HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome

Yogen Saunthararajah, Ryotaro Nakamura, Jun-Mo Nam, Jamie Robyn, Fausto Loberiza, Jaroslav P. Maciejewski, Toni Simonis, Jeffrey Molldrem, Neal S. Young, and A. John Barrett

The extent and importance of autoimmune mechanisms in myelodysplastic syndrome (MDS) and the role of immunosuppression in the treatment of this disease are not well defined. We report overrepresentation of HLA-DR2 and its serologic split HLA-DR15 in both MDS and aplastic anemia (AA). Four clinically and ethnically defined patient groups were analyzed. The HLA-DR15 antigen frequencies among North American white MDS patients (n = 72) and AA patients (n = 59), who received immunosuppressive treatment at the National Institutes of Health (NIH), were 36% and 42%, respectively.

These antigen frequencies were significantly higher than that of the control population of 240 North American white NIH blood donors typed for HLA antigens by the same molecular technique (HLA-DR15, 21.3%, P = .01 for MDS, P < .001 for AA). Among North American white patients reported in the International Bone Marrow Transplant Registry (IBMTR), 30% of 341 MDS patients and 33% of 364 AA patients were positive for HLA-DR2. These antigen frequencies were higher than those reported for the general North American white population (HLA-DR2, 25.3%, P = .089 for MDS, P = .01 for AA).

The DR15 and DR2 frequencies were significantly increased in MDS refractory anemia (RA) (P = .036 and P = .01, respectively) but not MDS refractory anemia with excess blasts. In the NIH MDS patients, HLA-DR15 was significantly associated with a clinically relevant response to antithymocyte globulin (ATG) or cyclosporine immunosuppression (multivariate analysis, P = .008). In MDS with RA, DR15 may be useful as a guide to pathophysiology, prognosis, and treatment.

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Patients and methods

MDS patients

Two cohorts were studied. Group 1 (National Institutes of Health [NIH] MDS, DR15 cohort) consisted of 82 patients (50 with refractory anemia [RA], 10 with RA with ring sideroblasts [RARS], and 22 with RA with excess blasts [RAEB]) referred for consideration for treatment in NIH National Heart, Lung, and Blood Institute (NHLBI) Institutional Review Board–approved protocols 96-H-0142, 95-H-0189, and 99-CC-0021 between March 1995 and January 2001. In the absence of karyotypic abnormality, marrow hypercellularity, ring sideroblasts, or myeloblasts in excess of 5%, the minimum criterion used to diagnose MDS was the presence of megakaryocytic dysplasia (single nucleus or few, small, round, separated nuclei and/or micromegakaryocytes). According to the International Prognostic Scoring System (IPSS),18 16 patients were low risk, 52 intermediate-1 risk, 8 intermediate-2 risk, and 6 high risk. The mean age was 59 ± 2.9 years, and the mean duration of red cell transfusion dependence prior to treatment was 776 ± 292 days. In those patients with bone marrow biopsies to allow evaluation of cellularity, 20 patients had

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hypocellular, 24 normocellular, and 31 hypercellular bone marrows. Fifty-three of 82 patients tested had normal cytogenetics. All patients had transfusion-dependent anemia with or without thrombocytopenia or neutropenia. Seventy-two North American whites (46 RA, 17 RAEB, 9 RARS) in this cohort were typed at the HLA-DR locus. Seventy-seven patients of all ethnicities were typed at the HLA-DR locus. All 82 patients in the cohort were evaluable for response. Correlation of pretreatment variables with response (which does not involve comparison to an ethnicity-based control population) was based on all the patients in the NIH MDS cohort.

Group 2 (International Bone Marrow Transplant Registry (IBMTR) MDS, DR2 cohort) consisted of 1289 patients with a diagnosis of RA, RAEB, RAS, RAEB in transformation (RAEB-T), or other unclassified MDSs who received allogeneic bone marrow stem cell transplants and were reported to the IBMTR between 1985 and 2000. Information on HLA class II (DR, DQ) was available in 1008 patients. Of these patients, 341 North American white MDS patients with a diagnosis of RA, RAEB, RAS, or RAEB-T were analyzed in this study (the remaining patients were either white but not North American, were of other ethnicities, or had unclassified MDS). Diagnosis of MDS subtype was made by the referring center according to published French-American-British (FAB) classification criteria: 84 had RA, 14 had RARS, 118 had RAEB, and 125 had RAEB-T. The mean age was 35.6 ± 0.8 years.

