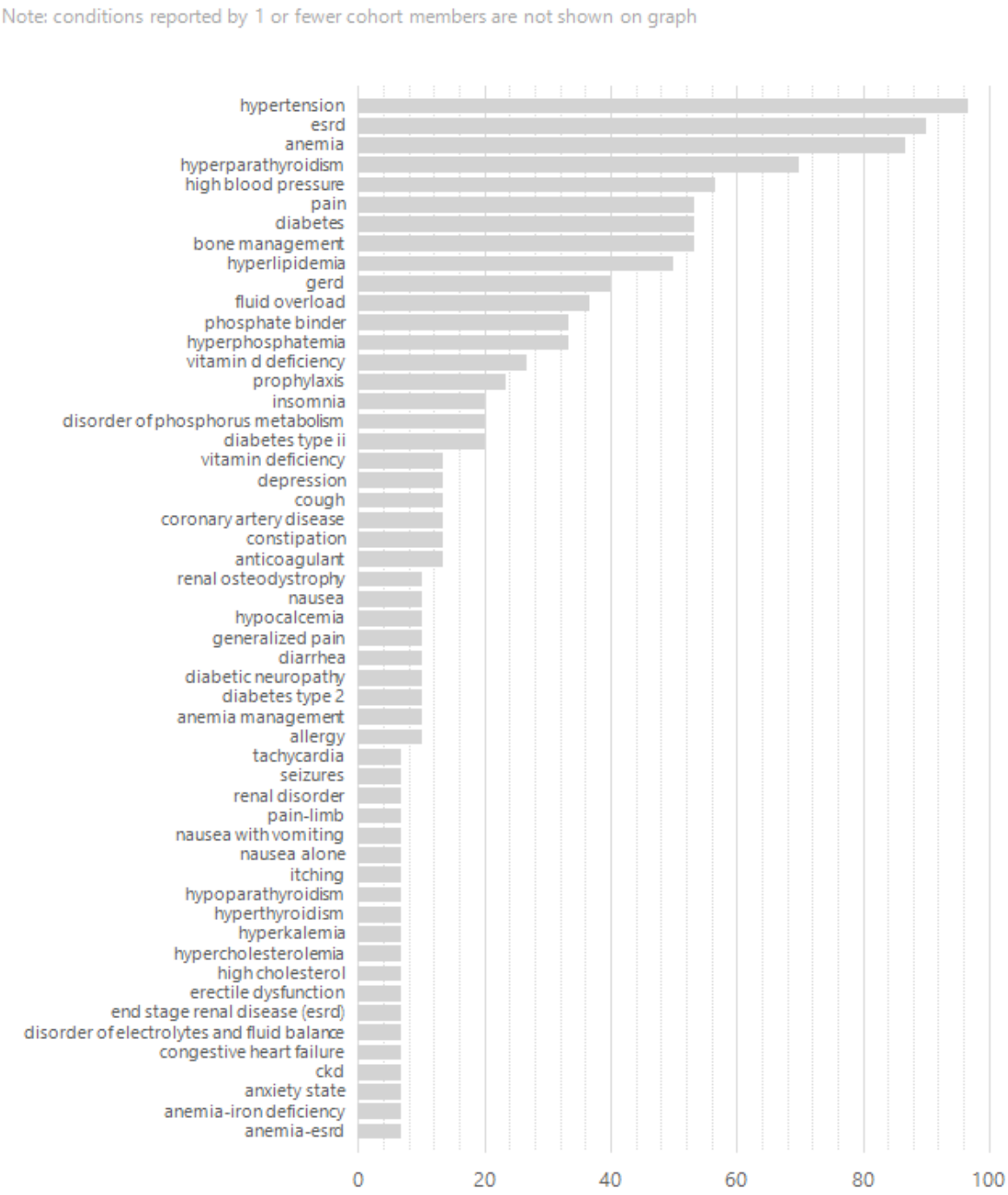

Figure 1: Baseline comorbidities of the study cohort

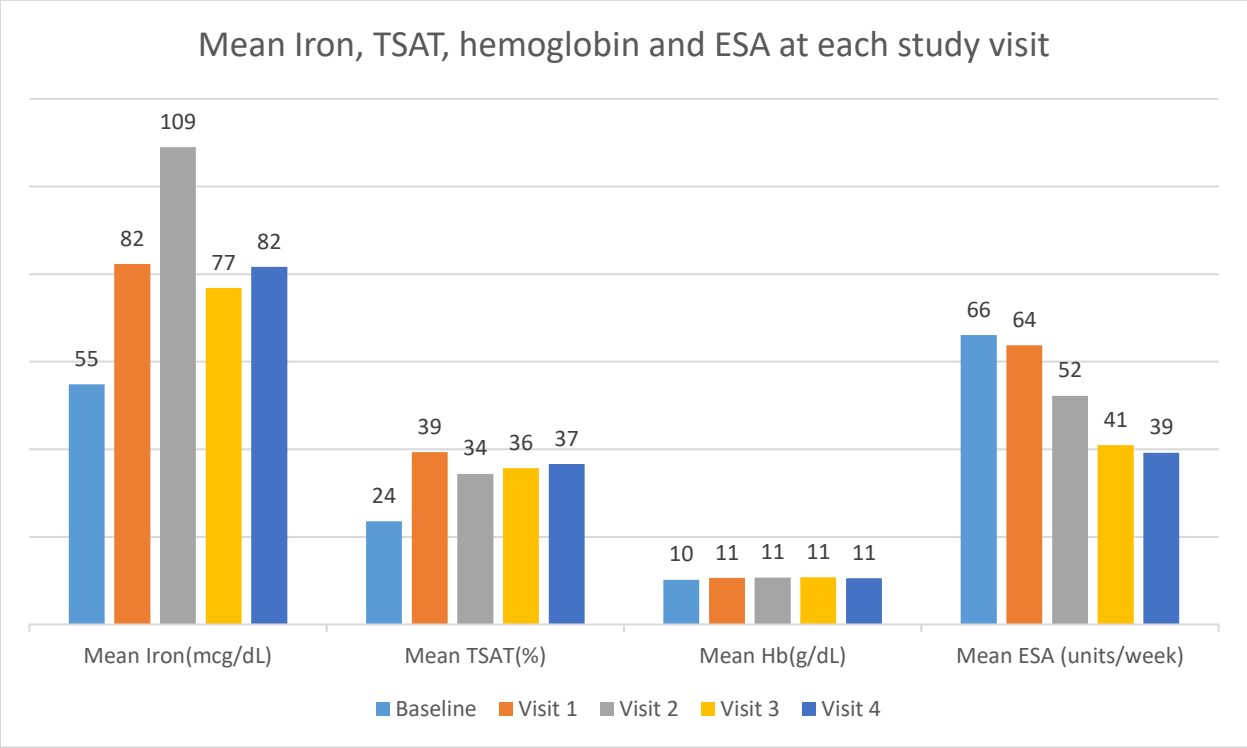

Figure 2: Hemoglobin and Iron parameters during the course of the study

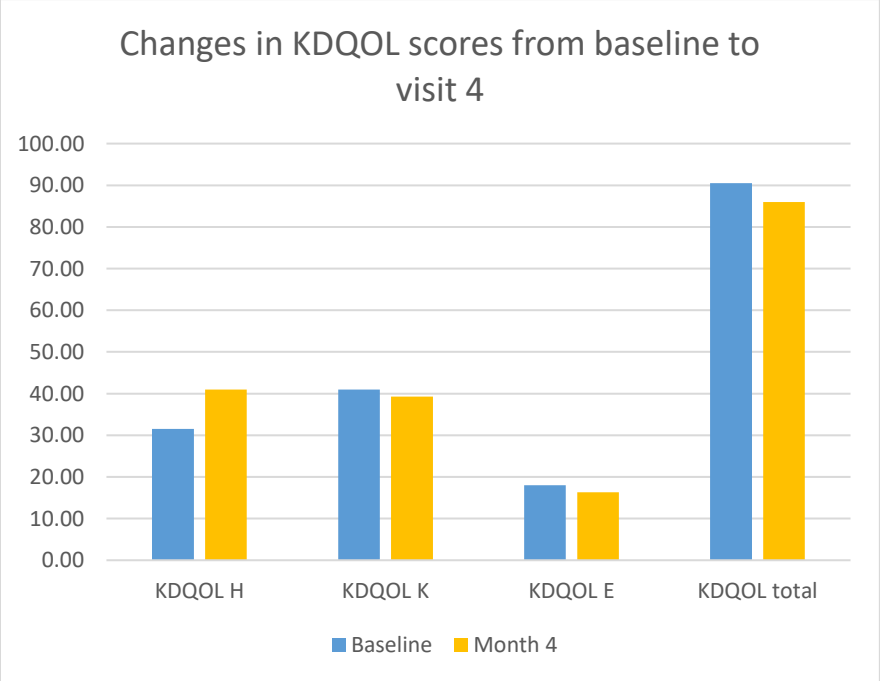

Figure 3: KDQOL 36 scores during the study period.

Submissions to International Meetings:

1. Kidney Week 2018, American Society of Nephrology Annual Meeting, San Deigo

   Abstract accepted

2. National Kidney Foundation Annual Meeting, March 2019; Poster presentation

3. Kidney Week 2019, American Society of Nephrology Annual Meeting, Nov 2019: Oral Presentation

4. World Congress of Nephrology 2020, International Society of Nephrology Annual Meeting, abstract submitted.

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