Switching to an alternative recombinant erythropoietin agent in patients with myelodysplastic syndromes: a second *honeymoon*?

Duration of response to recombinant (r)EPO in myelodysplastic syndromes (MDS) is limited and further options are scanty, such that most subjects finally become transfusion dependent. Several types of rEPO are available, including biosimilars, and their choice, dose and time of administration are still debated.[1–5] We evaluated the efficacy of an alternative rEPO product in patients with MDS refractory to, or who lose response after, the first rEPO course. Hematologic parameters have been analysed before each rEPO course and responses have been evaluated according to the International Working Group 2006 (Hb increase by 1·5 g/dl and/or transfusions reduction by ≥4/8 weeks compared with 8 weeks pretreatment).[6,7] The study was conducted according to Helsinki Declaration. Twenty-five patients, mostly MDS with ring sideroblasts, followed for a median of 51 months (12–225), have been included (Table I). Figure 1 shows rEPO agents used, treatment durations and relative responses. Median time from diagnosis to first rEPO was 3·4 months (0–87), median endogenous (e)EPO was 59 U/l (3–257) and 12 patients were transfusion dependent (median 4 units/8 weeks, range 2–7). The first rEPO types and doses are detailed in Table SI. Sixty percent of patients responded after 2·4 months (0·8–18), with a median Hb increase of 1·7 g/dl (1·5–3·6) and treatment duration of 20 months (2·4–81), irrespective of the rEPO type. Patients were switched to an alternative agent due to loss of response ($N = 17$) or inefficacy ($N = 8$), and all had been increased to the maximal dose for ≥8 weeks before switching. Most patients started the second course after about 1 month of discontinuation of the first product (at least 4 weeks washout before the switch). At switching, 14 patients were transfusion dependent, and pre-dose eEPO was 142 U/l (43–390), higher than before the first course. Most patients started the alternative rEPO at high dose (80 000 U/week, $N = 20$), given the supposed need of higher levels to elicit a response (Table SI). In detail, most subjects were shifted from epoetin-alpha biosimilar to the originator ($N = 9$) or vice-versa ($N = 2$), and the others from alpha to zeta ($N = 4$) or vice-versa ($N = 4$), from beta to alpha ($N = 3$) or vice-versa ($N = 1$) and from darbepoetin to alpha ($N = 2$). No patients were shifted to darbepoetin (not currently labelled for MDS in Italy). Forty-four percent of patients responded after a median of 1·9 months (0·7–5·2) from the switch, including three cases refractory to the first rEPO. Median Hb increase in responders was of 1·9 g/dl (1·6–2·7) and 3 patients became transfusion independent. Interestingly, switch to epoetin-alpha was associated with the best response rate: 10/11 responders had been switched to epoetin-alpha originator ($P = 0·03$ versus other switch modalities), and 8/11 had been switched from non-alpha to alpha EPO (including 1 patient switched to epoetin-alpha biosimilar, $P = 0·07$). In addition, response was mainly observed in transfusion independent subjects (only 27% of responders were transfusion dependent before the switch versus 78% non-responders $P = 0·01$), and in those who responded to the first rEPO course (82 versus 43%, $P = 0·05$). At the last follow up, six patients were still on rEPO, whilst eight had stopped it due to loss of response ($N = 6$) or intolerance ($N = 2$, grade 1 bruising at injection site due to thrombocytopenia) after a median of 15·8 months (11·6– 17·5). Notably, the drug had been discontinued in 12 weeks if there was no response at all. Five patients (four responder and one non-responder) died (one leukemic evolution).

In this experience, switching to an alternative rEPO after loss of response/refractoriness to the first agent was feasible and effective in nearly half of cases. Hb improvement after the second ESA course was comparable to that observed after the first agent, and associated with previous response to rEPO, transfusion independence and switch to epoetin-alpha. Other experiences compared the various rEPO agents and reported the feasibility of a switch,[8] but not in the "refractory/loss of response" setting. The question arises: Why should a refractory patient respond to a different rEPO? It may be speculated that response to chronic hypoxia is a dynamic event, relying on the efficiency of kidney–bone marrow axis that may be influenced by several factors such as kidney function, bone marrow cellularity, cytogenetic/molecular landscape, immune activation and chronic inflammation. These factors change over time, and variably contribute to bone marrow failure and to the physiologic response to anaemia. As a matter of fact, response to rEPO is maximal in patients with suboptimal endogenous levels and in those with higher residual marrow stemness.[9] Although a direct correlation among eEPO and response to switch was not possible given the limited number of patients, in this study all subjects displayed eEPO <500 U/l before the switch, higher than before the first rEPO course, but still permissive of response to a further product. This may suggest an

