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A New Approach to the Management of Anemia in CKD Patients: A Review on Roxadustat

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Abstract

A New Approach to the Treatment of Chronic Kidney Disease is an article that informs the reader of the current information available on a novel therapeutic agent and new class of drug for the treatment of anemia. The data shows promising results against erythropoietin stimulating agents and offers a time line of when Phase III data will be available. The information on this new drug and new drug class will change how nephrologists approach treating anemia within their patients.

Keywords: Anemia; Chronic kidney disease; ESA; Erythropoietin stimulating agent; Roxadustat; HIF inhibitor; HIF

Introduction

An important function of the kidneys is the production of erythropoietin, a hormone that stimulates production of red blood cells [1-3]. The kidneys produce this hormone in response to oxygen tension and extracellular volume [3]. In disease states such as Chronic Kidney Disease (CKD) the kidneys are not functioning at capacity and there can be a disruption in the production of erythropoietin that can lead to anemia [1,2]. Other causes of anemia in CKD are iron deficiency and inflammation. Anemia may be present in all stages of CKD and increases in prevalence as CKD progresses [2,4]. Current treatment of anemia includes iron replacement and use of Erythropoeitin (EPO) analogs. However, the FDA has issued warnings on the use of EPO analogs due to risk of death and serious cardiovascular events [5-7]. The cardiovascular safety findings of EPO analogs were based on a numbers of controlled trials which targeted hemoglobin values greater than 11 g/dl. The warnings stated that no trial has identified an Hb target level, ESA dose, or dosing strategy that does not increase these risks [8-11]. The FDA labeling recommends using the lowest epoetin alfa dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Roxadustat, also known as FD-4592 is a first in class small molecule oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) currently in Phase III development [12,13]. Fibrogen, Inc. has collaborated with Astellas Pharma Inc. and AstraZeneca in the development and commercialization of roxadustat and estimates completion of the Phase III trials for U.S approval in 2017.

Scientific Summary

Pharmacodynamics

Roxadustat offers a novel way of utilizing the body's natural compensatory mechanisms in response to hypoxia [4,12,14,15]. Hypoxia-inducible factors (HIF) are transcription factors that regulate expression of genes that stimulate erythropoiesis. When the body has normal oxygen levels HIF specific prolyl hydroxylase (HIF-PH) will degrade HIFα. In hypoxic conditions, such as at increasing altitudes HIF-PH activity is decreased to compensate for the reduced oxygen concentration. Roxadustat is a HIF-PH Inhibitor (HIF-PHI) that inhibits the degradation of HIFα. When HIFα accumulates it dimerizes with HIFβ and translocate to the nucleus to activate the transcriptional response to hypoxia by promoting erythropoiesis. Pase I and phase II roduxadustat trials provided evidence that erythropoiesis was stimulated by an accumulation of plasma endogenous erythropoietin and suppression of hepcidin, an indirect regulator of iron absorption and utilization [12]. When hepcidin levels are suppressed intestinal absorption of iron increases and the release of iron from storage sites are utilized.

Pharmacokinetics

Roxadustat is orally bioavailable with an estimated half-life of 12 hours [15]. In a placebo controlled dose-ranging study (NCT00761657) select patients who were being studied for treatment efficacy of roxadustat in NDD-CKD were also evaluated for pharmacokinetic and pharmacodynamics parameters [12]. Evaluations included measurement of endogenous erythropoietin (eEPO), iron indices including total iron-binding capacity (TIBC) and transferrin saturation (TSAT), as well as hepcidin levels. When roxadustat was administered in doses of either 1.0 mg/kg or 2.0 mg/kg twice weekly (BIW) or three times weekly (TIW) eEPO started to increase within 4 hours of the dose and peaked at 10 hours post dose. Endogenous EPO fell back to baseline at 24-48 hours post dose regardless of the dose given. Peak EPO increased with dose but not with frequency. At 6 week follow-up there was a decrease in TSAT and an increase in TIBC in the roxadustat group signifying increased iron utilization, as well as a significant decrease in hepcidin levels.

