

Safety and Efficacy of Subcutaneous Daratumumab in Systemic AL Amyloidosis

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Introduction: Systemic AL amyloidosis, a plasma cell dyscrasia, is characterized by the production of misfolded immunoglobulin light chain. These misfolded proteins aggregate into amyloid fibrils and deposit throughout the body, resulting in widespread organ dysfunction and ultimately death. Achieving rapid and maximal elimination of the plasma cell clone is crucial to long-term survival. Daratumumab, an anti-CD38 monoclonal antibody delivered intravenously, has been swiftly incorporated into standard first-line treatment regimens. A novel formulation of daratumumab has been developed that can be injected subcutaneously.

Areas Covered: As a retrospective qualitative review of prior publications involving daratumumab, this work briefly summarizes the existing data regarding the safety and efficacy of subcutaneous (SC) daratumumab, compared to intravenous (IV) daratumumab. SC daratumumab appears to deliver the same disease benefit as IV daratumumab to patients with decreased infusion-related reactions (IRRs), decreased time for administration, and similar rates of adverse events (AEs) intrinsically related to daratumumab.

Expert Opinion: SC daratumumab is preferred over IV daratumumab, but the clinical situation ultimately should determine route of administration. Further investigation into cost-effectiveness benefit is warranted.

Keywords: plasma cell dyscrasia, daratumumab, AL amyloidosis, adverse events, AE

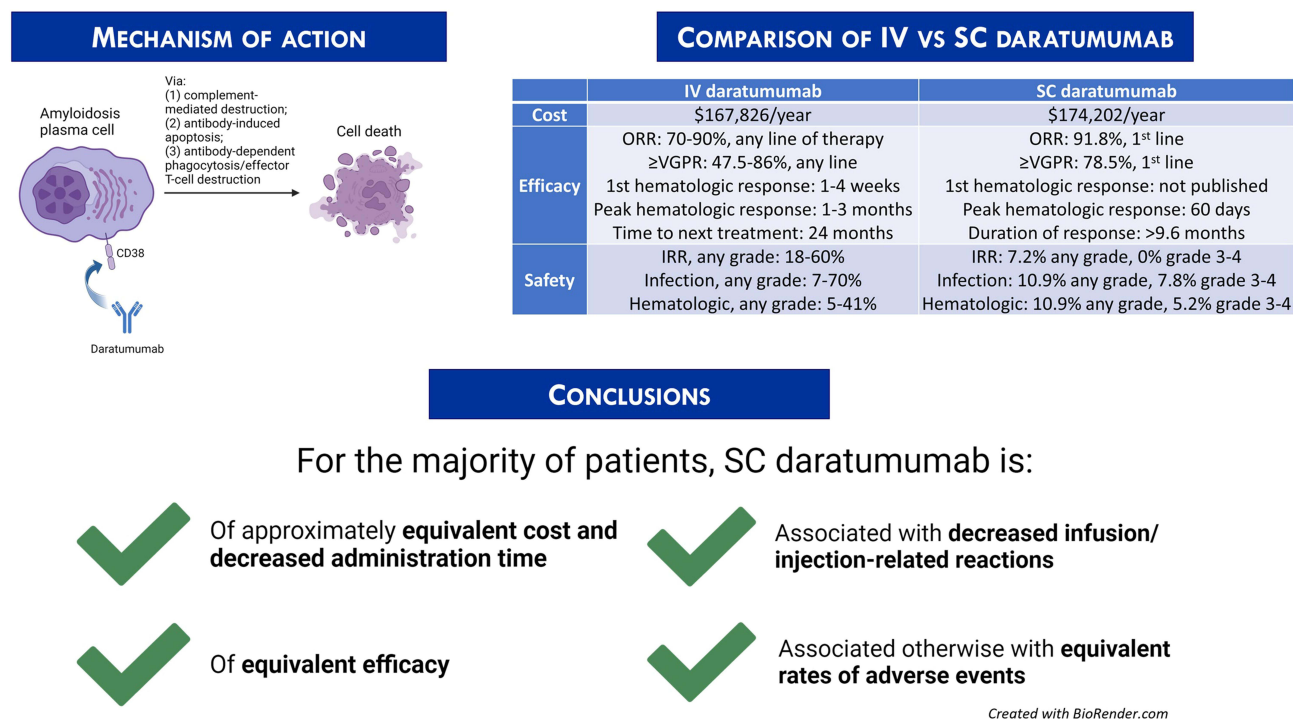
Introduction

Systemic immunoglobulin light chain (AL) amyloidosis, classified as a plasma cell dyscrasia, is comprised of a typically small clonal expansion of CD38+ plasma cells that, due to somatic mutations in the variable light chain (V_L) gene, produces and releases into the extracellular compartment significant amounts of monoclonal immunoglobulin light chains (LC) that misfold and form amyloidosis.¹⁻⁴ It is unknown why such misfolded, kinetically unstable LC are released by the plasma cell. Studies of the molecular stress induced by these abnormal LC, however, suggest that cellular quality control is simply overwhelmed.^{5,6}

The misfolded LC circulate in the extracellular compartment in a soluble globular configuration.⁷ Via a mechanism that has yet to be elucidated fully, at a critical concentration these LC undergo further conformational change and arrange into β -pleated sheets.³ Amyloid oligomers quickly form and provide nucleation sites for further aggregation. Fibrils precipitate out of the peripheral blood and deposit into tissues, with mild-moderate specificity for organs depending on V_L amino acid sequence.^{2,8} These fibrils, upon Congo red staining of specimen, are visible under polarized light microscopy with apple-green birefringence and form the basis for diagnosis of AL amyloidosis. Amyloid fibril deposition is currently thought to be the primary driver of cellular damage and organ dysfunction, via direct replacement of tissue parenchyma as well as direct cytotoxicity.⁹

