

**Case report****Eosinophilia After Exposure to Darbepoetin alfa: A Case Report**Namrata Singh<sup>1,2</sup><sup>1</sup>Department of Medicine, Punjab Institute of Medical Sciences, Punjab, India<sup>2</sup>George Washington University, School of Medicine and Health Sciences, Washington, DC**Abstract**

**Introduction:** Darbepoetin alfa differs from recombinant human erythropoietin (rEPO) by two additional oligosaccharide chains. These additional oligosaccharide chains are proposed to contribute to darbepoetin's adverse allergic profile. Allergic rashes and erythema can occur in 5% of patients taking darbepoetin. Though allergic reactions are known adverse events associated with this drug, eosinophilia that often accompanies allergic reactions has not been reported as an adverse event of darbepoetin. Herein, we report the first case of recurrent darbepoetin alfa related eosinophilia.

**Case Presentation:** 75-year-old gentleman with several comorbidities underwent trans-carotid artery revascularization (TCAR) procedure. During the prolonged hospitalization, he developed anemia, likely as a result of EPO deficiency in the setting of AKI on CKD. For anemia related to CKD, patient was started on darbepoetin alfa. Soon after, patient started developing asymptomatic eosinophilia. His hemoglobin gradually showed improvement, however, this was accompanied by concomitant eosinophilia, severity of which increased with each subsequent dose. During the period of follow up, patient continued to mount asymptomatic eosinophilia after each darbepoetin dose, without any concomitant hypersensitivity reactions.

**Conclusions:** We report the first case of darbepoetin related eosinophilia and it appears to be a clinically relevant adverse event. Lack of knowledge about this adverse event can result in interruption/dose reduction of unrelated but necessary medications. Additionally, it may lead to increased healthcare costs due to initiation of extended work up in pursuit to determine underlying etiology of eosinophilia, leading to a superfluous diagnostic odyssey for this rather mild and benign presentation.

**Keywords:** Darbepoetin alfa, Eosinophilia, Adverse events, Case report

**Introduction**

Darbepoetin alfa stimulates erythropoiesis in manner similar to recombinant human erythropoietin (rEPO). It differs from rEPO as there are two additional oligosaccharide chains in darbepoetin alfa.<sup>1</sup> These two chains increase the number of sialic acid residues within the molecule, thereby enhancing its half-life three-fold compared to rEPO.<sup>1</sup> U.S. Food and Drug Administration label for Darbepoetin alfa indicates that allergic rash and erythema can occur in 5% of patients taking darbepoetin alfa,<sup>2</sup> which may be due to the immunogenic nature of darbepoetin alfa owing to different amino acid and oligosaccharide chain sequences (compared to endogenous EPO and rEPO).<sup>3</sup> A few reports have described these allergic reactions as urticaria and wheals at the sites of subcutaneous injections of rEPO.<sup>4</sup> Generalized urticaria and pruritis after the 3rd dose of darbepoetin alfa was described in another report.<sup>5</sup> Although allergic reactions are known adverse events associated with darbepoetin alfa,<sup>6</sup> eosinophilia that often accompanies various allergic reactions has not been reported as an adverse event of darbepoetin alfa, to the best of our knowledge. We report the first case of recurrent darbepoetin alfa related eosinophilia without any concomitant hypersensitivity reactions persisting for more than one month and temporally associated with exposure to darbepoetin.

