



Desidustat for Pure Red Cell Aplasia in CKD Patients on Biosimilar Erythropoietin Preparations: A Case Series

Abstract

Erythropoietin (EPO) supplementation for anemia due to CKD rarely causes pure red cell aplasia (PRCA) initiated by anti-EPO antibodies. Treatment involves discontinuation of erythropoiesis-stimulating agents (ESAs) and administration of immunosuppressive agents like cyclosporine or corticosteroids. The latter increases risk for infection. Desidustat is a hypoxia inducible factor-prolyl hydroxylase (HIF-PH) inhibitor. Its advantage in EPO-induced PRCA in patients with CKD remains unclear. We report a case series on desidustat administration for treating 14 CKD patients with EPO-induced PRCA. Most patients (64%) responded to Desidustat therapy, with a median hemoglobin of 12.5 g/d (range: 8.5-13.6 g/d) at last follow-up. Desidustat can be potentially repurposed in this context with better tolerability. Further randomized controlled trials are warranted.

Keywords: CKD, Desidustat, Recombinant human erythropoietin, Pure red cell aplasia

Introduction

Erythropoietin (EPO) supplementation for anemia due to CKD rarely causes pure red cell aplasia (PRCA) by stimulating the formation of anti-EPO antibodies neutralizing all erythropoiesis-stimulating agents (ESAs), including endogenous EPO.¹ Most cases are associated with generic epoetin- α and manifest 2 to 63 months after initiation. Treatment involves ESA discontinuation and introduction of immunosuppressive agents like cyclosporine or corticosteroids.^{1,2}

The understanding that hypoxia stimulates endogenous EPO production through the hypoxia-inducible transcription factors (HIF) pathway is currently being explored. Inhibition of this pathway stimulates endogenous EPO production, even without hypoxia.³

Desidustat is an orally administered HIF-prolyl hydroxylase inhibitor, which stabilizes HIF and leads to endogenous EPO production and erythropoiesis. Desidustat was approved in India in March 2022.⁴⁻⁶ Animal studies showed desidustat's mechanism of improving EPO resistance by promoting EPO synthesis and decreasing hepcidin levels by HIF stabilization.

Case Series

We report 14 patients treated with desidustat for CKD with EPO-induced PRCA between May 2022 and May 2024. All patients were receiving generic EPO, IV iron, and vitamin D3. The treating nephrologist made the decision on dialysis adequacy or transfusion.

Diagnostic criteria for PRCA were based on KDIGO clinical practice guidelines for management of anemia of CKD, 2012. Anti-EPO antibody assay was performed in only one patient due to a lack of readily available laboratory support. Parvovirus infection and functional iron deficiency were ruled out with anti-Parvovirus IgM serology, and transferrin saturation and serum ferritin, respectively.

Patients with fever and elevated CRP were excluded. Thymoma was ruled out in all patients by imaging.

The clinical profile of the patients has been listed in Table 1a-b. The median age was 61 (range: 51-69) years, 13 were males, and 13 were on hemodialysis. Fourteen patients were on thrice-weekly hemodialysis, and one had CKD stage III. Serum EPO level, measured in four patients, was low. Anti-EPO antibody assay was performed in only one patient due to a lack of readily available laboratory support.

The median duration from EPO initiation and PRCA diagnosis was 10 (range: 4-38) months. The median hemoglobin at diagnosis of PRCA was 5.7 (range: 3.2-8.6) g/dL. Median mean corpuscular volume (MCV) was 83.4 (range: 76-93) fL. Median reticulocyte percentage was 0.2% (range 0.07-0.29%). Median erythroid colony percentage in bone marrow aspirate was 2.44% (range: 1-6%).

The treatment details have been included in Table 2. Thirteen patients received multiple transfusions; the median number of transfusions was nine (range: 1-40). Four patients had received immunosuppressant therapy. The median duration of immunosuppressant therapy was 6 months (range: 1-11 months). In the remaining 10 patients, desidustat was the first-line therapy for PRCA.

