

Daratumumab in combination with proteasome inhibitors, rapidly decreases polyclonal immunoglobulins and increases infection risk among relapsed multiple myeloma patients: a single center retrospective study

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Abstract

Background: Daratumumab (Dara) is generally well tolerated, but is associated with increased risk of infection.

Methods: We investigated hypogammaglobinemia occurrence in different Dara-based regimens. Multiple myeloma (MM) patients were treated with ≥ 2 cycles of Dara-based therapy during 2016–2020, mainly for relapsed/refractory disease. Data on patient characteristics, treatment regimens, polyclonal IgG (poly-IgG) and uninvolved free light chain (Un-FLC) levels during treatment, as well as predictors for hypogammaglobinemia and predictors for infections, were evaluated retrospectively.

Results: A total of 84 patients, median age 67.2 years, were included. Dara, mainly as ≥ 2 line therapy (88.1%, $n=74$), was combined with immunomodulating drugs (IMiDs) (53%), proteasome inhibitors (PIs) (15%), IMiDs-PIs (11%), or dexamethasone only (21%). Median treatment duration was 13 months. Median Poly-IgG levels at 0, 2, and 4 months were 7.1 g/L, 4.5 g/L, and 4 g/L, respectively, and remained low throughout treatment. Lower poly-IgG pre-Dara ($p=0.001$) and Dara-PIs (\pm IMiDs) regimen were associated with lower poly-IgG levels at 4 months ($p=0.03$). Only patients treated with Dara monotherapy had partial immune reconstitution, reflected by resumption of IgM levels. Most (85%) patients developed ≥ 1 infections, mostly grade 1–2 respiratory (76%). A lower poly-IgG level post Dara (RR = 1.137 $p=0.026$) predicted increased risk of any infection. Intravenous immunoglobulin (IVIG) was associated with a significant decrease in all infections.

Conclusion: Relapsed MM patients treated with Dara, often experience persistent hypogammaglobinemia, irrespective of responsiveness to treatment. Infections, especially respiratory, are frequent and apparently related to low Poly-IgG levels. IVIG should be considered for reducing infections in these patients.

Keywords: daratumumab, hypogammaglobinemia, infections, IVIG, multiple myeloma

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Introduction

Daratumumab (Dara) has become a major player in treating patients with relapsed/refractory (RR) multiple myeloma (MM), providing high response rates and long-term progression free survival (PFS) and overall survival (OS) as a monotherapy and especially when administered in combination with immunomodulating drugs (IMiDs) (Sirius Trial, Pollux Trial) or proteasome inhibitors (PIs) (Castor Trial, Candor Trial).¹⁻⁴ Recent studies also confirmed its role in newly diagnosed patients who were treated with Dara in combination with chemotherapy (Alcyone Trial),⁵ IMiDs (Maia Trial),⁶ or IMiDs + PIs (Cassiopeia Trial, Griffin Trial, Manhattan Trial).⁷⁻⁹ Although generally well tolerated, treatment with Dara appears to be associated with an increased risk of infections, with no clear cut evidence for higher rates of infections in patients treated at relapse *versus* those treated at diagnosis.²⁻⁸ Upper respiratory tract infections were observed in 25–63% of patients who were treated with Dara-based combinations, compared with 14–44% in patients treated in the control arms, which were comprised of Dara free regimens.²⁻⁸ (Supplemental Table S1 lists infections reported in prospective studies that evaluated the addition of Dara to PIs/IMiDs or IMiDs-PIs in newly diagnosed and in RRMM patients).²⁻⁸ Grade 3 neutropenia was reported in 9–51.9% of patients treated with Dara-based therapy,¹⁻⁸ but it was not associated with a significant risk for neutropenic infections.^{2,3,6-8} Immune suppression associated with Dara and leading to multiple infections may be due to the suppression of normal plasma cells, resulting in clinically significant hypogammaglobulinemia.¹⁰ The current study assessed the rate, dynamics, and severity of hypogammaglobulinemia in MM patients treated with Dara-based therapy, mostly for RR disease, by evaluating polyclonal-IgG (poly-IgG) and uninvolved free light chain (un-FLC) levels over time. We investigated the infection rate, the risk factors for infection, and the role of intravenous immunoglobulin (IVIG) treatment in patients receiving different Dara-based regimens.

Methods

The study was conducted in accordance with the declaration of Helsinki and approved by our center's institutional review board (approval number 0371-18), which waived informed consent for

this retrospective analysis. The myeloma database at the Tel Aviv Sourasky Medical Center was searched for all patients that had been treated with Dara-based therapy at diagnosis or at relapse between 2016 and 2020. Patients who failed to complete two full cycles of Dara-containing regimens (compatible with eight doses of Dara) were considered to be unsuitable for the assessment of Dara's impact on the development of hypogammaglobulinemia and treatment-related infections and were, therefore, excluded from the analysis. Data were collected from the patient's files, and those on patient demographics, MM characteristics at diagnosis, treatment at diagnosis and at subsequent relapses, details on Dara-based regimens, and response to therapy, were retrieved and evaluated according to the International Myeloma Working Group (IMWG) criteria.¹¹ Additionally, poly-IgG levels (measured as detailed below), reciprocal immunoglobulin levels (IgA in patients with IgG myeloma and IgM in all patients) and un-FLC levels; FLC-Kappa in patients with FLC-Lambda MM and FLC-Lambda in patients with FLC-Kappa excreting disease, evaluated before and every 2 months during Dara-based therapy, were recorded.