Severe AA patients
Two cohorts were studied. Group 1 (NIH AA, DR15 cohort) consisted of 148 patients with severe AA treated at NIH on NHLBI Institutional Review Board–approved protocols 90-H-146 and 97-H-117 between December 1989 and October 1999. The mean age was 34 years. Severe AA was defined as absolute neutrophil count less than 0.5 × 10^9/L (500/µL), absolute platelet count less than 20 × 10^9/L (20 000/µL), and absolute reticulocyte count less than 40 × 10^9/L (40 000/µL) in the setting of a hypocellular bone marrow biopsy. Ninety-nine patients in this cohort were typed at the HLA-DR locus, of whom 59 were North American white.

In group 2 (IBMTR AA, DR2 cohort), 2609 patients with severe AA received allogeneic stem cell transplantation from HLA-matched siblings reported to the IBMTR. Information on HLA class II (DR, DQ) was available in 1752 patients. Of these patients, 364 North American white severe AA patients were analyzed in this study (the remaining patients were either white but not North American or were of other ethnicities). Diagnosis was made by the referring center by blood and bone marrow examination. The mean age was 21 ± 0.7 years.

Control populations
A total of 240 North American white healthy blood donors at the NIH, typed at the HLA-DR locus, were used as controls for the NIH (group 1) AA and MDS patients. Analyses were also performed using the HLA-DR15 antigen frequency for 232 North American whites from the 11th International Histocompatibility Workshop. As controls for the IBMTR patients with AA and MDS (group 2), the HLA-DR2 antigen frequency for 1145 North American whites was obtained from the 8th International Histocompatibility Workshop.

HLA typing
HLA typing for NIH patients and controls was performed using standard antisera and later with DNA techniques. All subjects typed were typed for the serologic splits of HLA-DR2: HLA-DR15 and HLA-DR16. Because most of the IBMTR reports used HLA-DR2 frequencies and not the serologic split, the antigen frequency of HLA-DR2 was used as a surrogate for HLA-DR15 in this data set. Antigen frequency was defined as the percentage of the population possessing the antigen.

Immunosuppressive treatment (group 1, NIH patients)
A total of 69 MDS patients received 1 course of ATG, 40 mg/kg/d intravenously daily, for 4 days, and 13 received cyclosporine starting at 5 to 12 mg/kg/d, with dose adjustments to maintain therapeutic levels. Cyclosporine was continued indefinitely if a response was noted at 6 months. AA patients received ATG, 40 mg/kg/d intravenously daily, for 4 days and cyclosporine, 12 mg/kg/d, continued for at least 6 months with dose adjustments to maintain therapeutic levels. In MDS patients, response was defined as red cell transfusion independence (at least 6 weeks of freedom from transfusion occurring within 8 months of starting the protocol treatment). AA patients were classified as responders if they met 2 of the following 3 criteria: absolute neutrophil count more than 0.5 × 10^9/L (500/µL), platelet count more than 20 × 10^9/L (20 000/µL), and reticulocyte count more than 40 × 10^9/L (40 000/µL) (60 × 10^9/L [60 000/µL]) after January 1993.

Statistical analyses
SAS statistical software version 8.1 was used for analysis. P < .05 was considered significant in all analyses. The Pearson χ^2 goodness-of-fit test was used to validate the Hardy-Weinberg genetic equilibrium for phenotypic data. The χ^2 test was used to detect a difference between control and patient groups in antigen frequency of HLA-DR15 or HLA-DR2. Antigen frequency comparisons were only done for North American whites because of sample size and control group constraints. The χ^2 test and logistic procedure were used to analyze the association of individual pretreatment variables with response. Logistic regression with backward selection was used for multivariate analysis of the response variable with covariables of age (years), duration of red cell transfusion dependence (days), HLA-DR15 (present or absent), marrow myeloblast percentage (< or > 5%), cytogenetics (normal or abnormal), number of cytopenias (unicytopenias, bicytopenias, or tricytopenias), bone marrow cellularity (hypocellularity, normocellularity, or hypercellularity), paroxysmal nocturnal hemoglobinuria (PNH; present or absent by flow cytometric analyses), and IPSS score (low, intermediate-1, intermediate-2, and high risk).

