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Daratumumab may be the most effective treatment for post-engraftment pure red cell aplasia due to persistent anti-donor isohemagglutinins after major ABO-mismatched allogeneic transplantation

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TO THE EDITOR:

Recipients of allogeneic hematopoietic stem cell transplantation (AlloHCT) face numerous life-threatening complications, and even more perhaps not so severe but also incapacitating complications. Among the latter, pure red blood cell aplasia (PRCA) due to persistent anti-donor hemagglutinins in the setting of major ABO-mismatched transplantation is one of the most difficult to manage by most clinicians. We thus welcomed the two splendid manuscripts published concomitantly in the April issues of *Bone Marrow Transplantation* by Marco-Ayala et al. [1] and *British Journal of Haematology* by Longval et al. [2]. The manuscript by Marco-Ayala et al. is the most extensive review on all published articles on

PRCA, covering its incidence, risk factors, heterogeneous natural history, and the numerous treatments tested. The study by Longval et al. on the other hand is a multicenter study from Paris and the largest and most detailed cohort study including 631 recipients of major ABO-incompatible alloHCT; this study, of course, was not included in the review by Marco-Ayala et al. Both articles suggest that, although major ABO-incompatible alloHCT does not appear to have a relevant impact on overall survival, none of the treatments tested so far appeared to modify its natural history, and both articles and an accompanying editorial [3] suggested that daratumumab appears to be the most promising treatment, although based on only 4 published case reports [4–7]. We herein report two further cases of successful treatment of PRCA with daratumumab and suggest that it appears to be the best available treatment for this complication, as suggested by the characteristics of the ten successfully treated patients reported to date.

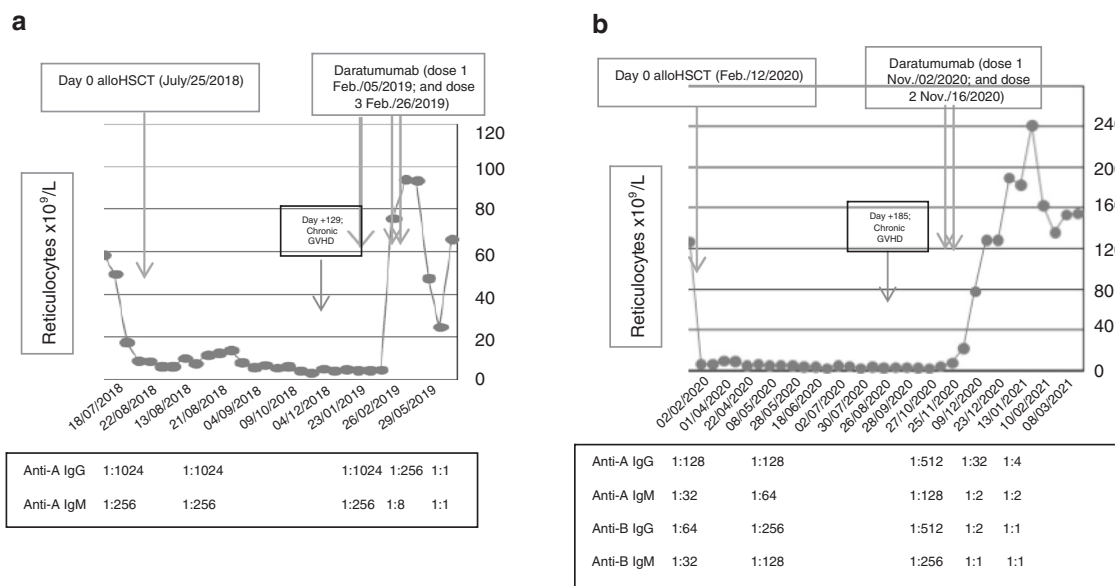


Fig. 1 Graphic summary of our two patients treated with daratumumab for PRCA. **a, b.** Reticulocyte count shown graphically post-transplant in our two case reports with times of day 0 and treatment with daratumumab shown with arrows. The anti-donor isohemagglutinin titers in each patient post-transplant are shown below each figure (only a few representative titers are shown for the sake of simplicity). **a** Corresponds to case #1 and **b** to case #2.

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Table 1. Details of the eight case reports reported to date (August 2021) and the two cases herein summarized on the use daratumumab for PRCA after major ABO-mismatched allogeneic HSCT and some characteristics supporting the recommendations made by the authors for its potentially most optimal use.