Though the incidence of AL amyloidosis has been estimated at 8–12 cases per 10⁶ individuals per year, with approximately 4000 per year in the United States, it is the most common amyloidosis subtype and continues to be underdiagnosed.^{10,11} Clinical manifestations arising from such a widespread pathophysiologic process are protean, and may lead to diagnostic dilemmas.^{11,12} Signs and symptoms of AL amyloidosis can be generally categorized into neuropathy, cardiomyopathy, malabsorption, renal insufficiency, and rarely coagulopathy. Dysautonomia and/

Graphical Abstract



or enteric nervous system neuropathy are frequent presentations of disease; so too is inexorably progressive diastolic heart failure with a classically thickened interventricular septum. Gastrointestinal amyloid deposition, depending on location, can result in malnourishment in critical macro- or micronutrients and may result in repetitive hemorrhage. Renal amyloid burden can result in severe tubular dysfunction and nephrotic-range proteinuria. Amyloid deposition in vascular endothelium increases vessel fragility, and amyloid-related interference in the conversion of factor X to activated factor X is well described. Without intervention, the disease is invariably deadly: 5 year overall survival in the modern day is estimated at 35%, and patients with any cardiac involvement have a median OS of 2.6 years.¹³

The current therapeutic approach for AL amyloidosis rests on two primary assessments: the status of the plasma cell clone, and the pre-existing amyloid organ burden. At this time, there are no FDA-approved treatments to reduce amyloid burden. Two engineered monoclonal antibodies have proceeded through early-phase clinical trials^{14,15} and are in Phase 3 trials (birtamimab: NCT04973137; anselamimab: NCT04504825, NCT04512235). Treatments for AL amyloidosis have historically attempted to eliminate the PC clone as rapidly as possible, thus minimizing further fibril aggregation. Regimens at first consisted of melphalan and prednisone.¹⁶ Autologous stem cell transplant (ASCT) was integrated into the therapeutic approach soon thereafter, with confirmed long-term survival benefit.¹⁷ Proteasome inhibitors were introduced in 2009 and increased survival.¹⁸ Nevertheless, rates of at least very good partial response (VGPR) remained at approximately 50% after first-line cyclophosphamide, bortezomib, and dexamethasone.¹⁹ One-third of those who achieve hematologic complete response also ultimately relapse.²⁰