Desidustat was initiated at a 100 mg dose thrice weekly in nine patients and 100 mg daily in the remaining five. After 1-3 months, the 100 mg thrice weekly was increased to 100 mg daily in two patients and to 150 mg thrice weekly in the another two.

Response was defined as attaining transfusion independence (Hb > 8 g/dL) for 6 months consecutively after initiation of therapy.

Two patients were lost to follow-up. Of the remaining 12, nine (64%) responded to desidustat, after a median duration of 4 (range: 3-8) months. Three remained transfusion-dependent. Median hemoglobin in responders at last follow-up was 12.5 g% (range: 8.5-13.6 g%). One patient

Table 1A: Clinical Profile

Case No.	Age/Sex	CKD	HD	EPO start	EPO stop	EPO duration (Months)	Transfusion dependency since
1	58/M	May 2021	May 2021	May 2021	June 2022	12	Jan 2022
2	61/M	July 2021	April 2022	July 2021	June 2022	12	n/a
3	52/M	Jan 2019	June 2019	June 2019	August 2022	38	August 2022
4	51/M	Jan 2021	Oct 2021	Oct 2021	June 2022	9	May 2022
5	63/F	Jan 2022	May 2022	May 2022	March 2023	10	Jan 2023
6	68/M	March 2020	Oct 2022	Oct 2022	Jan 2023	4	Dec 2022
7	63/M	June 2022	June 2022	June 2022	Feb 2023	8	Nov2022
8	58/M	Dec 2022	Dec 2022	Dec 2022	Aug 2023	8	July 2023
9	65/M	July 2022	July 2022	July 2022	Sep 2023	14	July 2022
10	60/M	Oct 2020	Oct 2020	Oct 2020	Dec 2023	38	Oct 2023
11	69/M	Feb 2021	Feb 2021	Feb 2021	Nov 2022	21	Feb 2022
12	59/M	March 2022	March 2022	March 2022	Dec 2022	10	Nov 2022
13	62/F	May 2023	No	May 2023	March 2024	10	March 2024
14	52/M	May 2022	May 2022	May 2022	Feb 2023	10	Jan 2023

CKD: Chronic kidney disease, HD: Hemodialysis, EPO: Erythropoietin

Table 1B: Clinical Profile

Case No.	Hb at PRCA (g/dL)	MCV (fL)	Retic %	ARC	BM Erythroid %	Parvo	TF %	Ferritin	EPO level
1	6	93	0.1	11200	2%	No	44	4320	No
2	8.6	86	0.1	7300	5%	No	38	856	No
3	5.6	91	0.2	1800	6%	No	48	2149	No
4	6.6	83	0.2	3600	4%	No	38	1320	No
5	5.7	76	0.07	2800	4%	No	61	3520	No
6	4.6	86	0.2	1400	2%	No	51	1022	No
7	7.6	83	0.2	7700	3%	No	38	624	No
8	6.9	86	0.2	10400	2%	No	39	450	No
9	6.4	82	0.2	2100	2%	No	48	2424	No
10	4.8	90	0.2	4600	2%	No	39	1817	0.01
11	5.3	82	0.2	1800	2%	No	48	7336	0.08
12	4.3	83	0.07	1200	3%	No	38	915	0.2
13	3.2	84	0.29	2400	2%	No	40	500	0.12
14	4.1	80	0.07	2800	2%	No	44	988	0.8

PRCA: Pure red cell aplasia, Hb: Hemoglobin in gram per desilitre, MCV: Mean corpuscular volume in femtolitre, Retic%: Reticulocyte percentage in peripheral blood, ARC: Absolute reticulocyte count in cells /microlitre, BM: Bone marrow, Parvo: Parvo virus serology IgM, TF%: Transferrin saturation, Ferritin in nanogram per millilitre. EPO levels in mU/mL,normal range 2.6 to 18.5,