Results
HLA-DR15 and HLA-DR2 antigen frequencies
The χ^2 goodness-of-fit tests for HLA-DR phenotype showed that all 4 patient populations (group 1 and group 2 MDS and AA) satisfied the Hardy-Weinberg law for genetic equilibrium. Because the predominant ethnic type in both group 1 and 2 patients was North American white, statistically valid comparisons of HLA antigen frequencies were only possible in this population. The HLA-DR15 and DR2 antigen frequencies of North American white patients were therefore compared with North American white control populations. In group 1 patients (NIH cohort), HLA-DR15 antigen frequency was 36% in 72 MDS patients and 42% in 59 AA patients. These frequencies were both significantly higher (P = .01 for the MDS patients, P < .001 for the AA patients) than the HLA-DR15 antigen frequency of 21% in 240 healthy blood donors at the NIH. Similar significant findings were observed in comparison to the HLA-DR15 antigen frequency of 20% in a population sample of 232 North American whites from the 11th International Histocompatibility Workshop. In group 2 (IBMTR) patients, HLA-DR2 antigen frequency was 30% in 341 MDS patients and 33% in 364 AA patients. The frequency in AA was significantly higher than the 25% HLA-DR2 antigen frequency in a population sample of 1145 North American whites (P < .01), and the figure in MDS was higher but did not meet statistical criteria for significance (P = .089) (Table 1).

HLA-DR15 and HLA-DR2 antigen frequency in MDS subtypes
Of the 72 North American white group 1 MDS patients, 46 had RA and 17 had RAEB. There was a 46% HLA-DR15 antigen frequency in RA, which was significantly higher than the frequencies of 20% and 21% in the North American white control populations (P < .001).
In RAEB, the DR15 antigen frequency of 18% was not significantly different from the control populations. In the 84 IBMTR MDS patients with RA there was an HLA-DR2 frequency of 36%, significantly higher than 25% in the North American white population sample (P = .036). In the 118 IBMTR MDS patients with RAEB, the DR2 antigen frequency was 28%, which was not significantly different from 25% in the control population (Table 1). Of patients with RARS, 2 of 9 NIH patients were positive for DR15 and 1 of 14 IBMTR patients was positive for DR2; conclusions regarding RARS and DR15 should be confirmed with larger patient numbers.

Association of HLA-DR15 with other pretreatment variables in NIH MDS patients

In univariate analysis, bone marrow myeloblast percentage 5% or below and the presence of paroxysmal nocturnal hemoglobinuria by flow cytometric analysis correlated significantly (χ², P < .05) with the presence of HLA-DR15. In univariate analysis, age and duration of red cell transfusion dependence were analyzed as continuous (logistic regression) and as categorical variables (χ² test) (Table 2); in both of types of analyses, age and duration of red cell transfusion dependence were not significantly associated with HLA-DR15. In multivariate analysis, only 5% or fewer myeloblasts correlated significantly with HLA-DR15 (Table 2). When only HLA-DR15−positive patients were analyzed, responders to immunosuppression were more likely to have a bone marrow cellularity of less than 30% (χ² test, P < .05). Among DR15−positive patients, responders were also more likely to be younger than 60 years of age or have coexistent PNH, although these differences were not statistically significant.