Details on the infections documented in the patients' medical charts during treatment, including neutropenic and non-neutropenic infections, anti-infectious prophylaxis, and administration of IVIG were recorded. According to the department's policy, IVIG was generally given to patients with recurrent infections in the presence of poly-IgG levels lower than 600 mg/dl and was administered every 3–4 weeks, at a dose of 0.3–0.5 g/kg. Factors associated with hypogammaglobulinemia and its reversal over time, as well as factors predicting a higher risk for infections were identified and evaluated. The article was performed by following the STROBE statement checklist

Evaluation of immunoglobulins and FLC levels

Monoclonal fraction (M spike) was determined by serum protein electrophoresis (SPE) on the Hydrasys 2 Scan (Sebia, France) instrument, and subtracted from the specific total immunoglobulin (IgG or IgA). Quantitative immunoglobulin concentrations (IgG, IgM, and IgA) were determined by nephelometry-based assay (N antisera, Siemens Healthcare GmbH, Erlangen, Germany)

on BNII nephelometer (Siemens Healthcare GmbH, Erlangen, Germany). A poly-IgG level referred to the total IgG level as measured by serum protein electrophoresis in patients with non-IgG MM, and to the non-monoclonal IgG level, as measured in patients with IgG MM, by subtracting the M protein level from the total IgG level. Hypogammaglobinemia was determined in the presence of a poly-IgG level lower than the lowest normal range (768 mg/dl). Free light chain assays were performed by the FreeLite assay (The Binding Site Group, Birmingham, UK) on BNII nephelometer (Siemens Healthcare GmbH, Erlangen, Germany).

Definitions

High *versus* standard risk disease was defined in the presence of an adverse fluorescence *in situ* hybridization result, including t(4;14), t(14;16), t(14;20), 17p13 del, and/or 1q21 gain, fulfilling the international myeloma criteria.¹¹ Treatment regimens were classified into four categories: (1) Dara-PIs: Dara administered in combination with dexamethasone and PIs (carfilzomib, bortezomib, or ixazomib); (2) Dara-IMiDs: Dara administered in combination with dexamethasone and IMiDs (lenalidomide, or thalidomide, or pomalidomide); (3) Dara-PIs-IMiDs: Dara administered with dexamethasone, PIs, and IMiDs; (4) Dara monotherapy: Dara administered with dexamethasone only.

An infection was defined by clear documentation of an infectious event in the patient's medical chart, and/or if a new anti-infection therapy had been initiated. Infections were classified into bacterial, viral, fungal, and pneumocystis jiroveci pneumonia (PJP). Bacterial infection was determined whenever an antibiotic was prescribed based on a positive sputum, urine, or blood culture result, a chest X-ray or a computerized tomography (CT) scan demonstrating lobar pneumonia, or based on the clinical judgment of the treating physician. Herpes simplex virus, cytomegalovirus, varicella-zoster virus, and PJP were determined by the presence of a positive polymerase chain reaction (PCR) test of a specimen from a bronchoalveolar lavage or from another source (e.g., skin vesicle). A fungal infection was defined by the presence of typical findings in a chest CT scan, in the presence of a positive galactomannan test, and/or a positive

fungal culture or stain, or proven candidemia. A viral respiratory infection was defined by the presence of a positive test for a viral respiratory pathogen or by the presence of acute respiratory symptoms with/without fever that resolved without antibiotics. Recurrent infections were determined in the presence of ≥ 2 documented infections within ≤ 3 months.

Statistics

IBM SPSS Statistics for Windows, Version 25.0, 2017 (IBM Corp., Armonk, NY, USA) was applied for the following statistical analysis, and significance was determined at $p < 0.05$. The Kruskal–Wallis test was applied to examine differences in median values between the four types of treatment groups. The Mann–Whitney test was applied to study the difference in median values between two groups. Considering the same type of treatment group across time, Friedman's Q test was applied to examine differences in median values between at least three time points, and the Wilcoxon signed-rank test was applied to examine differences in median values between two time points. Pearson's Chi-square and Fisher's exact tests were applied to examine the association between categorical variables and the four types of treatment groups. For OS and PFS, the time variable was calculated since Dara initiation until the date of an event (progression or death), or until the last date of follow up for non-event. Both OS and PFS were examined by the Kaplan–Meier estimator test and Spearman's correlation coefficient was used to evaluate the association between poly-IgG level (as a continuous variable) and continuous variables. A multivariable linear regression was used to study the association between poly-IgG levels and variables that were significantly associated in the univariate analysis. Poly-IgG levels were presented in a natural logarithm that was transformed in order to meet the regression assumptions. Univariate and multivariable Poisson regressions were used to study the association between the number of any infections or respiratory infections and various predictors. The calculation of accumulated total and respiratory infections was as follows: for each particular time interval and for a given type of treatment group, the total and respiratory infection rates, represented by the number of infections in a certain time interval divided by the total number of patients that were still followed at that

certain time interval, multiplied by 100, were determined. Poisson model was used to compare the rates of infectious events before and after IVIG administration. WINPEPI for Windows, Version 11.65 (23 August 2016) was applied to examine the difference between two infection rates (with person-time denominators), accompanied by 95% confidence interval (CI), which is considered as being significant when it does not include zero.

Results

Patient characteristics and treatment regimens

A total of 113 suitable patients were identified in the multiple myeloma database; 29 patients who had received <2 cycles of Dara-based therapy (having experienced disease progression) were excluded. Thus, 84 patients fulfilling the study criteria were included. Patient characteristics are presented in Table 1; 40% ($n=34$) were females. Median age at diagnosis and at Dara initiation was 67.2 and 70.4 years, respectively. A total of 50 patients (60%) had IgG MM, 14 (16%) had IgA MM, and 19 (22%) had light-chain MM (LC MM). Most patients (88%, $n=74$) received a Dara-based regimen for RR disease. The median time from diagnosis to Dara initiation was 24.2 months, and the median number of prior lines was 1 (range 0–5). High-risk cytogenetics was recorded in 34% and International Staging System (ISS) 3 was documented in 46%. Dara was administered in combination with dexamethasone and PIs in 15% ($n=13$), in combination with dexamethasone and IMiDs in 53% ($n=44$), in combination with both PIs and IMiDs in 11% ($n=9$) and with dexamethasone only in 21% ($n=18$). Treatment details are presented in Table 1. Upfront autologous hematopoietic stem cell transplantation (auto HCT) was performed in 46% ($n=39$). Prophylaxis with acyclovir (400 mg/day) was administered in 98% of the patients ($n=82$) and with trimethoprim/sulfamethoxazole (two tablets twice a day, twice a week) in 85% ($n=72$). The median duration of treatment until treatment cessation or until the last follow-up date was 13 months (range 0.8–35.0). As non-responders were excluded, the overall response rate was 100%, including 77% \geq very good partial responses and 18% partial responses. The median PFS was not reached. A total of 19 patients discontinued treatment, all due to progressive