Therapeutic trials

A Phase II randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (NCT00761657) evaluated the treatment of anemia in patients with CKD Stages 3-4 (eGFR: 15-59 ml/min/1.73 m^2) with anemia (Hb ≤ 11.0 g/dl) [12]. Patients were enrolled to receive doses of 0.7 mg/kg, 1.0 mg/kg, 1.5 mg/kg or 2.0

mg/kg and were then randomized in a 3:1 ratio to receive roxadustat or placebo administered as either BIW for 4 weeks or TIW for 26 days. Patients were followed for up to 12 weeks post treatment. Study patients were not permitted to receive EPO analogous, intravenous iron, androgens, or RBC transfusion. If patients were on oral iron they were kept at the original dose; oral iron was also given at the investigators discretion. The study defined Hb response as an increase in Hb ≥ 1 g/dl at any time from Day 1 to the 2-week follow up. Mean change in Hb was measured at the end of week 6. One hundred and seventeen patients were randomized and had comparable baseline characteristics with the exception of some differences between sex and race between groups. Hb response was higher in patients who received roxadustat compared to placebo. In pooled placebo groups 13% of patients had a Hb response compared to roxadustat given at 0.7 mg/kg BIW (60%), 0.7 mg/kg TIW (40%), 1.0 mg/kg BIW (80%), 1.0 mg/kg TIW (91%), and 100% response rates in patients who received doses of 1.5 mg/kg and 2.0 mg/kg administered as either BIW or TIW. The rates of Hb response were dependent on the dose administered. When patients received 1.5-2.0 mg/kg TIW they achieved a faster response in Hb compared to BIW groups. Fifty-two adverse events were reported in pooled placebo and roxadustat groups. These AEs were mostly related to the disease state and did not have any clinical differences between the two groups. Serious AEs (SAEs) were reported by 5% of patients who received roxadustat and 4% of patients who received placebo. SAEs included vascular access complications, femoral neck fracture, non-cardiac chest pain, and dyspnea. There were no incidences of cardiovascular events, seizure, or thromboembolism reported during the study. There were two recorded episodes of moderate exacerbation of hypertension, excessive fluid weight, and one episode of elevated ALT, AST, and bilirubin that were deemed unrelated to the study drug. The most common side effects of roxadustat were diarrhea, headache, back pain and fatigue. This evidence is limited to the small population size studied and the short treatment duration.

Anemia treatment in dialysis-dependent CKD

An open label, randomized study evaluated the effect of roxadustat therapy on anemia in dialysis patients and the exogenous iron requirements [4]. A total of 60 patients were enrolled: 24 patients undergoing hemodialysis (HD) received no exogenous iron supplement, 12 HD patients and 12 peritoneal dialysis patients received oral iron and 12HD were given intravenous (IV) iron. The average oral iron dose was 71 ± 50 mg; the IV iron dose was 50 or 62.5 mg weekly. The mean weekly dose, administered three times a week, of roxadustat (4 mg/kg-4.3 mg/kg) varied but did not significantly differ amongst groups and was adjusted based on hemoglobin (Hb) response. The patients included in this study had an average age of 50 ± 15 years, 52% men, majority (90%) white with an average time since first dialysis of 2.2 ± 0.9 months and a baseline Hb of 8.3 ± 1 g/dl. Mean Hb increases of ≥ 2 g/dl within 7 weeks was achieved in each group. In addition, the overall mean change from baseline of Hb was 3.1 ± 0.2 g/dl. The Hb response was greater in patients receiving iron supplement than those who did not; however, the response was similar regardless of the iron route of administration. Hepcidin levels decreased in all iron regimen groups with the largest drop (80%) observed in patients on HD not receiving iron. Other parameters, such as transferring saturation (TSAT) levels and reticulocyte Hb content did not change in the groups receiving iron, however a decrease was observed in patient not receiving iron. Adverse events (AEs) were reported in 50% of all patients, these AEs were typical of the patients' population undergoing dialysis. Most common AEs included hypertension (10%) and decreased TSAT (6.7%); all other AEs had an incidence of less than 5%. Two patients had abnormal electrocardiograms at baseline and through the treatment, one patient developed a first degree arteriovenous block, and 2 patients had a transient elevation in liver function tests unrelated to roxadustat. Two deaths were reported and determined to be unrelated to roxadustat. This study has a number of limitations including small sample size, open label design, short treatment durations and lack of comparison with standard of care such as erythropoetin analogue and iron therapy.