Table I. Clinical and haematologic features at diagnosis and before first and second recombinant erythropoietin (rEPO) treatment. Data are shown for all patients and according to response to rEPO switch. Molecular alterations were tested by next generation sequencing (NGS). *No patients experienced adverse events, except for 2 patients experiencing bruising at site injection due to thrombocytopenia. No patient received granulocyte colonies stimulating factor. Low and high transfusion were defined according the 2018 revision of the International Working Group Criteria.[6]

	All patients (N = 25)	Responders to second rEPO (N = 11)	Non responders to second rEPO (N = 14)
Male/Female	14/11	5/6	8/6
Age, years	73·6 (59–86)	75·6 (62–85)	72·4 (59–86)
MDS-MLD	7 (28)	4 (36)	3 (22)
MDS-SLD	2 (8)	0 (0)	2 (14)
MDS-RS	13 (52)	4 (36)	9 (64)
MDS del5q	2 (8)	2 (18)	0
MDS-EB1	1 (4)	1 (10)	0
Mutational status			
SF3B1	10 (40)	4 (36)	6 (43)
DNMT3A	1 (4)	0	1 (7)
TET2	1 (4)	1 (9)	0
IDH2	1 (4)	1 (9)	0
Data at first rEPO			
Hb g/dl	9·4 (6·6–11·8)	9·6 (6·6–10·3)	8·6 (7·1–11·8)
EPO U/l	58·9 (3–257)	59 (3–257)	54·9 (3·3–188)
Ferritin mg/dl	420 (43–733)	402 (43–733)	420 (211–593)
Transfusions	12 (18)	3 (27)	9 (64)
Low burden	4 (16)	2 (18)	2 (14)
High burden	8 (32)	1 (9)	7 (50)
Response to first rEPO	15 (60)	9 (82)	6 (43)**
Data at rEPO switch			
Median time to 2nd rEPO, months	0 (0–35)	0 (0–19)	0 (0–35)
Hb g/dl	9·1 (7·1–9·9)*	9·6 (9–9·9)*	8·3 (7·1–9·3)*
EPO U/l	115 (29–390)	73·4 (42·6–220)	21 (3·1–49·2)
Ferritin mg/dl	602 (103–911)	602 (103-911)	599 (291–883)
Transfusions	14 (56)	3 (27)	11 (78)^
Low burden	4 (16)	3 (27)	1 (7)
High burden	10 (40)	0	10 (71)

*Data may be influenced by recent transfusion.
**P = 0·05.
^P = 0·01.

impaired response to chronic hypoxia, although possibly confounded by recent transfusions and older age. Moreover, non-response to rEPO may be due to a block in the late-stage erythropoiesis, as also indirectly demonstrated by the efficacy of luspatercept, which inhibits TGF-beta and ameliorates anemia in ~40% of rEPO refractory cases.[10] It may be hypothesized that a further/novel stimulus on early-stage erythropoiesis by an alternative rEPO agent may overcome this block. Interestingly, 13 patients in this study belonged to MDS with ring sideroblasts category and responded to rEPO switch in 31% of cases. These data may suggest an attempt with a second rEPO agent in these patients even before luspatercept, and/or where the drug is not available, and/or prompt the exploration of future associations.

One limitation of our report is the high heterogeneity in observation lengths (before each rEPO). However, we did not observe differences in response to switch according to follow-up length.

Given the foreseen limited duration, the response to rEPO has been previously denominated "*honeymoon*", a term consistent with the wellness and quality of life experienced by responding patients. In this experience, we showed that a second *honeymoon* is possible, particularly in patients switching to the originator epoetin alpha. Although with a limited number of patients, this study might suggest initiation of treatment with an alternative agent and then a switch to epoetin alpha in case of relapse/refractoriness to the first product.