The introduction of the anti-CD38 monoclonal antibody daratumumab revolutionized the treatment landscape for AL amyloidosis and plasma cell dyscrasias more generally (Figure 1). Two formulations have been developed: intravenous (IV) and subcutaneous (SC). We herein provide a focused review of the safety and efficacy of SC daratumumab compared to IV daratumumab. Given the recent advent of the SC formulation and thus the relatively sparse data available, we describe the use of SC daratumumab in both myeloma and AL amyloidosis.

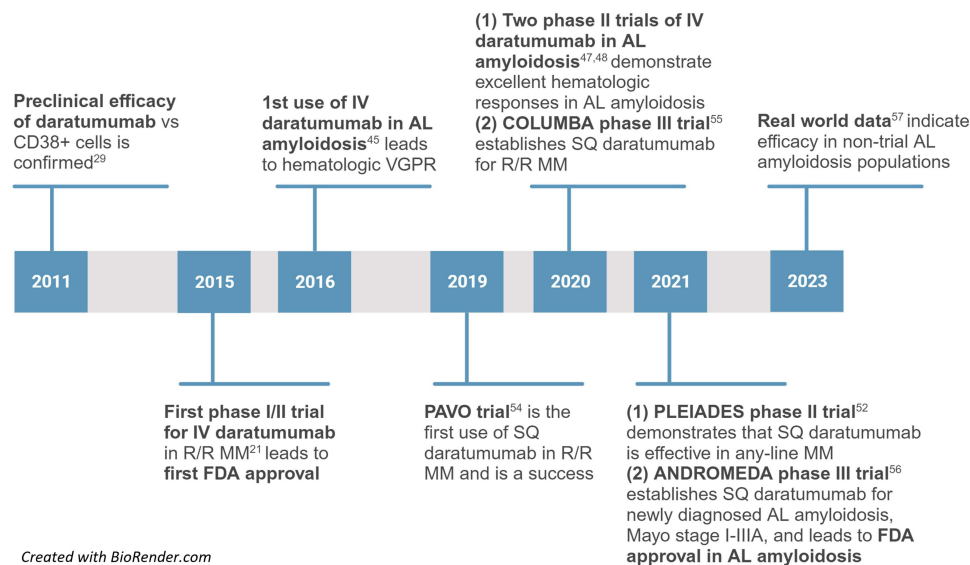


Figure 1 Summary timeline of major events involving daratumumab.

Daratumumab in Plasma Cell Dyscrasias

CD38 is a 48 kDa transmembrane glycoprotein with numerous adhesion and signaling functions. It is expressed highly and uniformly on the surface of plasma cells, and is not typically expressed at such levels on other cells; it has thus been a prime target for directed therapies.^{21,22} Daratumumab is an IgG1-kappa fully humanized monoclonal antibody that was initially administered intravenously. It binds to CD38 and exerts its effect via three primary mechanisms: (1) Fcγ receptor-mediated crosslinking, which induces programmed cell death through both antibody-dependent and independent mechanisms; (2) complement-dependent cytotoxicity; and (3) antibody-dependent cytotoxicity or phagocytosis.^{23–29} While daratumumab has been primarily deployed in plasma cell dyscrasias, it may have therapeutic benefit in multiple other settings. There have been reports of efficacy in relapsed/refractory T-cell acute lymphoblastic leukemia and in the management of advanced B-cell malignancies.^{30,31} Daratumumab may also be of clinical benefit in the non-malignant space: it has been considered for a role in desensitization protocols in patients with significant HLA presensitization prior to solid organ transplantation; refractory Sjögren's disease; and immune-mediated thrombocytopenia.^{32–34}