disease, and no patient discontinued therapy due to adverse effects. There were no statistically significant differences between the characteristics of patients that were treated with Dara + IMiDs, Dara + PIs, Dara + PIs + IMiDs, and Dara monotherapy, in terms of age, sex, cytogenetic risk groups, ISS, and median duration of exposure to Dara-based therapy. However, the patients who were treated with Dara monotherapy were more heavily pretreated ($p=0.001$), and the patients who received Dara + PIs or Dara + IMiDs + PIs had a shorter period from diagnosis to initiation of the Dara regimen ($p=0.014$). Table 1 presents the characteristics of patients treated with each of these Dara-based combinations.

Immunoglobulins and free light chains levels following treatment

The median poly-IgG level prior to Dara administration was 7.1 g/l (interquartile range 4.7–10.3). Lower poly-IgG levels at Dara initiation were observed in patients diagnosed with LC MM ($p=0.049$) and in those treated with Dara within a shorter period since diagnosis ($p=0.004$). Supplemental Table S2A and Table 2 present the univariate and multivariate analyses for factors associated with lower poly-IgG levels at Dara initiation. The median poly-IgG level declined by 47% to 4.5 g/l at 2 months, reaching 4.1 g/l at 4 months, 4.2 g/l at 6 months, and 4 g/l at 12 months (Figure 1a). A univariate analysis identified older age at diagnosis ($p=0.049$), low poly-IgG level prior to Dara administration ($p=0.001$), and the administration of Dara in combination with PIs with and without the addition of IMiDs ($p=0.001$ and $p=0.049$, respectively) as being associated with lower poly-IgG levels at 4 months since treatment initiation (Supplemental Table S2B). Of note, there were no differences in the degree of reduction or in absolute levels of poly IgG levels measured at 2 and 4 months since Dara initiation between patients treated with Dara + PIs compared with those treated with Dara + PIs + IMiDs. A multivariate analysis (Table 3) confirmed a low poly-IgG level prior therapy ($p=0.001$) and the administration of a Dara + PIs regimen (with/without IMiDs) ($p=0.044$) as being associated with significantly lower Poly-IgG levels at 4 months since the initiation of therapy (Figure 2a). Un-FLC levels also decreased rapidly and remained relatively low over time (Figure 1b). Un-FLC levels, measured at

Table 1. Patient characteristics (general and according to Dara-based combinations).

Patients characteristics		Dara monotherapy	Dara-PIs	Dara-IMiDs	Dara-IMiDs-PIs	<i>p</i> value ^a
N=84		n=18 (21.4%)	n=13 (15.5%)	n=44 (52.4%)	n=9 (10.7%)	
Age at diagnosis (years) median (range)	67.2 (41–91)	73.0 (46.2–91.3)	65.4 (45.8–81.8)	65.8 (41.2–89.5)	68.8 (53.1–84.4)	0.126
Age at Dara initiation (years) median (range)	70.4 (45.8–93.3)	75.8 (51.8–93.3)	68.2 (54.6–81.8)	69.1 (45.8–90.5)	67.8 (57.4–85.2)	0.079
Sex – males (%)	51 (60.7)	11 (61.1)	8 (61.5)	28 (63.7)	4 (44.4)	0.801
Heavy chain MM (%)	65 (77.4)	13 (72.2)	9 (69.2)	35 (79.5)	8 (88.9)	0.700
IgG	50 (59.5)	11 (61.1)	6 (46.1)	26 (59.1)	7 (77.8)	
Non IgG	15 (17.9)	2 (11.1)	3 (23.1)	9 (20.5)	1 (11.1)	
FLC type Kappa	52 (61.9)	12 (66.7)	8 (61.5)	24 (54.5)	8 (88.8)	0.325
Lambda	31 (36.9)	6 (33.3)	5 (38.5)	19 (43.2)	1 (11.1)	
Cytogenetic risk (%)						
High risk	29 (34.5)	3 (16.7)	5 (38.5)	16 (36.4)	5 (55.6)	0.534
Standard risk	37 (44.0)	11 (61.1)	5 (38.5)	19 (43.2)	2 (22.2)	
Not available	18 (21.4)	4 (22.2)	3 (23.1)	9 (20.5)	2 (22.2)	
ISS (%)	47 (56.0)	8 (44)	8 (61)	26 (59)	5 (55)	0.891
1	17 (20.2)	2 (11.1)	4 (30.7)	9 (20.5)	2 (22.2)	
2	8 (9.5)	1 (5.6)	2 (15.4)	4 (9.1)	1 (11.1)	
3	22 (26.2)	5 (27.8)	2 (15.4)	13 (29.5)	2 (22.2)	
Number of lines prior Dara, median (range)	1 (0–5)	3	1	1	1	0.001
Refractory or relapsed patients	74 (88.1%)	18 (100)	7 (53.8)	43 (97.7)	6 (66.7)	<0.001
AutoHCT prior Dara	39 (46.4)	8 (44.4)	3 (23.1)	25 (26.8)	3 (33.3)	0.143
Time from diagnosis to Dara (months), median(range)	24.2 (0.1–297)	31.9 (11.3–98.9)	4.9 (0.1–196.4)	24.2 (0.3–297.2)	10.4 (0.3–72.0)	0.014
Dara duration (months) median(range)	11 (3–35)	11.9 (0.8–34.9)	17.4 (5.9–26.9)	10.7 (3.4–35.0)	9.7 (2.8–15.4)	0.184
Prophylaxis						
TRM/SUL (%)	72 (85.7)	10 (55.6)	13 (100)	40 (90.9)	9 (100)	0.001
Acyclovir (%)	82 (97.6)	16 (88.9)	13 (100)	44 (100)	9 (100)	0.077
Hematologic response						
CR (%)	18 (21.4)	1 (5.6)	5 (38.5)	10 (22.7)	2 (22.2)	0.613
VGPR (%)	47 (56.0)	12 (66.7)	8 (61.1)	24 (54.5)	3 (33.3)	
PR/SD (%)	19 (22.6)	5 (27.7)	0	10 (22.7)	4 (44.5)	