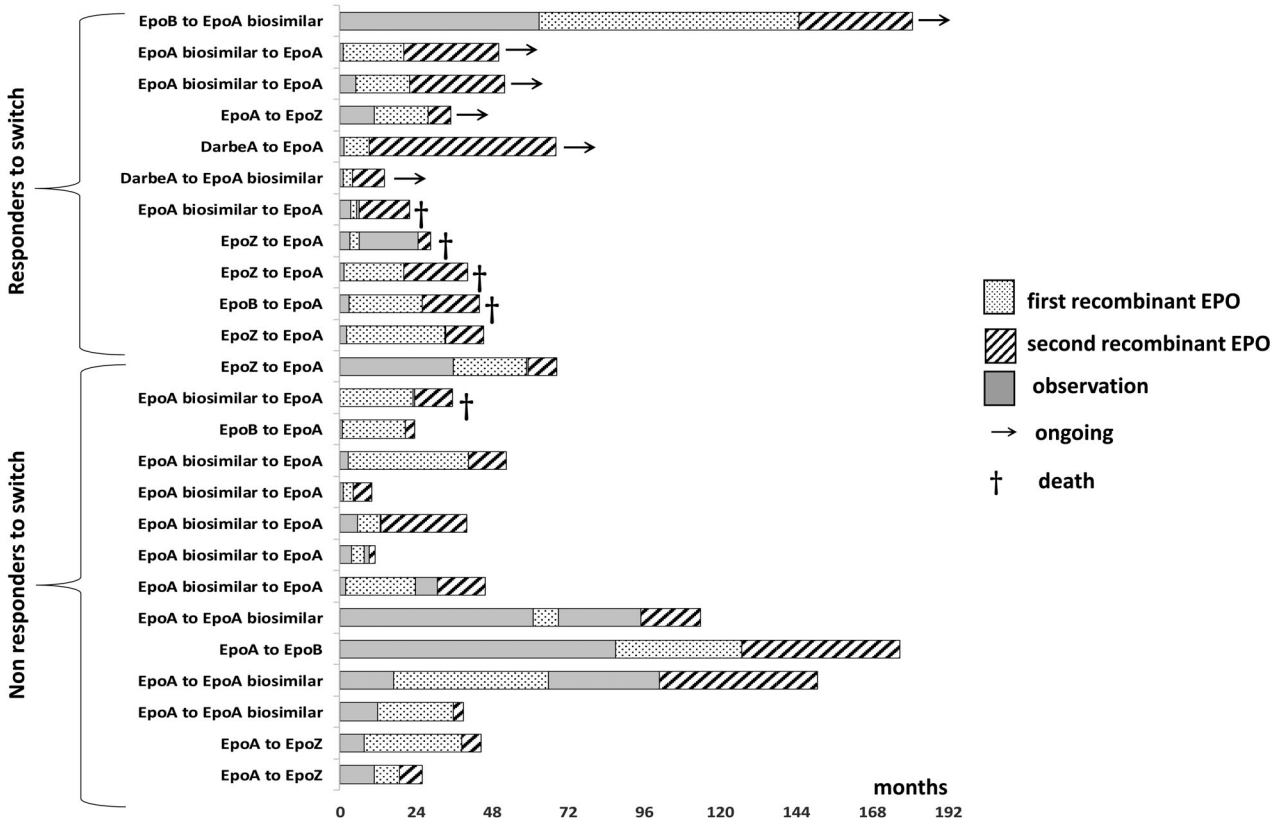

Fig 1. Timeline of recombinant erythropoietin (rEPO) switch in patients with low-risk myelodysplastic syndrome, divided according to response to rEPO switch. EpoB, rEPO beta; EpoA biosimilar, rEPO alpha biosimilar; EpoA, rEPO alpha originator; EpoZ, rEPO zeta; DarbeA, darbepoetin alpha.

Conflict of interest

All authors declare that they have no conflict of interest to disclose.

Author contributions

All Authors followed patients, collected data wrote the manuscript and revised it for important intellectual content.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Type and schedules of first and second recombinant erythropoietin agents.

References

1. Malcovati L, Hellström-Lindberg E, Bowen D, Adès L, Cermak J, del Cañizo C, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood*. 2013;**122**:2943–64.
2. Platzbecker U, Symeonidis A, Oliva EN, Goede JS, Delforge M, Mayer J, et al. A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. *Leukemia*. 2017;**31**:1944–50.
3. Fenaux P, Santini V, Spiriti MAA, Giagounidis A, Schlag R, Radinoff A et al. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-α in anemic patients with low-risk MDS. *Leukemia*. **32**(12):2648–58.
4. Gaipov A, Issanov A, Mursalova Z, Tulegenova N, Kakim Z, Baizakov M, et al. Dose equivalency and efficacy of biosimilar erythropoietin stimulating agents: data from real clinical practice. *Pharmacol Res Perspect*. 2020;**8**:e00594.

5. Castelli R, Deliliers GL, Colombo R, Moreo G, Gallipoli P, Pantaleo G. Biosimilar epoetin in elderly patients with low-risk myelodysplastic syndromes improves anemia, quality of life, and brain function. *Ann Hematol*. 2014;**93**:1523–9.
6. Platzbecker U, Fenaux P, Adès L, Giagounidis A, Santini V, van de Loosdrecht AA, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood*. 2019;**133**:1020–30.
7. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;**108**:419–25.
8. Patton JF, Sullivan T, Mun Y, Reeves T, Rossi G, Wallace JF. A retrospective cohort study to assess the impact of therapeutic substitution of darbepoetin alfa for epoetin alfa in anemic patients with myelodysplastic syndrome. *J Support Oncol*. 2005;**3**(6):419–26.
9. Hellstrom-Lindberg E, Negrin R, Stein R, Krantz S, Lindberg G, Vardiman J, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. *Br J Haematol*. 1997;**99**:344–51.
10. Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;**382**:140–51.