Recently, a formulation of daratumumab containing recombinant hyaluronidase in solution was developed. The hyaluronidase depolymerizes hyaluronan. Hyaluronan depolymerization locally and transiently increases permeability of the extracellular matrix that comprises human SC tissue. This allows for SC injected daratumumab to slowly and safely achieve peak and trough peripheral blood levels similar to an IV daratumumab infusion.³⁵

Intravenous Daratumumab

Administration and Cost

Standard dosing of IV daratumumab consists of 16mg/kg infused into a peripheral vein weekly for eight doses, then every two weeks for doses 9–16, then every month thereafter. Initial infusion is recommended to last seven hours; second infusion lasts four hours; and subsequent infusions last 3.25–3.5 hours.²³ Cost is \$7057 for the drug alone per infusion in 2020 US dollars.³⁶ Estimated total cost of administering IV daratumumab over 52 weeks, with 23 expected infusions, is US \$167,826.³⁷ For context, the mean cost of cyclophosphamide per 100mg infusion in 2023 US dollars is \$17.942, for an estimated total cost per 6 regimen cycles at dosing 300mg/m² in the average 1.91m² individual of \$1,291.82.³⁸ The mean cost of bortezomib per 0.1mg injection in 2023 US dollars is \$2.289, for an estimated total cost per 6 regimen cycles at dosing 1.3mg/m² in the average 1.91m² individual of \$1364.06.³⁹ Financial assistance programs are available via the pharmaceutical manufacturer Janssen and charitable organizations.

Table 1 Characteristics of Published Studies Investigating Daratumumab in AL Amyloidosis Patients, 2019–2022. All PubMed-Indexed Daratumumab, and All Prospective Cohorts of Daratumumab in AL Amyloidosis with at Least 15 Patients Who Received Daratumumab

Reference	Abeykoon et al Leukemia 2019 ⁶²	Al Saleh et al Blood Cancer J 2022 ⁶³	Chung et al Blood Adv 2020 ⁶⁴	Cohen et al Amyloid 2020 ⁶⁵	Gounot et al Leuk Lymphoma 2021 ⁶⁶	Kastritis et al Amyloid 2021 ⁶⁷	Kastritis et al N Engl J Med 2021 ⁵⁶	Kaufman et al Blood 2017 ⁴⁶
Group	Mayo Clinic	Mayo Clinic	Stanford	London	APHP, France	Greece	International	Stanford
Year	2019	2022	2020	2020	2021	2021	2021	2017
Regimen(s) tested	IV dara mono (50%); DPd 36%, DRd 32%, DVd 18%	Dara ± dex; DPd; DRd; DVd—unknown IV vs. SC	IV dara ± dex	IV dara	IV dara monotherapy ± dex	IV dara consolidation	SC daratumumab in combination with VCd	IV dara mono
Number of patients receiving daratumumab	44	292 (11 dara based rx)	72	50	25	25 (19 AL amyloidosis)	193	25
Study design	Retrospective single center	Retrospective single center	Retrospective single center	Retrospective single center; R/R AL amyloidosis	Retrospective stage III AL amyloidosis, single center	Prospective cohort study	Phase III RCT, 1 st line AL amyloidosis	Retrospective cohort study
Study period	1/1/15–2/15/18	9/1997–7/2019	1/2016–1/2019	2016–2019	Not reported, assumed prior to 2021	2/2018/2019	5/2018–8/2019	2017
IRR	22%; 7% dara mono 2% dara combined	Not recorded	50% (33/66)	7/50 grade 1–2	3/22 (12%) grade 1–2, no grade 3–4	3/19 grade 1–2	7.2% any grade, 0% ≥grade 3	15/25 = 60% grade 1–2 no grade 3–4
Infection	7%; 1% dara mono 2% dara combined	Not recorded	7.5%	5/50 grade 1–2	10/22 (40%); 2/22 grade 3–4	0/19	10.9% respiratory, grade 3–4 pneumonia 7.8%	2/25 hospitalized for infections; otherwise not reported
Neutropenia	Grade 1 10% grade 2 12% grade 3 7%; grade 1 1% grade 2 1% grade 3 0%	Not recorded	0	0/50	Not recorded	0/19	10.9% any grade, 5.2% grade 3–4	Not recorded
Anemia	Grade 1 41% grade 2 19% grade 3 2%	Not recorded	0	6/50 all grade 1/50 grade 3–4	2/22 (8%) grade 1–2	0/19	0%	1/25 required RC transfusion
Thrombocytopenia	Grade 1 38%	Not recorded	0	6/50 grade 1–2	Not recorded	0/19	0%	Not recorded
2 most common other major AEs	Anemia grade 1, TCP grade 1; fatigue 24% infusion reaction 22%	Not recorded	0	6/50 grade 1–2 fatigue; 6/50 all grade fluid overload 2/50 grade 3–4	Not recorded	0/19	Diarrhea, peripheral edema	Not recorded
Patients discontinuing treatment due to AE	3 (2 fatigue 1 neuropathic pain progression)	Not recorded	0	0/50	Not recorded	0/19	4.1%	4/25 due to grade 3–4 AE (PTX, decomp HF, infections)