Reference (year)	At least > 2 months post-transplantation	Complete donor engraftment (>95%) in myeloid (and T cells > 50%)	PRCA as major component of graft dysfunction	Post-engraftment presence of high titers of anti-donor IsoHG (IgG/IgM \geq 1/64)	Active GVHD	Dose of daratumumab after which reticulocytosis occurred ^a	Total number of doses given	Disappearance of IsoHG documented (timing)	Duration of response w/ or further treatment	Hypogammaglobulinemia reported as side effects (and details)
Chapuy (2018) [4]	Yes (day +390) ^b	Yes (from day +25)	Yes	Yes (Anti-A titer 1:128)	NR	2nd dose	6 (weekly)	Undetectable at 3 months	>1 year	NR
Bathini (2019) [5]	Yes (day +411) ^b	Yes (from day +30)	Yes	Yes (Anti-A IgG titer 1:256)	NR	1st dose	4 (weekly)	Anti-A IgG/IgM <1:8 at 4 months	20 months ^d	NR
Queraalt-Salas (2020) [6]	Yes (+32 months) ^b	Yes (from day +30)	Yes	Yes (Anti-A titer 1:128; and anti-B titer 1:64)	NR	6th dose	6 (weekly)	NR	1 year	NR
Rautenberg (2020) [7]	Yes (day +206) ^b	Yes (from day +28)	Yes	Yes (Anti-A titer 1:1024)	NR	1st dose	2 (10 day interval)	Undetectable 2 weeks after 2nd dose	19 months ^d	NR
Jeyaraman (2021) [14]	Yes (day +163) ^b	Yes (from day +30)	Yes	Yes (Anti-B IgG/IgM \geq 1:512; Anti-A IgG/IgM \geq 1:128)	No GVHD	3rd dose	4 (weekly)	Undetectable but timing NR	4 months	NR
Yates (2021) [15]	Yes (+13 months)	Yes (from day +25) ^c	Yes	Yes (Anti-A titer \geq 1:64)	No GVHD	1st dose	3 (weekly)	Anti-A 1:4 after dose 1 and undetectable after dose 3	11 months	Requires monthly IVIG, but relationship to data. NR
Bicsko (2021) [16]	Yes (day +60) ^b	Yes (from day +30)	Yes	Yes (Anti-A titer 1:128)	NR	2nd dose	4 (from +60 to +96)	Undetectable but timing NR	NR	NR
Henig (2021) [17]	Yes (day +320) ^b	Yes (from day +42)	Yes	Yes (Anti-A titer 1:512)	No GVHD	2nd dose	5 (weekly)	Anti-A 1:64 after dose 1 and undetectable after dose 4	12 months and ongoing	None. Mild COVID-19 at 6 months
Sant Pau case #1	Yes (day +205) ^b	Yes (100% myeloid on day +30; day +155 for T-cells)	Yes	Yes (Anti-A IgG 1:1024; IgM 1:256)	Yes. Mild cGVHD from day +129	2nd dose (2 weeks after first and 1 week after second)	3 (weekly)	Yes (After dose 2 Anti-A IgG 1:256; IgM 1:32; 3 weeks after dose 3 both undetectable)	2.5 years and ongoing	Yes, IgG and IgA dropped <300 and <20 mg/dL at 3 months and normalized at 22 months; post-COVID-19
Sant Pau case #2	Yes (day +270) ^b	Yes (100% myeloid on day +39; day +186 for T-cells)	No. Patient also had platelet count < 30 × 10 ⁷ /L pre-daratumumab	Yes (Anti-A and Anti-B both 1:512; and IgG 1:128 and 1:256)	Yes. Moderate cGVHD from day +185	2nd dose (4 weeks after first and 2 after second). Platelets also rose after second dose.	Two (2 week interval)	Yes (At 7 weeks Anti-A IgG 1:32 and Anti-B IgG 1:2; at 12 weeks 1:4 and 1:1)	9 months and ongoing	Yes, IgG still <300 mg/dL 9 months later. IgA normal.

GVHD graft-versus-host disease, IsoHG isohemagglutinins, Hypogammaglobulinemia, cGVHD chronic graft-versus-host disease, NA not reported, dara.=daratumumab.

^aThe dose of daratumumab used in all cases was 16 mg/kg intravenously daily (with standard premedication) weekly or every 2 weeks.

^bPatient received (and failed) multiple treatments for PRCA before daratumumab, and all treatments were started after day +60 post transplant.

^cChimerism of isolated bone marrow nucleated red blood cell precursors (CD71+ cells) showed 76% donor origin

^dThese patients' follow-up was updated by Yates et al. [15] after feedback from the authors of the original published case report.

Case 1. A 77-year-old woman with secondary AML in CR received an alloRIC based on fludarabine-busulphan and sirolimus plus tacrolimus as GVHD prophylaxis [8]. Details important for this discussion are summarized in Fig. 1a. Due to major ABO mismatch (Patient 0 positive and Donor A positive with high pre-alloHSCT isohemagglutinins [IsoHG] titers), she developed post-engraftment PRCA, which was not treated until day +205, when she received treatment with daratumumab following the report by Chapuy et al. [4], as detailed in Table 1. Prompt and brisk reticulocytosis occurred 2 weeks after the first dose and one week after the second dose. Response was long-lasting (2.5 years now), and the only side effect was a 70% reduction of IgG, IgA and IgM, which required monthly IVIG treatment for 9 months.