Association of pretreatment variables with response to immunosuppressive treatment in MDS

Altogether, 29% of MDS patients achieved durable transfusion independence (22 of 69 treated with ATG and 2 of 13 MDS patients treated with cyclosporine). Of these 24 responders, 19 remained transfusion independent with a median follow-up of 31 months. Among responders, 14 (64%) of 22 were DR15-positive compared with 15 (29%) of 55 nonresponders (P < .01, χ² test) (77 of 82 patients in the NIH MDS cohort were typed at the DR locus). A total of 14 (48%) of 29 DR15-positive patients and 8 (17%) of 48 of DR15-negative patients responded to immunosuppression. Other factors with significant positive associations with response in univariate analysis were younger age, shorter duration of red cell transfusion dependence, presence of an expanded clone of PNH cells, and pancytopenia. It is possible that the lack of a significant association of myeloblasts below 5% or normal cytogenetics with response to immunosuppression was because of the relatively small number of patients with myeloblasts above 5% (22 of 82) and abnormal cytogenetics (29 of 82). On multivariate analyses of pretreatment variables (logistic regression, backward selection), HLA-DR15, age, and duration of red cell transfusion dependence remained significantly associated with a response to immunosuppression (Table 3). The adjusted odds ratio for the effects of these pretreatment variables on the probability of response were as follows: 8.53 times more likely to respond if DR15-positive, 1.56 times more likely to respond for each 90-day decrease in duration of red cell transfusion dependence, 2.18 times more likely to respond for each 5-year decrease in age. The addition of DR15 into a logistic regression model to predict response to immunosuppression that included only age and duration of red cell transfusion dependence produced a significant increment in the likelihood ratio statistic from 43.9 to 48.4 (P = .03; this P value is based on the increase in the likelihood ratio and is therefore different from the P = .008 obtained from the χ² test in the logistic regression backward selection model). The addition of DR15 into a logistic regression model that included only age, duration of red cell transfusion dependence, and PNH produced a significant increment in the likelihood ratio statistic from 45.8 to 52 (P = .01) (Table 3).

HLA-DR15 and response to immunosuppressive treatment in AA

Of the AA patients typed at the DR locus (all ethnicities), 63 (64%) of 99 patients responded to immunosuppression. Thirty-two of 47 HLA-DR15−positive and 31 of 52 HLA-DR15−negative patients responded to a combination of ATG and cyclosporine. In multivariate analysis, only age associated significantly with response (P < .01).

Discussion

The 49% frequency for DR15 antigen noted in NIH AA patients was similar to 50% reported in 52 patients in Argentina and 61% reported in 59 patients in Japan. The 39% antigen frequency for DR2 in IBMTR AA patients corresponded closely with an earlier report of 38% in 42 patients. Our data therefore confirm the high

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**Table 1.** HLA-DR15 and HLA-DR2 antigen frequencies in North American white MDS and AA compared with North American white control groups

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group 1 (NIH): HLA-DR15</th>
<th></th>
<th>Group 2 (IBMTR): HLA-DR2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antigen frequency (%)</td>
<td>P</td>
<td>Antigen frequency (%)</td>
<td>P</td>
</tr>
<tr>
<td>MDS</td>
<td>72</td>
<td>.01</td>
<td>341</td>
<td>.089</td>
</tr>
<tr>
<td>RA</td>
<td>46</td>
<td>.00048</td>
<td>84</td>
<td>.036</td>
</tr>
<tr>
<td>RAEB</td>
<td>17</td>
<td>.00048</td>
<td>118</td>
<td>.53</td>
</tr>
<tr>
<td>RARS</td>
<td>9</td>
<td>.94</td>
<td>14</td>
<td>.11</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>—</td>
<td>—</td>
<td>125</td>
<td>.22</td>
</tr>
<tr>
<td>AA</td>
<td>59</td>
<td>.0008</td>
<td>364</td>
<td>.0059</td>
</tr>
</tbody>
</table>

Table 2. Association of HLA-DR15 with pretreatment variables in NIH MDS patients

<table>
<thead>
<tr>
<th>HLA type</th>
<th>Myeloblasts more than 5% in bone marrow†</th>
<th>Coexistent PNH*</th>
<th>Abnormal cytogenetics</th>
<th>Hypocellular bone marrow (less than 30% cellularity)</th>
<th>IPSS low risk and intermediate-1</th>
<th>Fewer than 6 mo RBC tx dependence</th>
<th>Age less than 60 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR15-negative, %</td>
<td>15</td>
<td>4.4</td>
<td>38.3</td>
<td>21.7</td>
<td>85.1</td>
<td>43.8</td>
<td>37.5</td>
</tr>
<tr>
<td>DR15-positive, %</td>
<td>2.0</td>
<td>22.2</td>
<td>17.2</td>
<td>34.5</td>
<td>93.1</td>
<td>44.8</td>
<td>48.3</td>
</tr>
</tbody>
</table>

RBC tx indicates red blood cell transfusion.