Abbreviations: IV, intravenous; IRR, infusion/injection-related reaction; AE, adverse event; R/R, relapsed/refractory; RCT, randomized controlled trial; PNA, pneumonia; bortezomib, dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone; VCd, bortezomib, cyclophosphamide, dexamethasone.

Retrospective Investigations of Daratumumab in AL Amyloidosis with at Least 25 Patients Who Received

Kimmich et al Blood 2020 ⁶⁸	Kimmich et al Am J Hematol 2021 ⁶⁹	Lecumberri et al Amyloid 2020 ⁷⁰	Milani et al Am J Hematol 2020 ⁷¹	Roussel et al Blood 2020 ⁴⁸	Sammartano et al J Pers Med 2022 ⁷²	Sanchorawala et al Blood 2020 ⁷⁷	Shragai et al Eur J Hematol 2021 ⁷³	Szalat et al Am J Hematol 2022 ⁷⁴
Heidelberg	Heidelberg	Spain	Italy	France/Italy	Regional Tuscan Myeloma network	BU	Israel	BU
2020 IV dara-dex ± bortezomib	2021 IV dara-len-dex	2020 IV dara	2020 IV dara ± len or bortezomib	2020 IV dara	2022 IV dara ± len-dex or V-dex	2020 IV dara	2021 Likely IV dara ± numerous other combinations	2022 IV dara at least, ± combo
168	44	38	72	40	33	22	49	107
Prospective observational cohort	Retrospective cohort stratified by 1q21 gain	Retrospective cohort	Retrospective R/R AL amyloidosis	Prospective phase 2 R/R AL amyloidosis	Prospective observational cohort study, multisite	Prospective phase II clinical trial	Retrospective multisite study	Retrospective cohort
6/2016–7/2019	Not reported-6/2020	Not reported	10/2016–7/2018	9/2016–4/2018	7/2018–8/2021	4/2017–8/2018	10/2016–3/2019	4/2017–12/2020
Not reported	Not reported	1/38 grade 3	11% grade 2--bronchospasm, cutaneous rash, rhinorrhea	17/40 grade 1–2	12/33 grade 1–2	4/22 grade 1 N/V requiring antiemetic	Not reported	Not reported
Not reported	55%; 7/44 severe PNA 3/44 severe (grade 3–4) colitis-assoc perf 2/44 severe skin abscesses	3/38 grade 3 (1/38 pna)	7/72 grade 3 (4 PNA 3 other infections)	28/40 with 22/28 bronchitis and 9/28 PNA	5/33 grade 3	4/22 grade 3–4 all respiratory	39/49 all grade, 12/49 grade 3–4; 18/49 PNA all grade 5/49 grade 3–4	Not reported
Not reported	At least 1/44 grade 5 (death from neutropenic sepsis)	Not reported	2/72 = 2% grade 3	0/40	2/33 grade 3	0/22	0/49	Not reported
Not reported	Not reported	Not reported	0/72	2/40 = 5%	0/22	2/22 grade 1–2	0/49	Not reported
Not reported	Not reported	Not reported	2/72 = 2% grade 3	0/40	0/22	0/22	0/49	Not reported
Not reported	Lymphocytopenia 58%, grade 3/4 25%; fatigue/ impaired qol 36%	2/38 grade 3 fluid overload/ HF	Atrial fibrillation 2/72	Asthenia at administration site 10/40, edema 10/40	3/33 grade 3 HF	4/22 afib grade 3–4 3/22 CHF grade 3–4 3/22 lymphopenia grade 3–4	“cardiovascular toxicity” 7/49 all grade 4/49 grade 3–4; peripheral neuropathy 14/49 all grade 4/49 grade 3–4, dyspnea 11/49 all grade, 4/49 grade 3–4	Not reported
Not reported	At least 36% due to fatigue/ impaired qol	5/38 due to any AE	0/72	0/40	0/33	0/22	0/49	Not reported

