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Impact of Daratumumab on Anti-HLA Antibodies Level in Patients with Multiple Myeloma, a Role in Transplantation?

*Floriane Theves[1], David Kheav[3], Alexis Talbot[1], Marie-Noelle Peraldi[2], Camille Villesuzanne[1], Stephanie Harel[1], Bruno Royer[1], Anne-Claire Lepretre[4], Maryvonnick Carmagnat[3], Jean-Luc Taupin[3] and Bertrand Arnulf[1]**

[1]Department of Immunohematology, APHP University of Paris, France

[2]Department of Nephrology and Transplantation, APHP University of Paris, France

[3]Immunology Laboratory, APHP University of Paris, France

[4]Department of Transfusion, Etablissement Français Du Sang, France

Abstract

Daratumumab, a humanized anti-CD38 monoclonal antibody, has demonstrated anti-plasma cell activity alone and in combination with other drugs in Multiple Myeloma (MM) and in light chain Amyloidosis (AL). Allogenic anti-Human Leukocyte Antigen (HLA) antibodies are frequently encountered in patients awaiting kidney transplantation, complicating the access to a compatible transplant and represent a major risk factor of humoral rejection. Durably removing the antibodies or eliminating the producing cells is an objective that is currently out of reach. The objectives of our study were to evaluate the frequency of anti-HLA antibodies in MM and AL patients, and to determine the effect of daratumumab on them.

Eligible patients with diagnosed MM or AL were selected (n=182), among whom 84 had anti HLA antibodies (46%). Forty-nine patients (45 MM and 4 AL) were retrospectively included.

Patients were treated with a combination of an alkylating agent, an Immunomodulatory imide Drug (IMiD), a Proteasome inhibitor, with (n=22) or without (n=22) daratumumab. Five patients received daratumumab alone. Treatment with daratumumab lowered anti-HLA antibodies in 85% (23/27) of cases including complete loss in 56% of cases (15/27) compared to 77% (17/22) and 45% (10/22) respectively, p=0.8.

This study couldn't find a statistic impact of daratumumab to lower HLA antibody in this cohort. The association with chemotherapy could be an important bias and this hypothesis will be evaluated in ongoing studies enrolling patients undergoing kidney transplantation.

Keywords: Anti-HLA antibodies; Daratumumab; Kidney transplantation; Multiple myeloma

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Correspondence:
Bertrand Arnulf, Department of Immunohematology, Saint Louis Hospital, APHP University of Paris, France,
E-mail: Bertrand.arnulf@aphp.fr

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Introduction

Multiple Myeloma (MM) is characterized by a proliferation of clonal plasma cells highly expressing the CD38 antigen [1]. The treatment of MM is based on front-line treatment for young and healthy patients with combinations of steroids, Immunomodulatory imide Drug (IMiD), Proteasome Inhibitor (PI), alkylating agents, and autologous transplantation [2]. Daratumumab is a humanized IgG1k monoclonal antibody targeting CD38 tumoral and non-tumoral plasma cells. The mechanism of action of daratumumab comprises immune-mediated effects, including complement-dependent and antibody-dependent cell-mediated cytotoxic effects, antibody-dependent cellular phagocytosis, and apoptosis by cross-linking. Daratumumab has significantly improved the efficiency of treatment in MM. Daratumumab alone is effective in relapsed MM [3,4]. Moreover, it has demonstrated better efficacy in combination with PI or IMiDs in relapsed disease, and in front line treatment [5-10]. In addition, daratumumab presents an outstanding safety profile with non-considerable side effects. Altogether, this suggests it could potentially be used in other non-tumoral plasma cell-mediated pathologies.

The presence of anti-HLA antibodies prior to transplantation is associated with a decreased number of donors and a longer waiting time. Furthermore, non-immunized patients can also develop

de novo antibodies after transplantation due to HLA mismatches. The presence of anti-HLA antibodies after kidney transplantation promotes hyperacute rejection, acute and chronic humoral rejection, and early graft loss [11]. Kidney survival and overall survival are lower in immunized patients with anti-HLA antibodies and chronic humoral rejection is nowadays considered as the leading cause of graft loss [12,13]. The standard desensitization protocols include plasmapheresis associated with high dose polyvalent Intravenous Immunoglobulins (IVIG) [14-16]. However, in strongly immunized patients this strategy is insufficient and other therapies are proposed such as antibodies targeting IL6 or its receptor, in order to control antibody production, the synthesis of antibodies by inhibition of B lymphocytes and plasma cells, and complement inhibitors, to regulate antibody main effect or function. All these therapies are either poorly effective or evaluated in small non-randomized controlled studies [17-20]. Particularly in patient's refractory to conventional treatments with IVIG and plasmapheresis, the desensitization protocols prior to or after renal transplantation are not standardized yet. Moreover, these therapeutic approaches have a major immunosuppressive impact with a significantly high risk of infections. Thus, plasma cells are a logical target of therapy given their critical role in antibody production and high level of CD38 expression. Daratumumab could be an effective drug for plasma cell depletion and desensitization.