*P < .05, χ² test (univariate analysis).

†P < .05, logistic regression (multivariate analysis).
prevalence of HLA-DR15 or HLA-DR2 in patients with AA previously reported.14-17 In MDS, a small case series previously described a possible association between HLA-DRB1*1501 (serologically HLA-DR15) and response to cyclosporine but without statistical analysis.26 Here, we show for the first time an overrepresentation of HLA-DR2 and its serologic split HLA-DR15 in MDS. Comparable frequencies were found in 2 distinct, well-defined MDS patient populations: 36% of the North American white MDS patients in the NIH MDS series had the HLA-DR15 antigen, and 30% of the North American white MDS patients from the IBMTR database were positive for HLA-DR2. Our goal in analyzing 2 different cohorts of patients (NIH and IBMTR) was to see if the conclusions we were deriving from analyses on NIH patients would hold up when a different patient cohort not referred to us for immunosuppression was analyzed. However, the data should be interpreted with caution. It is possible that our 2 patient cohorts, for different reasons, do not accurately represent the general MDS population. Patients who received immunosuppressive therapy at the NIH had less advanced disease overall: They suffered mainly from the consequences of bone marrow failure rather than from leukemic transformation. A total of 27% (20 of 74) of these patients had hypocellular marrows, in contrast to the frequency of hypocellular MDS in other cohorts, which has been reported in the 7% to 11.6% range.27-29 This higher frequency of hypocellular MDS in the NIH cohort most likely reflects the fact that most MDS patients were referred specifically for immunosuppressive treatment. Given the diagnostic difficulty of separating some cases of MDS from AA, it could be argued that the frequency of hypocellular MDS is lower in the NIH cohort because the diagnosis of MDS was made in many different centers. Nonetheless, certain biases were possible: Patients undergoing stem cell transplantation and reported to the IBMTR were mostly under 50 years of age; if one were to consider the frequency of HLA-DR2 “common,” the proportion of patients with a matched sibling donor who possess HLA-DR2 might then be greater than the proportion of patients who possess HLA-DR2 in general. However, such a bias was unlikely because there was no increase in the HLA-DR2 frequency among the IBMTR MDS patients with RAEB.

MDS is a heterogeneous group of syndromes, and various patient characteristics can be used to predict different evolution patterns and prognoses.18,30 HLA-DR15 and DR2 were significantly associated with RA but not RAEB in both the NIH and IBMTR cohorts (Table 1). This finding, together with the significant association of DR15 with a response to immunosuppression in MDS patients (Table 3), the association of DR15 with PNH in these patients (Table 2), and its association with AA (Table 1), suggests that DR15/DR2 typing may identify a subset of MDS with a more favorable prognosis and an immune pathophysiology similar to that of AA.12,28 In contrast, and in support of previous findings, DR15 did not associate with a response to immunosuppression in patients with AA.15,31 A clinical diagnosis of AA effectively identifies a group of patients with immune-mediated marrow failure. On the other hand, a clinical diagnosis of MDS captures a heterogeneous population in which DR15 indicates a subset with immune-mediated marrow failure. The discrepancy between the impact of HLA-DR15 status in AA and MDS, and the fact that responses with AA and MDS also occurred in DR15-negative subjects, suggests that other factors also favor response to immunosuppressive therapies. In MDS, young age and a short duration of red cell transfusion dependence were other pretreatment variables associated with response to immunosuppression in multivariate analysis.