PTX, pneumothorax; HF, heart failure; DPd, daratumumab, pomalidomide, dexamethasone; DVd, daratumumab,

Efficacy

IV daratumumab was initially deployed in multiple myeloma, demonstrating encouraging overall response and survival benefit in a Phase I/II trial reported in 2015.²¹ Daratumumab was granted initial FDA approval in 2015, and swiftly moved into first-line therapy in multiple combinations for both ASCT-eligible and -ineligible patients.^{23,40–44}

IV daratumumab was applied in systemic AL amyloidosis soon after its introduction into the myeloma therapeutic space. The Mayo group reported the first-in-human use for AL amyloidosis in 2016.⁴⁵ One patient with multiply refractory Mayo 2012 stage IIb AL amyloidosis suffering from amyloid-related rectal hemorrhage and secondary transfusion-dependent anemia achieved for the first time hematologic VGPR and within months thereafter saw the resolution of his transfusion dependence. A second patient with AL amyloidosis with primarily renal involvement received daratumumab after his disease progressed post-ASCT and CyBorD: he achieved hematologic complete remission within three months. The Stanford group reported the impact of daratumumab in a retrospective cohort of 25 heavily pretreated AL amyloidosis patients soon thereafter.⁴⁶ Overall response rate (ORR) was 76%, with 60% achieving at least VGPR. Median time to maximum response was one month. Only two of 25 patients experienced hematologic progression during the study duration; median follow-up time was not reported.

Two simultaneous Phase II trials conducted soon after the publication of such retrospective data confirmed the striking response rates and impressive time to maximal response associated with IV daratumumab. The Boston University Amyloidosis Center reported an ORR of 90%, with 86% achieving at least VGPR; median time to first response was four weeks, and median time to deepest response was three months.⁴⁷ Only three of 22 patients at time of publication progressed, at a median of 3 months from daratumumab initiation. The French AL amyloidosis network reported ORR of 70%, with at least VGPR in 47.5%.⁴⁸ Reported median time to any response was one week, with most patients achieving their deepest responses within three months. Organ response after hematologic response was confirmed in both studies, with a delay between hematologic complete response and first organ response consistent with prior findings.⁴⁹