Table 2: Treatment details

Patient No.	Age (years)	IST Rx	IST Rx start	Response	Desidustat start	Dose	Last Tx	Last f/p	Hb at last f/p(g/dL)	Transfusion independence	Months since last transfusion
1	58	Nil	N/A	N/A	June 22	100 mg 3/7	Aug 22	Feb 2024	12.4	Yes	18
2	61	Nil	N/A	N/A	June 22	100 mg 3/7	Jan 23	March 2024	12.9	Yes	13
3	52	Nil	N/A	N/A	Aug 2022	100 mg 3/7	Oct 22	Jan 2024	11.2	Yes	16
4	51	W	May 22	No, High Sugar	June 2022	100 mg 3/7	Aug 22	April 2024	12.8	Yes	20
5	63	Nil	N/A	N/A	March 2023	100 mg 3/7	N/A	N/A	N/A	Lost to F/P	Lost to F/P
6	68	Nil	N/A	N/A	Feb 2023	100 mg 3/7 increased to 100 mg OD	Feb 24	March 2024	6.4	No	N/A
7	63	Nil	N/A	N/A	March 2023	100 mg 3/7, increase to 150 mg 3/7	May 23	Feb 2024	13.6	Yes	9
8	58	Nil	N/A	N/A	Aug 2023	100 mg 3/7	Oct 2023	Feb 2024	12.7	Yes	6
9	65	W	Sep 23	No, High Sugar	Nov 2023	100 mg 3/7 increase to 100 mg OD	March 2023	March 2024	5.6	No, Desidustat Stop	N/A
10	60	Nil	N/A	N/A	Jan 2024	100 mg OD increase to 150 mg 3/7	March 2024	Lost to F/P	4.2	No	N/A
11	69	W-High sugars, CPM	Jan 2023	No	Sep 2023	100 mg OD	Dec 23	May 2024	10	Yes	6
12	59	W-then CSA	Jan 2023	No	Oct 2023	100 mg OD	Dec 23	May 2024	10	Yes	6
13	62	Nil	N/A	No	May 24	100 mg OD	April 24	April 2024	N/A	No, Desidustat stop	N/A
14	52	N/A	N/A	N/A	Jan 23	100 mg OD	March 23	April 2024	12	Yes	13

IST: Immunosuppression treatment, Rx: Treatment, F/P: Follow up, N/A: Not applicable, W: Wysolone, CSA: Cyclosporine, CPM: Cyclophosphamide

developed clinical depression while on therapy; however, it is unclear whether this was related to desidustat. No other major adverse effects were observed. All 12 patients were last followed up between January and May 2024.

Discussion

There is limited published literature on successful management strategies for EPO-induced PRCA in CKD beyond immunosuppressants. Many of these are case reports, mostly on roxadustat, another HIF-PH inhibitor, and less frequently desidustat.⁵¹⁻⁵⁴ These case reports also show a response with a median of 3 months.

Ours is by far the largest case series demonstrating the effectiveness of desidustat for EPO-induced PRCA. The limitations of our study include its retrospective nature, the lack of anti-EPO antibody data, the absence of EPO level testing in all patients, and the failure to exclude other EPO resistance factors, such as secondary hyperparathyroidism and the effects of Angiotensin Converting Enzyme (ACE) inhibitors (ACEI) or angiotensin receptor blockers (ARB). Our results indicate that desidustat can be potentially repurposed to reverse EPO refractoriness with better tolerability. Further randomized controlled trials are warranted.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest: There are no conflicts of interest.