^aStatistical analysis performed as described in the Statistics section in Methods to determine significant differences between the four types of treatment groups.

AutoHCT, autologous hematopoietic stem cell transplantation; CR, complete response; Dara, daratumumab; FLC, free light chain; IgG, immunoglobulin G; IMiDs, immunomodulating drugs; ISS, international staging system; PD, progression of disease; PFS, progression free survival; PIs, proteasome inhibitors; PR, partial response; SD, stable disease; TRM/SUL, trimethoprim/sulfamethoxazole; VGPR, very good partial response.

Table 2. Multivariate analysis for factors associated with lower poly IgG levels prior initiation of Dara.

Variable	Percent	95% CI	p Value
MM type: LCMM versus HCMM	-38.6 ^a	-4.7 -83.5	0.023
Time from diagnosis to Dara ≤12 months	-37.3 ^a	-0.9 -86.9	0.043

^aThe degree of reduction in Poly IgG levels, presented by percentages. CI, confidence interval; Dara, daratumumab; HCMM, heavy chain MM; LCMM, light chain MM; MM, multiple myeloma; poly IgG, polyclonal IgG.

4 months since treatment initiation, were significantly lower in patients who received Dara + PIs containing regimens compared with those who received other Dara-based combinations ($p=0.019$) for MM-Kappa patients (Figure 2b), and ($p=0.004$) for MM-Lambda patients, with no significant differences between patients treated with Dara + PIs or Dara-PIs-IMiDs (Figure 2c). The achievement of a marked clinical response was not associated with reconstitution of poly-IgG and un-FLC levels. Reciprocal immunoglobulin median levels at Dara initiation, referring to IgA for 50 IgG MM patients and IgM for all 84 patients, were 0.4 g/l and 0.21 g/l, respectively. Both globulins declined markedly following Dara administration: IgA decreased to 0.26 g/l at 2 and 4 months and IgM decreased to 0.18 g/l at 2 and 4 months. In contrast, the IgA levels remained low continuously, irrespective of treatment type or response to treatment, whereas the IgM levels gradually increased in patients treated with Dara monotherapy but remained low in patients treated with Dara + PIs ±vIMiDs and Dara + IMiDs (Figure 2d).

Infections following treatment

A total of 72 (85%) patients had at least one documented infection during their Dara-based treatment. The median time to first infection was 2 months; 22% of the patients ($n=19$) had ≥ grade 3 infections, including 8% ($n=7$) who developed neutropenic infections. An antibiotic was prescribed in 49% ($n=41$). None of the infectious episodes were fatal. Table 4 presents the types of infection for the entire cohort and according to treatment type. There was a median of two documented infections per patient (range 0–6), and the infection rate was 2.5 per year (0.2 per month). The cumulative risk of infection at 2, 4, 6, and 12 months was 0.5, 0.8, 1.2, and 2.5 percent, respectively (Figure 3a). A univariate analysis found high-risk cytogenetics ($p=0.01$), Dara + PIs ($p=0.04$), Dara + PIs + IMiDs ($p=0.01$), and low poly-IgG ($p=0.02$) measured at 2 months post-Dara initiation, to be associated with increased risk of infection (Table S3A, supplemental file). A multivariate analyses confirmed high-risk cytogenetics (relative risk = 1.53, $p=0.018$) and lower poly-IgG levels at 2 months post-Dara initiation (relative risk = 1.15, $p=0.026$) to be the most predictive factors for an