Safety

Severe adverse events (AEs) attributable to IV daratumumab occur in a small but nontrivial proportion of both multiple myeloma and AL amyloidosis patient populations. In the multicenter phase II SIRIUS trial investigating daratumumab monotherapy in multiple myeloma, anemia, thrombocytopenia, and neutropenia occurred at any Common Terminology Criteria for Adverse Events (CTCAE) grade in 33%, 25%, and 23% of patients, respectively.⁵⁰ Grade 3–4 anemia was noted at an incidence of 24%, thrombocytopenia 19%, and neutropenia 12%. Nonsevere (grade 1–2) fatigue (40%) and nausea (29%) were common. Five percent of patients experienced a grade 3 infusion-related reaction (IRR); 42% of patients experienced an IRR of any grade. The IRRs were characterized by sinopulmonary symptoms, bodily chills, and vomiting. IV daratumumab-associated AEs in subsequent Phase III studies largely recapitulated AEs seen in the SIRIUS trial. Of note, however, the representative CASSIOPEIA trial⁴⁰ reported an any-grade sinopulmonary infection incidence of up to 38%, with 4% grade 3–4 pneumonia. Despite pre- and post-infusion supportive medications, IV daratumumab infusions were delayed or simply skipped in nine of 440 (2%) patients due to IRRs, and they were interrupted in 93 of 440 (21%) for a median of 3.75 months due to the same. In pooled analysis, IRRs occurred in 37% of patients upon initial administration of IV daratumumab.²³ Daratumumab-induced interference with standard indirect antiglobulin testing was noted in the majority of patients throughout these trials. Immunogenicity has been observed in less than 1% of the population.²³

Reported IV daratumumab-associated AE incidence remained much the same in the AL amyloidosis sphere (Table 1). The overwhelming majority of studies investigating daratumumab in AL amyloidosis employed the IV formulation, as they were mostly conducted prior to the development and use of SC daratumumab. We detail studies of particular interest and seminal prospective studies below.

While no patients required adjustment of diuretic dosing for infusion-related heart failure events in the Stanford group's initial retrospective study, 15 of 25 patients (60%) experienced grade 1–2 IRRs after initial administration of IV daratumumab.⁴⁶ Two of 25 were hospitalized for infections, type and grade unspecified. One patient required at least one transfusion of red blood cells. There were no cases of leukopenia or thrombocytopenia. Overall, four of 25 patients (16%)

required daratumumab discontinuation due to assorted grade 3–4 AEs: pneumothorax, decompensated heart failure, and infections.

The Boston University phase II trial found an 18% grade 1–2 IRR incidence; an 18% grade 3–4 respiratory infection rate; and a 9% incidence of grade 1–2 anemia.⁴⁷ Ten of 22 patients (45%) ultimately required premature discontinuation of IV daratumumab due to varied grade 3–4 AEs. The French AL amyloidosis network phase II trial reported an IRR incidence of 42.5%, with nine grade 1–2 and 3 (cutaneous rash) grade 3–4.⁴⁸ Twenty-eight of 40 patients (70%) experienced infection of any grade, with 22 suffering bronchitis and nine suffering pneumonia. Five percent of patients had anemia of any grade. No patients discontinued treatment due to AEs; data on delays or interruptions in treatment were not published. No adverse effects lasted significantly past discontinuation of daratumumab for any reason. Daratumumab does not appear to interfere with metabolism of drugs via the CYP system. Preclinical studies suggest that daratumumab may depress fetal immunity and decrease fetal bone density.^{23,35}

Subcutaneous Daratumumab (Daratumumab-Hyaluronidase)

Administration and Cost

Daratumumab-hyaluronidase is FDA- and EMA-approved for injection into the SC tissue of the abdomen weekly for eight doses, then every two weeks for doses 9–16, then every month thereafter, in combination with cyclophosphamide, bortezomib, and dexamethasone.^{35,51} The FDA indication does not include Mayo stage IIIB disease at this time. Median duration of administration was five minutes per injection in a recent study.⁵² Projected cost is US \$7574 (2020), and US \$174,202 for 23 projected administrations over a 52 week period.⁵³ Of note, SC edema in patients with heart failure can theoretically impair dispersal of drug; to our knowledge, there are no published data examining this phenomenon. As with the IV formulation, financial assistance programs are available via the pharmaceutical manufacturer and charitable organizations.