**Case Presentation**

A 75-year-old gentleman with several comorbidities, hypertension, type 2 diabetes mellitus, hyperlipidemia, chronic kidney disease (CKD) and atrial fibrillation was admitted to the hospital for an elective minimally invasive trans-carotid artery revascularization (TCAR) procedure. Post-procedure, he was transferred to the intensive care unit after clinical course was complicated by acute-respiratory failure requiring intubation, acute kidney injury (AKI) on CKD requiring renal replacement therapy (RRT) and acute blood loss anemia secondary to psoas hematomas. During the prolonged hospitalization, he developed anemia, etiology of which was multifactorial in the setting

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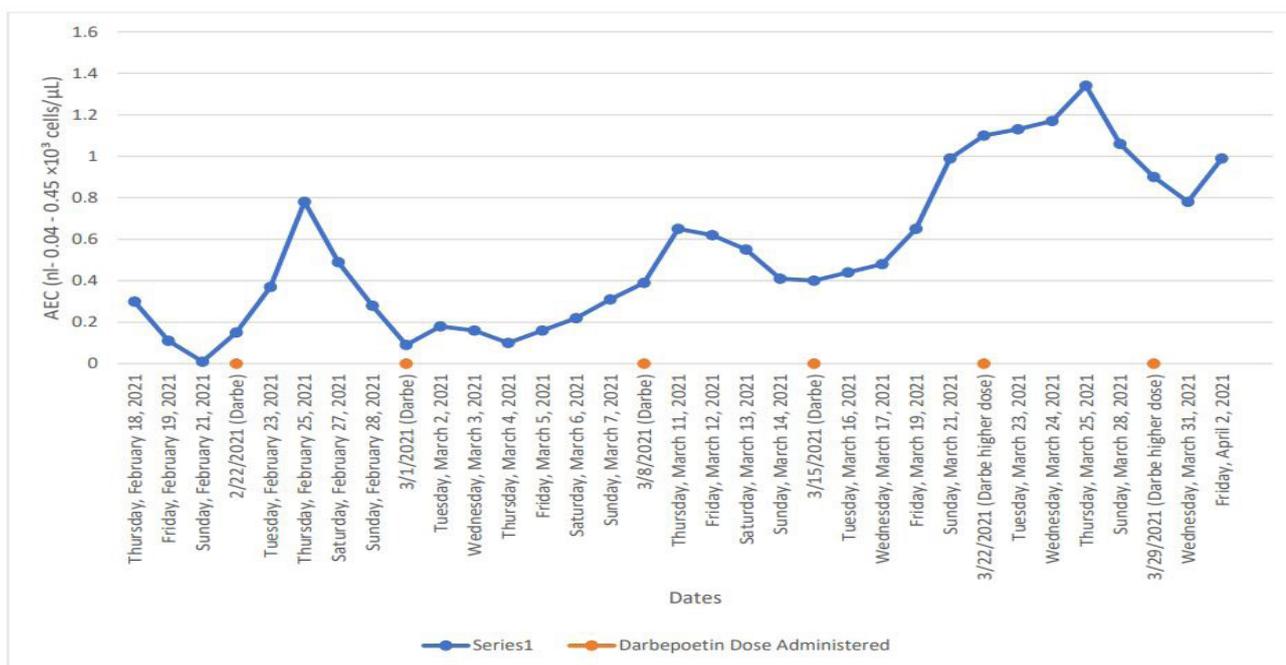
Dates	AEC	Darbepoetin Dose
Wednesday, February 17, 2021	0.14	
Thursday, February 18, 2021	0.3	
Friday, February 19, 2021	0.11	
Sunday, February 21, 2021	0.01	
2/22/2021 (Darbe)	0.15	40 mcg
Tuesday, February 23, 2021	0.37	
Thursday, February 25, 2021	0.78	
Saturday, February 27, 2021	0.49	
Sunday, February 28, 2021	0.28	
3/1/2021 (Darbe)	0.09	40 mcg
Tuesday, March 2, 2021	0.18	
Wednesday, March 3, 2021	0.16	
Thursday, March 4, 2021	0.1	
Friday, March 5, 2021	0.16	
Saturday, March 6, 2021	0.22	
Sunday, March 7, 2021	0.31	
3/8/2021 (Darbe)	0.39	40 mcg
Thursday, March 11, 2021	0.65	
Friday, March 12, 2021	0.62	
Saturday, March 13, 2021	0.55	
Sunday, March 14, 2021	0.41	
3/15/2021 (Darbe)	0.4	40 mcg
Tuesday, March 16, 2021	0.44	
Wednesday, March 17, 2021	0.48	
Friday, March 19, 2021	0.65	
Sunday, March 21, 2021	0.99	
3/22/2021 (Darbe higher dose)	1.1	60 mcg
Tuesday, March 23, 2021	1.13	
Wednesday, March 24, 2021	1.17	
Thursday, March 25, 2021	1.34	
Sunday, March 28, 2021	1.06	
3/29/2021 (Darbe higher dose)	0.9	60 mcg
Wednesday, March 31, 2021	0.78	
Friday, April 2, 2021	0.99	