Anemia treatment in patients with dialysis-dependent CKD who previously had hb Levels maintained with Epoetin alfa

A phase II, randomized, open-label, dose-ranging, active control study (NCT01147666) evaluated the safety and efficacy of roxadustat in maintaining Hb levels in patients on maintenance dialysis therapy and who had maintained Hb levels with IV EPO analog, epoetin alfa [15]. The study also evaluated the optimum starting dose and dose adjustment regimens of roxadustat in this patient population. ESRD adult patients were included in the study if they were maintained on a three times weekly dialysis schedule for a duration of ≥ 4 months with Hb 9.0-13.5 g/dl for 8 weeks, and stable EPO analogs at dosages ≤ 450 U/kg/week for 4 weeks. Part I of the study was conducted in 52 patients over 6 weeks with an 8 week follow up to evaluate the roxadustat doses of 1.0, 1.5, 1.8 or 2.0 mg/kg three times a week. Part 2 was 19 weeks with a follow up of 4 weeks which evaluated 90 patients in 6 cohorts to evaluate roxadustat with various starting doses compared to continuation of EPO analog. In part I of the study patients who received the lowest dose of roxadustat 1.0 mg/kg TIW had a comparable Hb response rate of -0.5 g/dl or greater from baseline compared to EPO analog. Roxadustat doses ≥ 1.5 mg/kg TIW maintained higher Hb response rates (79%) compared to EPO analog (p=0.03). Pooled roxadustat patients had an overall mean increase in Hb from baseline of 0.3 g/dl compared to a decrease of 1.0 g/dl in patients who received EPO analog (p=0.04).

In Part II of the trial patients who received any dose of roxadustat achieved a maintenance Hb ≥ 11 g/dl over the last 4 weeks of the 19 week treatment compared to EPO analog (51% and 36% respectively). Individual roxadustat dose cohorts treated for 19 weeks did not significantly differ from EPO analog treated patients in change in Hb at any time. Hb was maintained with a mean roxadustat dose of 1.68 ± 0.65 mg/kg TIW with starting doses based on weight or weight tiers. C-reactive protein (CRP), which increases during an inflammatory state, was correlated with increased EPO analog dose used but there were no differences in dose requirements of roxadustat in patients with inflammation. There was a greater increase in measured blood EPO levels 12 hours post treatment in patients who received EPO analog compared to a modest EPO increase in patients who received roxadustat. Pooled patients who received roxadustat had decreases in hepcidin as well as increases in reticulocyte Hb content. There were no significant differences between either groups in regards to change in TSAT, serum iron, and total cholesterol. Safety profiles were comparable between roxadustat and EPO analog. In the safety population 24.1% and 17% of patients experienced at least 1 SAE with roxadustat and EPO analog respectively. Of roxadustat patients 63.9% of patients experienced at least 1 AE and 12% experienced a cardiovascular composite safety endpoint compared to patients who received EPO analog, 61.1% and 17% respectively.

Roxadustat was effective at maintaining Hb levels in patients with ESRD compared to a wide range of EPO analog doses not receiving IV iron. Roxadustat was more effective at doses ≥ 1.5 mg/kg TIW compared to lower and less frequent doses of roxadustat. Roxadustat and EPO analog had comparable safety profiles.

Adverse events

Roxadustat was well tolerated in Phase II trials and most documented adverse events were typical for patients with CKD [4,12]. Common documented side effects were diarrhea, headache, back pain, fatigue, increases in blood pressure and liver enzymes [4,12,15]. Cardiovascular events were comparable in patients who received roxadustat compared to EPO analog, however larger trials must be conducted to confirm these results [15]. Since HIF-inhibitors effectively increase EPO and Hb, it can be hypothesized that there may be potential long-term cardiovascular and/or malignant side effects that may become apparent with longer duration trials and post-marketing analysis.