To measure the effect of daratumumab on serum anti-HLA antibodies level, we studied two cohorts of patients treated or not with daratumumab for symptomatic MM or AL. The objectives of our study were to determine the frequency of anti-HLA antibodies in MM and AL patients and to evaluate the impact of daratumumab on the evolution of anti-HLA antibody levels.

Patients and Methods

In this retrospective, single-center study at Saint Louis Hospital, eligible patients with symptomatic MM or AL were tested for anti-HLA antibodies during treatment in two sera samples between June 2014 and October 2019. Mean times between two samples were 176 days [21-1384]. All patients provided informed consent and this trial was approved by an independent local ethic committee. The inclusion criteria were patients with symptomatic MM or AL requiring treatment according to the recommendation from IMWG (International Myeloma Working Group) [21].

Sixty two patients were involved in a test cohort and the frequency of anti-HLA antibodies was evaluated. The results were validated on a second cohort of 120 patients. The aim was to monitor the level of anti-HLA antibodies in patients treated with and without daratumumab. Transfusion history for red blood cells, platelets and plasma was obtained from the EFS (Établissement Français du Sang). Cytogenetic characteristics of patients were performed with FISH technique searching for 17p deletion, t(4;14), and t(11;14) translocations.

Daratumumab was used in front line in the "Cassiopeia" study (NCT02541383) or in relapse at the dose of 16 mg/kg either in monotherapy or in combination with PI or IMiD. Daratumumab was administered intravenously once per week (days 1, 8, 15 and 22) during cycles 1 and 2, once every 2 weeks (on day 1) during cycles 3 to 6, and once every 4 weeks thereafter. In the second group, patients received a treatment combining either alkylating agent, IMiD, or PI, without daratumumab.

Research and identification of anti-HLA antibodies were carried out in the immunology laboratory of Saint Louis Hospital in Paris using the Luminex technology and the screening kit for anti-HLA antibodies for class I and for class II (ref LSM12, One Lambda, Canoga Park, CA). Results are expressed as a ratio between the highest MFI (Mean Fluorescence Intensity) of the sample against a negative control provided by the manufacturer. Identification of anti-HLA antibody specificities in the positive sera could not be performed for this study. The anti-HLA antibody level is considered as reduced if the ratio decreases by at least 40% in at least one class. Statistical analyzes were performed using Fisher's exact test with $p<0.05$.

Results

Characteristics of the patients in the test cohort

The test cohort included 62 patients (median age 63 years, sex ratio M/F=1.9). Anti-HLA antibodies were found in 23% (14/62) of the patients. Among the 14 patients with positive anti-HLA antibodies, 9 had a second sample available, and anti-HLA antibodies disappeared in 6 of them after daratumumab treatment (Figure 1). All patients received treatment including PI and IMiD and half received an alkylating agent (Table 1). Most of the patients in this cohort had a previous history of transfusion (7/9).

Evolution of anti-HLA antibodies in the test cohort

In this cohort, the median time between the first and the second anti-HLA antibody sample was 290 days [40-1384] and in the daratumumab group, the median time was 251 days. Three patients received daratumumab as monotherapy, and 5 in combination with PI, IMiD, or Alkylating agent. In patients treated with daratumumab, anti-HLA antibodies disappeared in 75% of cases (6/8). Considering both decrease and loss of anti-HLA antibodies, the rate reached 88% (7/8).

Characteristics of patients in the validation cohort

The validation cohort included 120 patients. Anti-HLA antibodies were detected in 70 patients (58%). A second sample was available for 42 patients and 2 patients were excluded because the interval between the two samples was less than 5 days. Twenty-one patients showed positive anti-HLA antibodies on their second sample (Figure 1).

We further studied 40 patients (37 MM and 3 AL) who received a median of 2 lines of treatment [0-4]. Eleven patients were not yet treated at the time of the first sample. Of the 29 patients under treatment, 26 (90%) received a PI, 22 (76%) patients received an IMiD, 11 (40%) received an alkylating agent, and 15 patients (52%) underwent high dose chemotherapy followed by an autologous stem cell transplant (Table 1).

Half of the patients received a transfusion (red blood cells, platelets and plasma) (20/40). Among the 24 males in this cohort, 13 (33%) did not have any prior history of transfusion.