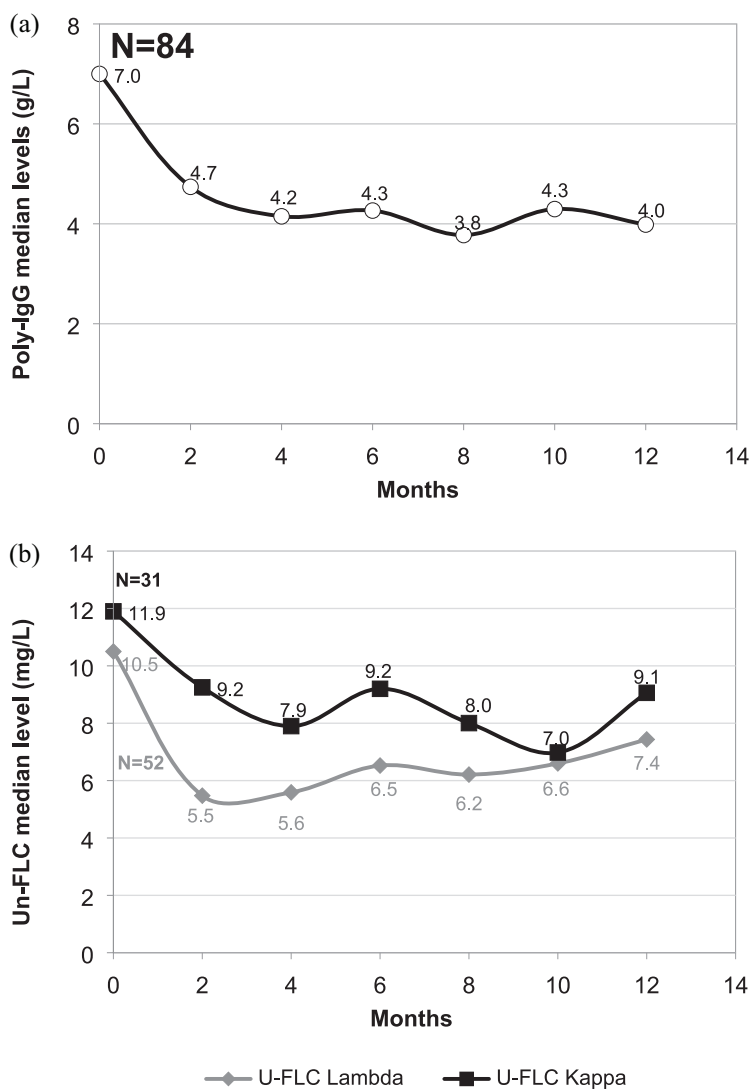


Figure 1. Median poly-IgG (a) and un-FLC (b) levels following Dara initiation (independent on treatment type). Dara, daratumumab; n, number of patients at initiation time (time = 0); poly-IgG, polyclonal IgG; un-FLC, uninvolved free light chain.

increased infection rate (Table 5). Of all documented infections, 76% ($n=122$) were respiratory. A univariate analysis revealed lower poly-IgG levels that were measured at 2 ($p=0.014$) and 4 months ($p=0.008$) since Dara initiation and treatment with Dara-PIs ($p=0.04$) or Dara + PIs + IMiDs ($p=0.018$) as being associated with increased risk for respiratory infections (Supplemental Table S3B and Figure 3b). A multivariate analysis confirmed that treatment with Dara + PIs + IMiDs (relative risk=1.642, $p=0.048$) and lower poly-IgG levels at 2 months since Dara initiation (relative risk=0.89, $p=0.029$) were associated with an increased rate of treatment-related respiratory infections (Table 6).

Impact of IVIG therapy on rate and severity of infections

In all, 16% ($n=14$) of the patients received IVIG therapy. The median time to IVIG administration was 9 months following the initiation of Dara (range 2–21 months), and IVIG was given for a median period of 6.2 months (range 2–13). The indication for IVIG administration in 86% of patients ($n=12$) was recurrent infections in the presence of a decreased poly-IgG level (median 3.34 g/l, range: 1.8–6 g/l). In 14% ($n=2$), IVIG was started due to a low poly-IgG levels of 2.6 g/l and 3 g/l, respectively. The administration of IVIG resulted in a significant decrease in total infection rate [relative risk=0.344, 95% confidence interval (CI) 0.163–0.724, $p=0.005$] and respiratory infection rate (relative risk=0.274, 95% CI 0.126–0.0595, $p=0.001$). Figure 4 shows the decrease in cumulative infections rate after IVIG administration. No grade ≥ 3 infections were reported following the initiation of IVIG. There were no adverse events reported due to IVIG administration.

Discussion

Dara has emerged as one of the most potent therapeutic agents in the treatment of MM. Its administration in combination with IMiDs and/or PIs was shown to significantly improve the outcome of newly diagnosed and RR MM patients, providing stronger and longer-lasting responses compared with IMiDs/PIs Dara-free based regimens^{1–8,12} Moreover, Dara in combination with PIs + IMiDs^{7,13} was shown to provide the best minimal residual negativity rates ever reported,

Table 3. Multivariate analysis for factors associated with lower poly IgG levels at 4 months post Dara initiation.

Variable	Percent	95% CI	p value	
Dara + PIs ± IMiDs versus Dara + IMiDs/Dara mono	-18.7 ^a	-0.52	-32.6	0.044
Poly-IgG level prior Dara	0.28 ^b	0.12	0.44	0.001

^aThe degree of reduction in Poly IgG levels, presented by percentages.
^bA higher level of Poly IgG of 1% prior Dara, predicted a higher level of Poly IgG level (of 0.28%) at 4 months post Dara.
 CI, confidence interval; Dara, daratumumab; IMiDs, immunomodulating drugs; mono, monotherapy; PIs, proteasome inhibitors; poly-IgG, polyclonal IgG.

supporting the expanding employment of this new combination in newly diagnosed MM patients. However, treatment with Dara in patients with RR disease was shown to be followed rapidly by a steep decrease in un-FLC and immunoglobulin levels caused by its depleting effect on non-malignant plasma cells.^{10,14} In our cohort, including patients mostly with RRMM, we observed that un-FLC and poly-IgG levels reached their nadir within 2–4 months, and that those levels remained low irrespective of the patient's responsiveness to treatment. Our observation is in line with data presented by Frerichs *et al.*,¹⁰ who reported a rapid decline in poly-IgG levels in RRMM patients who were receiving Dara monotherapy, together with the achievement of sustainably low poly-IgG levels, reflecting a residual proportion of normal plasma cells that “downregulated” CD38 on their cell surface. According to our data, the greatest immunoparesis observed following Dara was detected in patients who presented with the lower poly-IgG levels at the initiation of Dara treatment, as well as in those treated with Dara + PIs/Dara + PIs + IMiDs. Indeed, patients in the Dara-PIs cohort (treated or untreated with additional IMiDs) had lower poly-IgG levels prior to Dara administration compared with their Dara + IMiDs counterparts. This finding is either incidental or reflects the differences between patients treated with Dara + PIs and those treated with a Dara + IMiDs/Dara monotherapy-based regimen. Despite the fact that both Dara + PIs and Dara + IMiDs were used mainly as second-line treatment, time from diagnosis to Dara administration was significantly shorter among patients treated with Dara + PIs, suggesting that the marked pre-Dara immunoparesis observed in these patients, was an indication of their refractoriness to