Ongoing clinical trials

There are currently 9 phase III clinical trials studying the safety, efficacy, and long-term effects of roxadustat in patients with various degrees of CKD; including dialysis, non-dialysis dependent, and on newly initiated dialysis [14]. The trials are comparing the use of roxadustat in comparison to either placebo or an active control such as darbepoetin alfa and epoetin alfa. The long-term effects of roxadustat are currently being studied in an open-label 5-year extension study to evaluate the safety and efficacy of roxadustat for long-term maintenance use. This study should yield some insight on the potential cardiovascular and malignant side effects that may occur (Table 1).

Trial Name	Comparator(s)	ClinicalTrials.gov Identifier	Estimated Primary Completion Date
Roxadustat in the treatment of anemia in chronic kidney disease (ckd) patients, not on dialysis, in comparison to darbepoetin alfa (Dolomites)	Darbepoetin Alfa	NCT02021318	Jul-17
Evaluation of efficacy and safety of roxadustat in the treatment of anemia in stable dialysis subjects	Epoetin Alfa	NCT02273726	Jun-17
Safety and efficacy study of roxadustat to treat anemia in patients with chronic kidney disease, on dialysis	Epoetin Alfa	NCT02174731	Feb-17
Roxadustat in the treatment of anemia in chronic kidney disease patients not requiring dialysis (ALPS)	Placebo	NCT01887600	Jan-18
Safety and efficacy study of roxadustat to treat anemia in patients with chronic kidney disease (CKD), not on dialysis	Placebo	NCT02174627	Mar-17
Roxadustat in the treatment of anemia in end stage renal disease (ESRD) patients on stable dialysis (Pyrenees)	Darbepoetin Alfa Epoetin Alfa	NCT02278341	Jun-17
Safety and efficacy study for treatment of anemia in ESRD newly initiated dialysis patients (Himalayas)	Epoetin Alfa	NCT02052310	Jun-17
A study of FG-4592 for the treatment of anemia in chronic kidney disease patients not receiving dialysis	Placebo	NCT01750190	Jun-17
Open label extension study for the long-term efficacy and safety of fg-4592 in dialysis and non-dialysis chronic kidney disease patients	N/A	NCT01630889	Oct-18

Table 1: Ongoing phase III Roxadustat clinical trials.

Conclusion and Current Status

The Phase II roxadustat trials have demonstrated the effectiveness of roxadustat in the treatment of anemia (defined as Hb increase ≥ 1 g/dl) and maintenance of Hb levels (defined as Hb not falling more than 0.5 g/dl) in patients with ND-CKD and dialysis dependent CKD [4,12,15]. Roxadustat has been documented to increase endogenous EPO and suppress hepcidin which may have positive effects on the utilization and mobilization of iron [4,12]. The efficacy of roxadustat is dose dependent. Doses higher than 1.5 mg/kg TIW may possibly be an alternative to EPO analog, however since the use of IV iron was prohibited during the study the ESA may not have been able to raise Hb by its full potential [15]. The safety profile of roxadustat is comparable to that of EPO analog; however data from larger studies will have to confirm these results. Common adverse events experienced with the roxadustat included diarrhea, headache, back pain and fatigue [12]. The data presented is limited because of the small sample sizes and short durations of the Phase II trials reviewed [2,4,15].

There is multiple small molecule HIF-inhibitors currently in clinical development for the treatment of anemia [16]. Molecules such as vadadustat, molidustat, and daprodustat share the same mechanism of action as roxadustat however they may differ in dose and frequency of administration [17-19]. The HIF pathway plays a vital role in homeostasis; animal and biochemical studies reveal many possibilities to either harness or disrupt this pathway for the treatment of various diseases [20]. The HIF pathway plays a protective role in

cardiovascular health, wound healing and conditions of tissue stress and injury while in contrast contributes to the pathogenesis of pulmonary arterial hypertension and cancer [21,22]. Preclinical data reveals that disrupting HIF-2α can cause gene disruption that may be involved in tumor growth, proliferation, and angiogenesis [23]. The multiple uses of either harnessing or disrupting the HIF pathway has many potential disease modifying therapies and in contrast may have many potential side effects. If the phase III trials for the approval of roxadustat reveals positive results in 2017, the manufacture expects to file an NDA in 2018 [13,14]. This will make roxadustat a first in class HIF-inhibitor for the treatment of anemia [8].

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