Evolution of anti-HLA antibodies in the validation cohort

In the validation cohort, the median time between the two serum samples was 92 days [21-779 days] and in the daratumumab group, the median time was 63 days. Nineteen out of 40 patients received treatment including daratumumab, in monotherapy (n=2), and in combination with a PI, IMiD, or alkylating agent (n=17). Twenty-one patients received only treatment a PI, IMiD, or alkylating agent. The rate of anti-HLA antibody loss was similar in patients treated with daratumumab (47%) or without (48%).

A subgroup of 16 out of 19 (84%) patients treated with

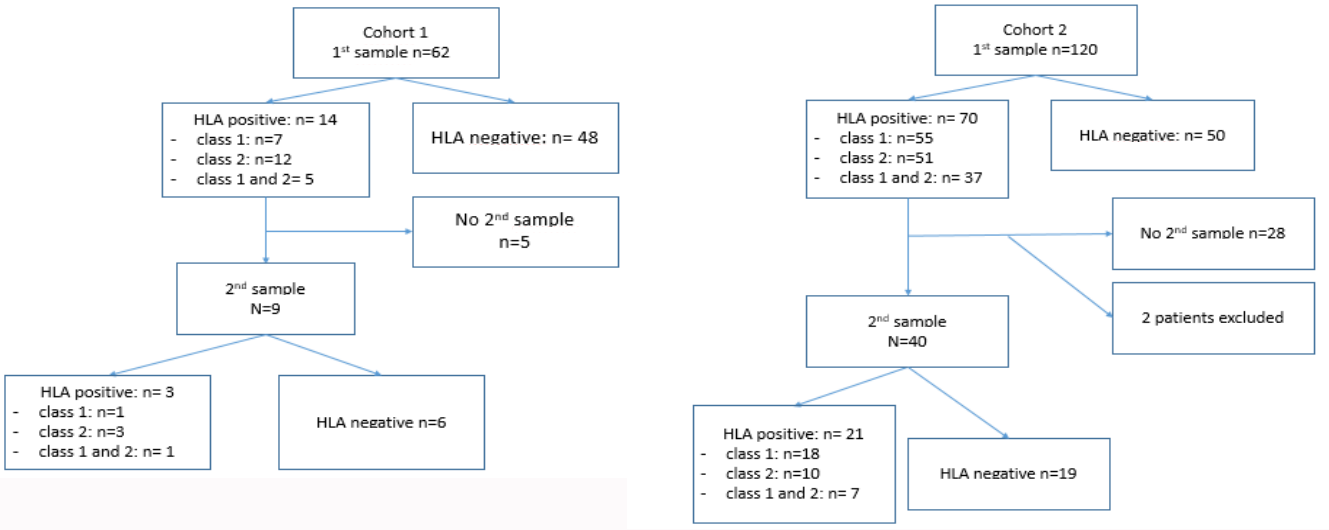

Figure 1: Flow chart of the test and validation cohorts.

Table 1: Characteristics of patients in both cohorts at the time of the first sample.

	Cohort 1	Cohort 2
Myeloma (n)	8	37
AL amyloidosis (n)	1	3
Pt with anti Class 1 HLA abs (n)	5	33
Pt with anti Class 2 HLA abs (n)	7	26
Pt with anti Class 1 and 2 HLA abs (n)	3	19
Polyclonal gammaglobuline (mean, g/L)	5.6	4.8
Nb of line of treatment (n, range)	2 [1-6]	2 [0-4]
No treatment (n)	0	11
Alkylating agent (n)	5	11
Imids(n)	9	22
PI (n)	9	26
ASCT (n)	7	15
Total (n)	9	40

daratumumab had complete loss or decreased anti-HLA antibody levels. In the subgroup treated without daratumumab, loss or decrease of anti-HLA antibodies was observed in 81% (17/21).

Evolution of anti-HLA antibodies in the whole cohort

To analyze the effect of daratumumab on a larger number of patients, the two cohorts were combined. Therefore, we considered an overall cohort of 49 patients, including 27 patients treated with daratumumab and 22 patients without. Among the 25 patients with negative anti-HLA antibody levels, 15 patients (60%) received daratumumab versus 10 patients (40%) without daratumumab, p=0.57.

85% (23/27) of patients treated with daratumumab, either reduced or completely lost anti-HLA antibodies, as compared to 77% (17/22) for patients treated without daratumumab (Figure 2) (p=0.83).

In the 25 patients achieving anti-HLA antibodies level complete loss, the median treatment exposure was shorter in the presence of daratumumab than with other therapies: 112 days [27-516] versus 169 days [31-779], respectively (Figure 2).