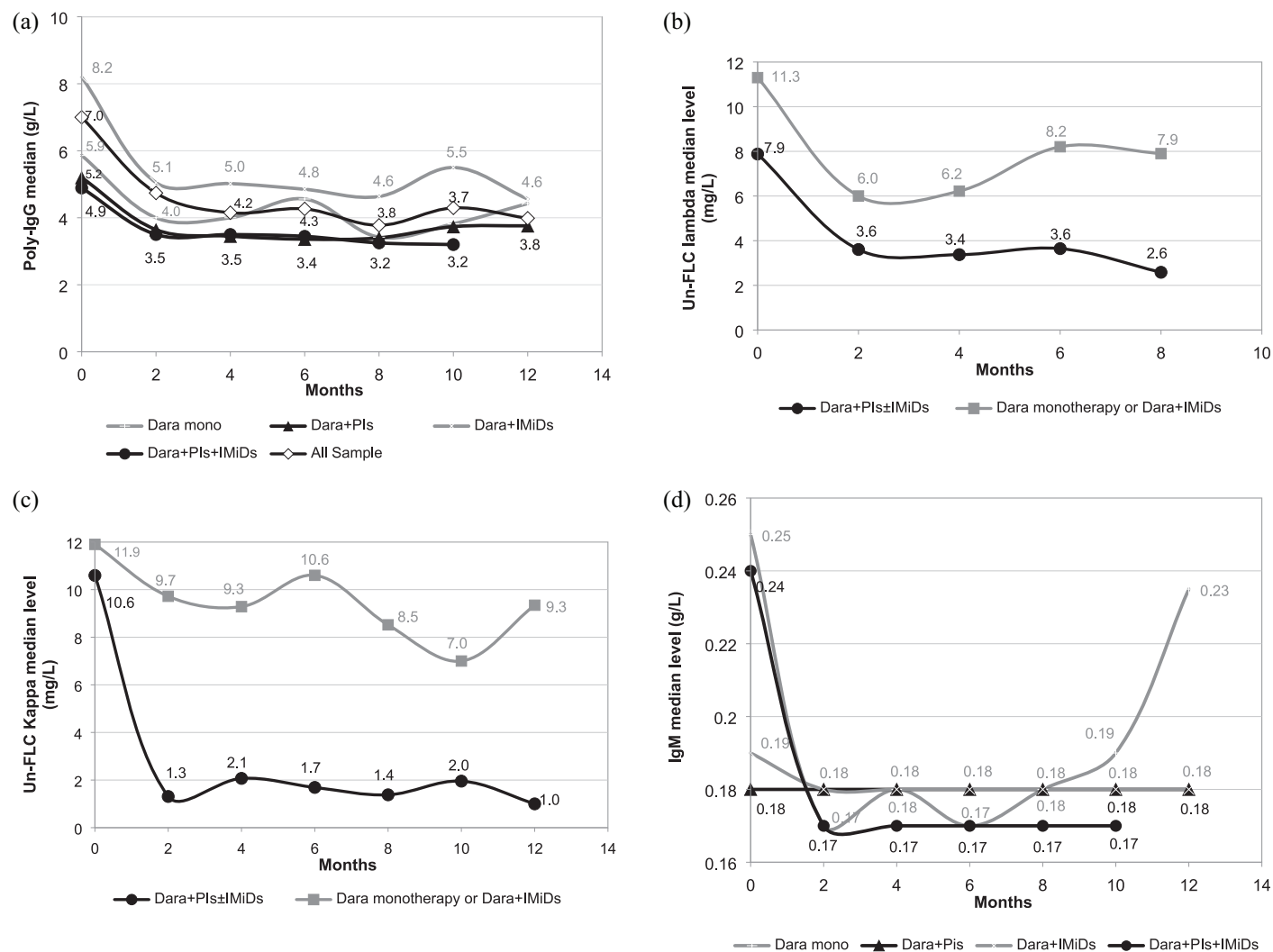


Figure 2. Median levels of poly-IgG (a), un-FLC lambda (b), un-FLC Kappa (c), and IgM (d), following Dara initiation, dependent on treatment type. There were no statistically significant differences in poly IgG and un-FLC levels between Dara + PIs *versus* Dara + IMiDs + PIs patients. (d) There were no statistically significant differences in IgM levels between the four treatment groups in general and pairwise, and there were no significant trends in IgM levels among Dara monotherapy patients across time. Dara, daratumumab; FLC-K-MM, free light chain kappa multiple myeloma; FLC-L-MM, free light chain lambda multiple myeloma; IMiDs, immunomodulating drugs; Mono, monotherapy; PIs, proteasome inhibitors; poly-IgG, polyclonal IgG; un-FLC, uninvolved free light chain.

first-line treatment, requiring an early employment of a second-line Dara-based treatment. Nevertheless, the Dara + PIs-containing regimen was independently associated with greater hypogammaglobinemia than any other tested regimen, most probably due to the remarkable non-selective plasma cell-depleting effect that was induced, particularly by PIs.^{15–17} Interestingly, all of the Dara-based regimens with the exception of Dara monotherapy resulted in a sustained decline in IgM levels, whereas Dara monotherapy was associated with a gradual recovery in IgM levels. That observation was recently reported by Frerichs

et al., who investigated patients who were solely receiving Dara monotherapy.¹⁰ Those authors proposed that response indicated a preserved differentiation of B cells into plasma cells during Dara treatment.¹⁰ Infections appear to be one of the most common adverse events among Dara-treated patients, having been reported in 86% of patients treated with Dara + RD in the Maia Trial,⁶ 65% with Dara + VTD (Cassiopeia),⁷ and 91% with Dara + VRD (Griffin),⁸ higher than reported in the Dara-free comparable cohorts. A higher incidence of infections was also demonstrated in patients treated with Dara based triplets for RR disease

Table 4. Type and sites of infections dependent on treatment type.