Case 2. A 62-year-old woman with high-risk MDS received an alloRIC based on low dose thiotepa-fludarabine-busulphan and post-transplant cyclophosphamide plus tacrolimus as GVHD prophylaxis [9]. Again, relevant details for this discussion are shown in Fig. 1b. Due to major ABO mismatch (Patient 0 positive and Donor AB positive with high pre-alloHSCT IsoHG titers), she developed post-engraftment PRCA, as seen in Fig. 1b, which was not treated until day +270, when she received treatment with daratumumab (2 doses 2 weeks apart). The patient had moderate chronic GVHD requiring treatment with steroids and sirolimus and secondary thrombocytopenia, as detailed in Table 1. Prompt and brisk reticulocytosis occurred 4 weeks after the first dose and 2 weeks after the second dose, with dramatic reduction in the titers of IsoHG. Response lasts 10 months as of September 2021, and she also developed severe reduction in IgG, and moderate in IgA and IgM, which requires monthly IVIG treatment. The platelet count also rose above $100 \times 10^9/L$ 6 weeks post daratumumab.

Some features that the authors of this manuscript would like to emphasize of the current two case reports and the eight other cases reported to date are shown in Table 1.

As emphasized by Marco-Ayala et al. [1] and Longval et al. [2], it is difficult for clinicians to know when PRCA requires treatment beyond transfusions or simply requires patience since spontaneous resolution may occur within few weeks. This explains why most patients are treated many months after alloHSCT, often having tried numerous other treatments and having developed severe iron overload. However, from all these reports and the current state of knowledge one can conclude the following:




- The most important risk factor for PRCA and its duration beyond 2–3 months post-alloHSCT is a pre-transplant titer of IsoHG $> 1:64$ [1, 2].
- PRCA has a “biomarker”, since the titers of IsoHG must progressively decrease until they disappear. Persistently high titers beyond 2–3 months, and, especially, rising titers (as in our two case reports) is a clear indication for therapeutic intervention. In other words, therapeutic intervention would ideally be done when we can exclude the mere presence of residual pre-alloHSCT host IsoHG which simply take time to disappear (first 2–3 months) AND suspect that there are persistent host IsoHG-producing plasma cells. In this respect, the median time to IsoHG disappearance in patients who do not develop prolonged PRCA is around 60 days, while it is beyond 90 days in prolonged PRCA [1, 2, 10, 11].
- GVHD can have a strong graft-vs.-plasma cell effect and is a major predictor of disappearance of IsoHG and recovery from PRCA [1, 2, 10, 11]. Since both of our patients developed cGVHD, we expected remission of their PRCA, but this did not occur, prompting a therapeutic intervention.
- PRCA can be a significant problem following major ABO-mismatched transplantation, resulting in a significant need for long-term transfusions, significant increase in the need for patient care and leads to marked iron overload.

- All treatments tested in PRCA have significant potential toxicities. Withdrawal of immunosuppression can result in resolution of PRCA in many patients, but can also lead to significant GVHD. High-dose steroids, plasma exchange, bortezomib, rituximab and many others have been used, with some cases of clear response, but no true evidence of having a good efficacy-to-risk balance [1].
- Patients who have severe pancytopenia and thus a poor graft function may also be candidates to treatment with daratumumab if they have IsoHG-linked PRCA. However, these patients have a poor prognosis [12], and treatment with eltrombopag or romiplostim may be of benefit [13], although eliminating high-titer IsoHG should also be a target in such cases.


From the ten cases reported to date and summarized herein, it appears that two to four doses of daratumumab can obtain prolonged remission of IsoHG-mediated PRCA, without relevant side effects except hypogammaglobulinemia, whose incidence and duration remains to be determined. The rapid response in all ten cases confirms the hypothesis that eliminating the residual recipient plasma cells leads to cure of PRCA since in a context of complete donor chimerism these residual plasma cells cannot reappear once eliminated by a short-course of daratumumab. Based on the available data, we suggest using 2–4 doses of daratumumab as the first-line treatment of PRCA, and believe that a few logical variables should be met to optimize its efficacy.

- Patients should be treated at least 60 days post transplantation and 30 days post engraftment.
- Complete donor chimerism should be present in myeloid cells and predominant in T cells ($>50\%$), since recipient plasma cells could theoretically reappear in a bone marrow environment of mixed myeloid and, especially, T-cell chimerism [11].
- Persistently (and even rising) high titers of anti-donor IsoHG are present (this is, in fact, the major “biomarker” for using daratumumab).

The characteristics of the ten cases shown in Table 1 support these characteristics when requesting daratumumab as compassionate use.

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AUTHOR CONTRIBUTIONS

All three co-authors (RM, IG-C, and AE) contributed to the conception and execution of this brief manuscript. RM was the main author responsible for its drafting and managing its review process.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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