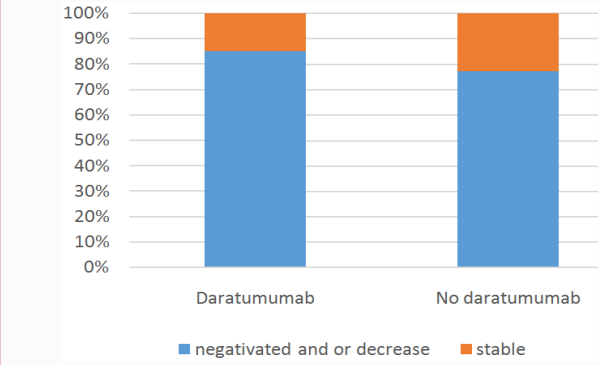

Figure 2: Evolution of HLA antibody according to daratumumab in the global cohort.

Impact of daratumumab as monotherapy or in combination

Five patients were treated with daratumumab in monotherapy and 22 patients received daratumumab in combination with PI or IMiD: 2 out of 5 patients had negative anti-HLA antibodies levels versus 13 out of 22 patients respectively (p=0.6). In addition, 4 out of 5 (80%) patients treated with daratumumab alone decreased or lost anti-HLA antibody level as compared to 19 out of 22 (86%) other patients, p=1.0. Hence, daratumumab alone or in combination should have a similar impact on the anti-HLA antibody level.

Discussion

The objectives of our study were to evaluate the rate of anti-HLA antibodies in MM and AL, to evaluate the impact of daratumumab on anti-HLA antibodies in a first test cohort (n=62) and to confirm the results in a validation cohort (n=120).

Anti-HLA antibodies were found in 23% and 53% in the test and validation cohort, respectively. In the literature anti-HLA antibodies were found in around 20% in patients with hematological malignancies [22,23]. Patients with prior organ transplantation, pregnancies, or blood transfusions have an increased likelihood of becoming sensitized by developing anti-HLA antibodies [24]. In this study, the major risk factor for anti-HLA antibodies was transfusion (78% and 50%, respectively), and the majority of patients were males

making the risk factor caused by pregnancy unlikely.

In our study, after conventional therapy with a PI, IMiD, or Alkylating agent plus daratumumab, the frequency of anti-HLA antibodies decreased to 58% (23/40) of patients, versus 42% (17/40) without daratumumab. Anti-HLA antibody disappeared (n=25) in 60 % (15/25) with daratumumab, *vs.* 40% (10/25) without. A quantitative study with anti-HLA antibodies specificities could be done therefore to assess more precisely the evolution of these antibodies over time. However, no statistically significant difference was found. This could be explained by the small number of patients and the bias with the association with chemotherapy. The effect of daratumumab alone on anti-HLA antibodies is difficult to assess given the few patients that received daratumumab in monotherapy even if there were no statistical difference between the 2 groups of daratumumab (combination and monotherapy).

In the 25 patients who negative anti-HLA antibodies with and without daratumumab, the median duration of treatment was shorter in the presence of daratumumab than with the other treatments: 112 days [27-516] *vs.* 169 days [31-779], respectively. Daratumumab could therefore lead to a quicker clearance of anti-HLA antibodies than other therapies (IP, IMiDs, alkylating agents, steroids) within a median time of 3 months. In the treatment of MM, daratumumab in monotherapy acts faster again tumoral plasma cells with a median time to response of 1 month [3].

In preclinical study on macaques immunized, the use of daratumumab pre-transplant allowed significantly longer kidney graft survival [25]. Also in a case report on kidney transplantation, daratumumab helped to decrease anti HLA antibody and improved antibody-mediated rejection [26]. A phase 1 to 2 study (NCT04204980) is underway on the use of daratumumab to desensitize highly immunized patients awaiting kidney transplantation. The first step is a dose escalated step from 4 mg/kg to 16 mg/kg. For the second step, patients will receive daratumumab at a dose of 16 mg/kg weekly for 8 weeks.

A remaining open question is the optimal dose and schedule of daratumumab for this particular purpose. In fact, the monoclonal anti-CD20 antibody rituximab is used at different doses in lymphoproliferative syndromes and in dysimmune pathologies [27-29].

Besides transplantation, daratumumab may have other indications in other non-tumor situations through its cytotoxic action on normal plasma cells. Several clinical cases have reported the efficacy of daratumumab in autoimmune cytopenias in post allogeneic bone marrow transplantation [30,31].

In conclusion, this study couldn't find a significant effect of daratumumab to lower HLA antibody. The association of chemotherapy in both groups is an important bias. We find nevertheless a quicker clearance of anti-HLA in daratumumab group. These results need to be confirmed in larger trials including immunized patients waiting for a transplant or with acute humoral rejection.

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