Long-term biological effects in sickle cell disease: insights from a post-crizanlizumab study

Sickle cell disease (SCD) is a multisystem disorder caused by inheritance of a mutated variant of adult haemoglobin (sickle haemoglobin allele [*HbS*]).[1] SCD is characterised by haemolytic anaemia, endothelial damage, and acutely painful vaso-occlusive crises (VOCs) that cause chronic and potentially life-threatening complications.[2] Crizanlizumab is approved to reduce VOC frequency in patients aged ≥16 years with SCD. In the phase II SUSTAIN study (ClinicalTrials.gov Identifier: NCT01895361), crizanlizumab reduced the median rate of VOCs by 45% (1·63 vs. 2·98) over placebo.[3] SUCCESSOR was a retrospective, non-interventional cohort study of a subset of 48 American patients that evaluated real-world outcomes and treatment patterns after SUSTAIN trial completion. The SUCCESSOR population comprised a subset of SUSTAIN patients who received crizanlizumab 2·5 mg/kg (n = 18), crizanlizumab 5·0 mg/kg (n = 15), or placebo (n = 15) (Figure S1). During SUCCESSOR, patients received neither placebo nor crizanlizumab. Medical records from 52 weeks after SUSTAIN completion were evaluated, and post-SUSTAIN VOCs in patients who received crizanlizumab during SUSTAIN were the primary outcome. Demographics and baseline characteristics are reported in Table SI and Table SII. During SUCCESSOR, the median time to first VOC was 6·1 months in patients who received crizanlizumab 5·0 mg/kg during SUSTAIN, 2·7 months in patients who received crizanlizumab 2·5 mg/kg during SUSTAIN, and 2·6 months in patients who received placebo during SUSTAIN (Fig 1). The time-to-first VOC in the crizanlizumab 5·0 mg/kg group may be reflective of physiological changes induced by P-selectin inhibition. Use of anti-P-selectin drugs has been shown to increase microvascular flow and reduce white blood cell rolling,[4] which is known to contribute to a cycle of endothelial injury, inflammation and adhesion.[5–8] We hypothesise that the interruption of this cycle through P-selectin inhibition for 1 year during SUSTAIN may have led to endothelial remodelling and reduced inflammation, which may have delayed the time to first VOC during SUCCESSOR; however, additional clinical research is needed to confirm this hypothesis. There is evidence in preclinical animal models demonstrating the effects of inhibiting P-selectin-mediated leucocyte recruitment on decreased inflammation and endothelium remodelling.[9]

The majority of patients experienced at least one VOC during SUCCESSOR. The respective mean [standard deviation (SD)] annual rates of VOCs during SUSTAIN in patients treated with crizanlizumab 5·0 mg/kg and off-treatment in SUCCESSOR were 2·3 [2·5] and 2·7 [3·3] (Fig 2). The mean (SD) annual rates of VOCs during SUSTAIN in patients treated with crizanlizumab 2·5 mg/kg were 3·8 (2·2) and in SUCCESSOR were 3·9 (4·6) (Fig 2). In the subset of patients treated with placebo during SUSTAIN, the mean (SD) annual rate of VOCs was 4·7 (4·3) and 5·4 (5·4) during SUSTAIN and off treatment during SUCCESSOR, respectively (Fig 2).

While patients did not continue crizanlizumab in SUCCESSOR, they were managed as per current standard of care. SCD treatment used during SUCCESSOR is shown in Table SIII. Almost all patients (n = 47/48; 98%) used opioids. Among patients who used opioids, the mean (SD) annual rate of opioid use was 316 (105) days, with 92% of patients receiving opioids for ≥61 days. During SUCCESSOR, 33 patients (69%) used hydroxyurea, with a median annualised duration of usage of 364 days. A total of 10 patients (21%) received blood transfusions for SCD during SUCCESSOR.

In SUCCESSOR, patients treated with crizanlizumab 5·0 mg/kg during SUSTAIN visited the emergency department (ED) a mean (SD) of 3·4 (3·6) times. The SUCCESSOR patients who received crizanlizumab 2·5 mg/kg during SUSTAIN visited the ED a mean (SD) of 2·9 (2·5) times. Among patients in the subset treated with placebo during SUSTAIN, the mean (SD) number of ED visits was 4·8 (3·8).