Infections presented by pathogen					
Treatment combination	Dara monotherapy	Dara + IMiDs	Dara + PIs	Dara + PIs + IMiDs	All regimens
	N= 18 (%)	N= 44 (%)	N= 13 (%)	N= 9 (%)	(N= 84) (%)
Viral	13 (39.4)	35 (46.6)	13 (44.8)	10 (43.5)	71 (43.6)
Bacterial	17 (51.5)	35 (46.6)	14 (48.3)	13 (56.5)	82 (50.3) ^a
PJP	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	1 (0.6)
Fungal	1 (3.0)	0 (0.0)	1 (3.4)	0 (0.0)	2 (1.2)
Not specified	2 (6.1)	5 (6.4)	0 (0.0)	0 (0.0)	7 (4.3)
Entire number of infectious events	33	75	29	23	160
Infections presented by sites					
Respiratory	23 (69.7)	58 (77.3)	24 (82.8)	17 (73.9)	122 (76.3)
GI	2 (6.1)	6 (8.0)	0 (0.0)	2 (8.7)	10 (6.3)
GU	6 (18.2)	5 (6.7)	1 (3.4)	0 (0.0)	12 (7.5)
SSTI	1 (3.0)	2 (2.7)	2 (6.9)	2 (8.7)	7 (4.4)
Other	1 (3.0)	4 (5.3)	2 (6.9)	2 (8.7)	9 (5.6)
Total	33	75	29	23	160

^a50.3% bacterial events, involving 49% of patients, were reported.
Dara, daratumumab; IMiDs, immunomodulating drugs; GI, gastrointestinal; GU, gynecological; PJP, pneumocystis jiroveci pneumonia; PIs, proteasome inhibitors; SSTI, skin soft tissue.

(Pollux, Castor, and Candor trials) (Table S1).²⁻⁴ Van de donk *et al.* pooled 710 newly diagnosed MM patients treated with Dara through the Alcyone and Maia studies, and identified age ≥ 75 years, elevated baseline alanine aminotransferase ALT, a high LDH and albumin level ≤ 35 g/l (both known to predict a high risk disease), to be associated with increased risk for ≥ 3 grade infections.¹⁸ (Table S1, supplemental file, presents infections being reported in phase III, 2b studies, investigating the addition of Dara in patients with newly diagnosed or relapsed disease).²⁻⁸ Despite being reported in 9–51.9% of Dara-treated patients,¹⁻⁸ grade ≥ 3 neutropenia has rarely resulted in neutropenic infections. Contrarily, we now demonstrate that decreased poly-IgG levels and high-risk cytogenetics (potentially, being a surrogate for higher employment of PI), were both associated with higher risk of infections. In line with other studies,^{2-9,12} the infections sustained in our cohort were mainly respiratory and observed mostly

among the Dara + -VRD-treated patients. Nevertheless, most infections were only grade 1–2, as reported by others,^{2,3,6-8,12} suggesting that infections, though frequent, are unlikely to be life-threatening and are often self-resolving. The fact that most of our patients had RRMM (*versus* newly diagnosed disease) might contributed to the relatively high risk of infections observed in our study. Indeed, RRMM was shown to be associated with profound immunodeficiency,¹⁹ resulting in an increased risk of infection compared with that reported in patients with a newly diagnosed disease.^{19,20} As mentioned earlier, treatment type has also an impact on immune function; for example, PIs depletes alloreactive T cells and dexamethasone also suppresses cell-mediated immunity,^{21,22} whereas monoclonal antibodies induce a significant hypogammaglobulinemia.⁹ In line with previous publications, administration of IVIG has led to a significant reduction in infection rate.^{23,24} Despite the lack of IVIG-related adverse events in our

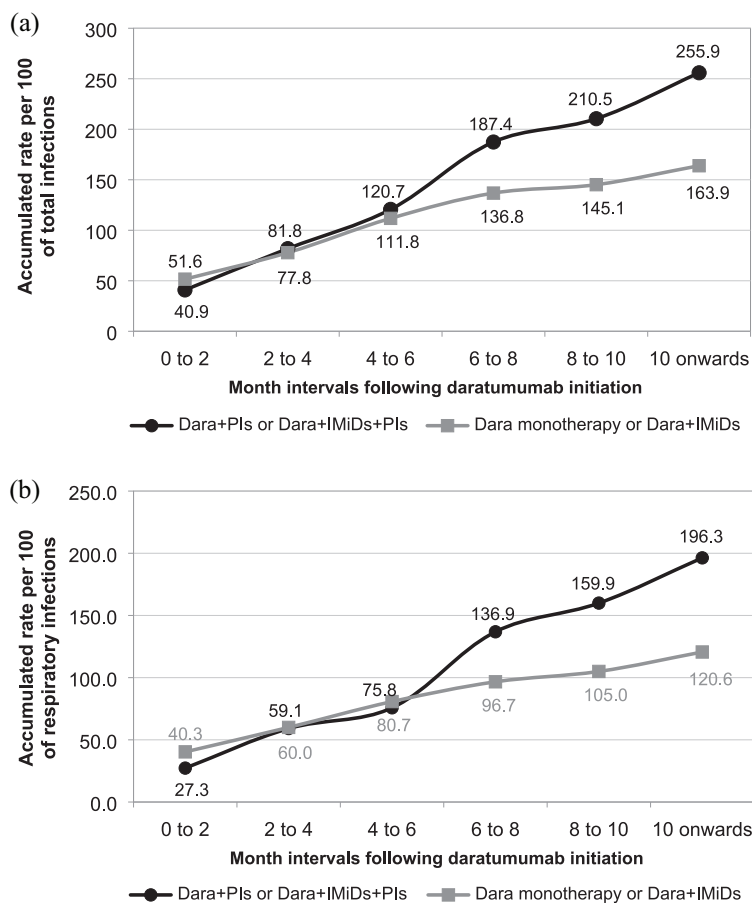


Figure 3. Accumulated rates of total (a) and respiratory (b) infections, following Dara initiation, dependent on treatment type. The infection rate in a certain month interval represents the number of infections in a certain time interval divided by the total patients that were still being followed up at that certain time interval, multiplied by 100. Each accumulated rate in a certain month interval represents the sum of the infection rate of that certain month interval with its preceding month interval’s accumulated rate of infections.
 Dara, daratumumab; IMiDs, immunomodulating drugs; PIs, proteasome inhibitors.