A recently completed study from our group analyzed HLA antigen frequencies in patients with PNH who had either AA or hypoplastic MDS.12 There was significant overrepresentation of DR2 with the PNH abnormality, and DR2 was found to predict response to immunosuppressive treatment in these patients, supporting the possibility that the PNH defect was the determinant of treatment response. However, the group was ethnically disparate and we had to extrapolate differences in DR2 frequency from a mixed control population. Furthermore, we did not define whether the association was with HLA-DR2 or more precisely with its molecular counterpart DR15. The current study represents a larger patient cohort and actual controls restricted to a North American white population. We extend the earlier observation that HLA-DR2 frequency is increased in PNH with AA and MDS. However, we found PNH was not an independent predictive variable for response to immunosuppression, but rather HLA-DR15 was the most relevant marker of immunopathophysiology. This would also explain why other possible correlates of an immunopathophysiology—

### Table 3. Pretreatment variables associated with a response to immunosuppression in NIH MDS patients (all ethnicities)

<table>
<thead>
<tr>
<th>Favorable factors (n = patients with feature/informative patients)</th>
<th>Significance in univariate analysis, *P</th>
<th>Significance in multivariate analysis, backward selection, †P</th>
<th>Adjusted odds ratio in logistic regression‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for HLA-DR15 (n = 29 of 77)</td>
<td>.003</td>
<td>.008</td>
<td>8.53 times more likely to respond if positive for DR15 (95% CI 1.59-45.66)</td>
</tr>
<tr>
<td>Shorter duration of red cell transfusion dependence</td>
<td>.009</td>
<td>.023</td>
<td>1.56 times more likely to respond for each 90-d decrease in duration (95% CI 1.08-2.25)</td>
</tr>
<tr>
<td>Younger age (n = 82, continuous variable, mean ± SD = 59 ± 29.9 y)</td>
<td>.0002</td>
<td>.001</td>
<td>2.18 times more likely to respond for each 5-y decrease in age (95% CI 1.36-3.48)</td>
</tr>
<tr>
<td>Less than 5% marrow blasts (n = 60 of 82)</td>
<td>.06</td>
<td>.834</td>
<td></td>
</tr>
<tr>
<td>Normal cytogenetics (n = 53 of 82)</td>
<td>.077</td>
<td>.473</td>
<td></td>
</tr>
<tr>
<td>Increased no. of cytopenias (n = 38 of 82)</td>
<td>.033</td>
<td>.321</td>
<td></td>
</tr>
<tr>
<td>Decreased bone marrow cellularity (n = 20 of 82)</td>
<td>.076</td>
<td>.145</td>
<td></td>
</tr>
<tr>
<td>Low IPSS score§ (n = 68 of 82)</td>
<td>.12</td>
<td>.120</td>
<td></td>
</tr>
<tr>
<td>PNH present by flow (n = 8 of 77)</td>
<td>.0002</td>
<td>.136</td>
<td></td>
</tr>
</tbody>
</table>

*P values (the last 6 rows) derived from the Wald χ² test during backward selection for a logistic regression model that initially included all the variables based on 69 informative patients and, also, P values of the first 3 rows from the multivariate analysis. †Adjusted odds ratio derived from logistic regression model including only the first 3 variables based on 74 informative patients. §Low IPSS score is IPSS low risk and intermediate-1.

95% CI indicates 95% confidence intervals.
for example, hypoplastic bone marrow—correlated with response to
immunosuppression in univariate analyses but not in multivariate
analyses including DR15. Together, our data suggest a shared immune
mechanism in the cytopenia of MDS RA, PNH, and AA.

The reason for the association of HLA-DR15 and DR2 with bone
marrow failure syndromes is not known. We speculate that specific
HLA molecules may efficiently present a bone marrow cell–
derived antigen, causing marrow failure by an autoimmune process.
Alternatively, HLA expression might be a surrogate for a particular
cytokine profile: HLA-DR2 is associated with decreased spontaneous
tumor necrosis factor-α production but increased release after inter-
feron-γ priming.3,14 Overexpression of tumor necrosis factor-α has
been reported both in AA and MDS and has been proposed to be linked
to the etiology of the cytopenia in these conditions.2,3,35

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