**Figure 1:** Fluctuations in Absolute Eosinophil Counts (AEC) in chronological order in relation to darbepoetin alfa at two different doses. Darker shades represent rising AEC subsequent to each darbepoetin alfa (Darbe) exposure.

of blood loss, bone marrow suppression secondary to inflammation from critical illness, medications and EPO deficiency in the setting of AKI on CKD. Iron studies were consistent with anemia of chronic inflammation. B12, folate stores were replete. Therefore, for anemia related to CKD, patient was started on darbepoetin alfa at a dose of 0.45 mcg/kg subcutaneously once every week. At the time of darbepoetin alfa initiation, patient had been in the hospital for over a month and had no prior evidence or history of peripheral eosinophilia. Soon after darbepoetin alfa initiation, we noted after every injection, patient mounted significant asymptomatic eosinophilia (absolute eosinophil counts delineated in Figure 1). With subsequent weekly doses, his hemoglobin showed improvement, however, this was accompanied by concomitant eosinophilia. This appeared to be cumulative and dose dependent effect as with subsequent and higher doses, eosinophilia increased as depicted by rising eosinophilic peaks in Figure 2. He did not develop any skin reactions, pruritis, or wheals at the site of injections but to date, continues to mount asymptomatic eosinophilia post-exposure to each dose. Subcutaneous Darbepoetin alfa's half-life is about two days in CKD patients on RRT and after 2-3 half-life eliminations, the eosinophilia tends to downtrend in our patient, which is followed by steep up rise upon re-exposure (Figure 2). At the time of last follow up, he was gradually recovering from all his illnesses, had been transferred out of the intensive care unit, and was undergoing physical therapy to regain strength. He was able to get off darbepoetin, with associated downtrend in eosinophil count.

**Conclusions**

We report the first case of darbepoetin related eosinophilia and it appears to be a clinically relevant adverse event. Lack of knowledge about this adverse event can result in interruption/dose reduction of unrelated but necessary medications. Additionally, it may lead to increased healthcare costs due to initiation of extended work up in pursuit to determine underlying etiology of eosinophilia, leading to a superfluous diagnostic odyssey for this rather mild and benign pre-



**Figure 2:** Graphical representation of changes in Absolute Eosinophil Counts (AEC) in relation to darbepoetin alfa at initial and subsequent exposures

sensation. The etiology of the eosinophilia in this patient was not clear. Darbepoetin alfa has a different amino acid sequence from the endogenous erythropoietin, which can be immunogenic.<sup>3,6</sup> A plausible explanation can be that there may be very mild injection site reaction leading to mast cell degranulation and T helper type 2 cells activation causing eosinophilic accumulation and activation.<sup>7</sup> Regardless of the etiology, the temporal relationship between administration of darbepoetin alfa and immediate rise in eosinophils makes darbepoetin alfa the likely offender. Additionally, the widely used The Adverse Drug Reaction Probability Scale (or Naranjo Score)<sup>8</sup> was 5, indicating a probable adverse effect.

#### Declarations

- i. Funding. Not applicable
- ii. Conflicts of interest/Competing interests. Author discloses no conflicts of interest or competing interests.
- iii. Availability of data and material. Available upon request.
- iv. Code availability. Not applicable.
- v. Authors' contributions. Conceptualization, data curation, formal analysis, visualization: NS. Writing-review & editing: NS.

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