Table 5. Multivariate analysis for factors associated with increased risk of infections.

Infections rate				
Variable	Rate ratio	95% CI		p value
Poly-IgG levels at 2 months	0.88	0.79	0.99	0.026
Cytogenetic risk	1.53	1.08	2.19	0.018

CI, confidence interval; poly-IgG, polyclonal IgG.

series, however, the administration of IVIG might be associated with allergic reactions, acute renal failure, thrombotic events and hypertension.²⁵

Therefore, deciding upon IVIG administration should be individualized.

Our study has several limitations, mainly attributed to its retrospective nature and the limited number of patients in our cohort. Low levels of both poly-IgG and Dara + PIs were independently associated with increased risk for sustained hypogammaglobulinemia and infections, yet, patients treated with Dara-PIs already had lower poly-IgG levels prior to Dara initiation. This raises the question of whether Dara-PIs ±IMiDs is indeed a worse regimen than Dara + IMiDs in term of immunosuppression, or merely reflects greater immunosuppression among these patients prior to Dara initiation. Moreover, a physician’s decision to add PI might reflect a selection of patients with high risk disease with more aggressive features and reduced MM response, which could also contribute to their immunosuppression. Another drawback is that, despite the very careful monitoring of our patients and the availability of an “emergency room” service in our day-care unit (providing rapid investigation and management of treatment-related complications), it is likely that treatment-related infections, especially self-resolving grade 1–2 infections, were underreported. Moreover, the discrimination between viral and bacterial infections might be inaccurate, since they often relied upon clinical assessment or chest X-ray results rather than cultures. As the vast majority of patients in our cohort were RR myeloma patients, it was not possible to directly assess the effect of disease stage (newly diagnosed *versus* RR) on immunosuppression or infection rate. Finally, the retrospective design of this study precluded our ability to investigate the patient’s quality of life, which might be adversely affected by recurrent infections.²⁶

In conclusion, Dara-based therapies, especially PI-containing regimens are associated with rapid development of hypogammaglobulinemia and higher risk of infections compared with their Dara-free counterparts (Supplemental Table S1)^{2–9} at least in patients with RRMM, which accounted for the majority of our cohort. The decrease in levels of immunoglobulins occurs rapidly and is predictive of a higher risk for subsequent infections. Early introduction of IVIG appears to be useful and safe, and it should be considered for patients treated with Dara-based combinations, especially if they include PIs. The specific impact of different therapeutic regimens

and the role of prophylactic antibacterial antibiotics in patients at higher risk for infections should be further evaluated, even though most of the infections were self-limited and/or easily controlled in an outpatient setting.

Author contributions

RV and DN (equal contribution) collected data and wrote the final manuscript; SL and TZB analyzed the data; NB, ST, and MM collected data; RBY and BZK performed the laboratory tests, IA and YC collected data and reviewed and edited the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data sharing statement

The collected data is stored on our medical center's server, and it is accessible only the authors of this manuscript, in accordance with the regulations of our medical center's institutional review board.

Supplemental material

Supplemental material for this article is available online.

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Table 6. Multivariate analysis for factors associated with increased risk of respiratory infections.

Respiratory infections rate				
Variables	Rate ratio	95% CI	p value	
Poly-IgG at 2 months	0.89	0.80	0.99	0.029
Dara Pls-IMiDs versus other combinations	1.64	1.01	2.68	0.048

CI, confidence interval; Dara, daratumumab; IMiDs, immunomodulating drugs; Pls, proteasome inhibitors; poly-IgG, polyclonal IgG.

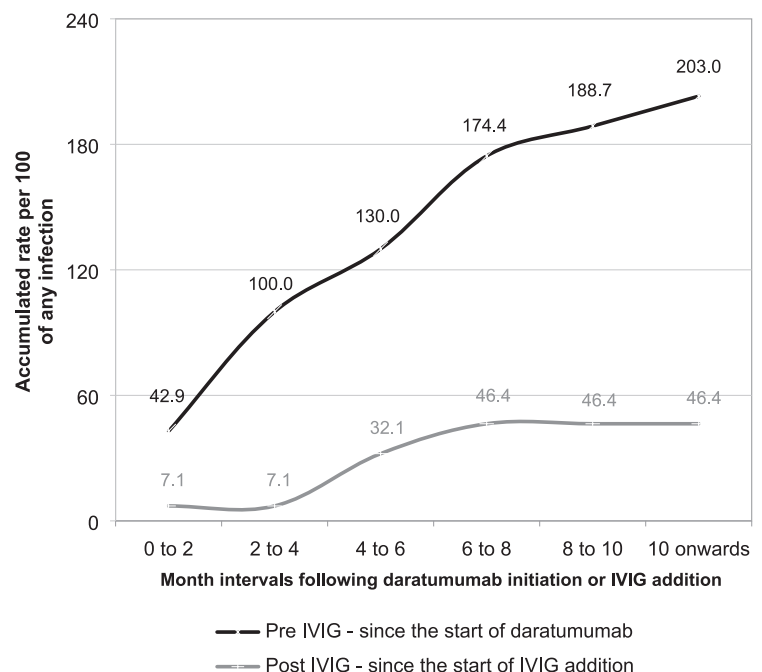


Figure 4. Pre and post IVIG administration's accumulated rates of any infection. The infection rate in a certain month interval represents the number of infections in a certain time interval divided by the total patients that were still being followed-up at that certain time period, multiplied by 100. Each accumulated rate in a certain month interval represents the sum of the infection rate of that certain month interval with its preceding month interval's accumulated rate of infections. IVIG, intravenous immunoglobulin.

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