Arathy Ambattu¹, S.N Rahmathullah² , Mullapillil Raghunath³, Raghuv eer Santhakumara Prabhu², Sreeraj Vasudevan¹

¹Department of Clinical Hematology, Amala Institute of Medical Sciences, Thrissur, Kerala, ²Department of Clinical Hematology, IQRAA International Hospital, Calicut, ³Department of Nephrology, Amala Institute of Medical Science, Thrissur, Kerala, India

Corresponding author: Sreeraj Vasudevan, Department of Clinical Hematology, Amala Institute of Medical Sciences, Thrissur, Kerala, India. E-mail: sreerajfleming@gmail.com

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Utility of Genetic Analysis in Rare Tubulopathies Presenting with Bilateral Nephrocalcinosis in Adults - Avoiding Harm with Precision Care: A Case Series

Abstract

Two rare cases of nephrocalcinosis (NC) due to a genetic mutation remained undiagnosed till adulthood. A 19-year-old male presented with a fever and was diagnosed with bilateral NC and renal dysfunction. He underwent a renal biopsy, which suggested nonspecific chronic tubulointerstitial nephritis. His blood chemistry review showed persistent severe hypouricemia, pointing to possible xanthinuria. The second case was a 25-year-old male, re-evaluated for bilateral NC with persistently high serum parathyroid hormone despite successful parathyroidectomy. His metabolic workup suggested possible Bartter's syndrome (BS) with characteristic biochemical derangement. Whole exome sequencing detected a pathogenic homozygous mutation in the *MOCOS* gene in the first case and a *KCNJ1* mutation in the second case. Soft clues like hypouricemia in the first and hypokalemia with metabolic alkalosis in the second case need to be recognized in NC for the appropriate work-up. Tailored management has stabilized the renal outcome in both patients.

Keywords: *Bartter, KCNJ1, MOCOS, Nephrocalcinosis, Xanthinuria*

Introduction

Nephrocalcinosis (NC) is a condition associated with a wide variety of genetic and metabolic causes, which poses a significant diagnostic challenge.¹ We report two such cases of NC where genetic testing helped resolve the diagnosis odyssey and stop unnecessary interventions.

Case Series

Case 1

A 19-year-old male, born out of consanguineous marriage, had bilateral renal NC diagnosed by imaging [Figure 1]. He had a history of painless graveluria. Investigations showed raised serum creatinine with hypocalcemia, hypokalemia, hypomagnesemia, and hypouricemia [Table 1]. Renal biopsy showed a pattern of chronic tubulo interstitial disease [Figure 2a-b]. Genetic evaluation identified a homozygous pathogenic mutation of the *MOCOS* gene, confirming undiagnosed xanthinuria type 2. He suffered once metabolic seizure from hypocalcemia. He was receiving low-dose sodium bicarbonate, magnesium supplementation, calcitriol, levetiracetam, high fluid intake, and a purine-restricted low-protein diet, remained well with one episode of passing two small stones during 1 year follow up.

Case 2

A 25-year-old was diagnosed with bilateral medullary NC [Figure 3], osteoporosis, and raised parathyroid hormone

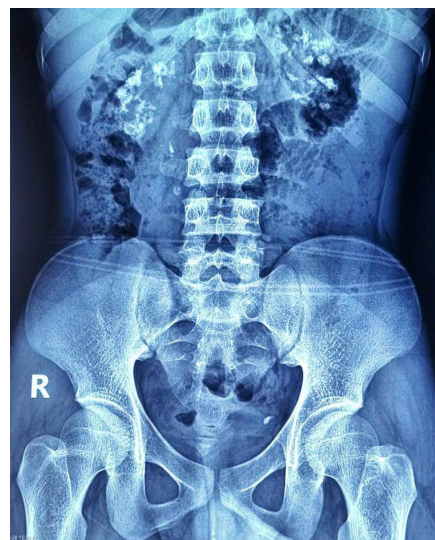


Figure 1: Radiograph of the kidney, ureter, bladder (KUB) region demonstrates bilateral nephrocalcinosis along with two radiographic densities adjacent to L2 and L3 vertebrae on the right and a radiopaque density on the left side of the pelvis, suggesting ureteric calculi.

(PTH) during evaluation for backache. He had undergone parathyroidectomy 2 years ago for a parathyroid adenoma. However, his postoperative PTH did not normalize. He gave a history of excessive thirst with polyuria from childhood.