Efficacy

The PAVO trial was the first instance of prospectively studied single-agent SC daratumumab administration in humans.⁵⁴ Fifty-three patients with relapsed/refractory multiple myeloma in total received the drug, 45 at an 1800mg dosage irrespective of weight. ORR was 42.2% for those treated with 1800mg per dose, and the pharmacokinetic profile of 1800mg SC daratumumab recapitulated that of IV daratumumab.

The COLUMBA noninferiority trial established SC daratumumab as a viable therapeutic option in relapsed/refractory multiple myeloma.⁵⁵ Five hundred twenty-two patients with multiply relapsed/refractory multiple myeloma accrued from 10/2017 to 12/2018 were divided into SC (n = 263) and IV (n = 259) open-label treatment arms. Patients who had been previously exposed to anti-CD38 agents; undergone recent ASCT; had meningeal involvement; significant obstructive lung disease; or significant cardiac disease were excluded. Patients received a median of six cycles in each group. ORR was 41% for SC daratumumab and 37% for IV daratumumab, meeting noninferiority thresholds. There were no differences between SC and IV daratumumab efficacy in subgroup analysis, or among differing body weights. SC daratumumab by pharmacokinetic analysis reached a trough dose equivalent to IV daratumumab, qualifying as adequate exposure. At median follow-up of 7.5 months, progression of disease had been observed in 51% of patients in each arm. Median progression-free survival was 5.6 months for SC daratumumab vs. 6.1 months for IV daratumumab; median time to next treatment was 9.7 months for SC daratumumab and 8.7 months for IV daratumumab. Median duration of response had not been reached in either arm; median overall survival had not been reached in either arm. SC daratumumab was thus concluded to be at least noninferior to IV daratumumab in the relapsed/refractory multiple myeloma setting.

The open-label, international phase II PLEIADES study investigated the effect of SC daratumumab in multiple combinations across first- and second-line therapy, and constitutes the body of prospective evidence thus far for SC daratumumab use in newly diagnosed multiple myeloma.⁵² 199 patients were assigned to three treatment arms: daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) in newly diagnosed transplant-eligible multiple myeloma; daratumumab, bortezomib, melphalan, and prednisone (D-VMP) in newly diagnosed transplant-ineligible myeloma; and daratumumab, lenalidomide, and dexamethasone (D-Rd) as second-line therapy for relapsed/refractory disease. High-risk cytogenetic disease was appropriately represented in the study population. ORR for the D-VRd arm at

3.9 months median follow-up was 97%, with 71.6% achieving at least VGPR and 11.6% achieving CR. ORR for the D-VMP arm at 14.3 months median follow-up was 89.6%, with 77.6% achieving at least VGPR and 47.8% achieving CR. ORR for the D-Rd arm at 14.7 months median follow-up was 93.8%, with 78.5% achieving at least VGPR and 38.5% achieving CR. The results are equivalent to previously published results from trials of IV daratumumab-containing regimens in newly diagnosed multiple myeloma.

Based on the encouraging data from multiple myeloma, the phase III ANDROMEDA trial included SC daratumumab in the upfront treatment of AL amyloidosis.⁵⁶ From May 2018 to August 2019, 388 patients with newly diagnosed AL amyloidosis were randomized in a 1:1 ratio to a control arm ($n = 193$) receiving six cycles of cyclophosphamide, bortezomib, and dexamethasone (VCd), or to an experimental arm ($n = 195$) receiving six cycles of SC daratumumab with VCd and 18 injections of SC daratumumab maintenance thereafter. The study was not blinded. Notably, patients with Mayo stage IIIB cardiac AL amyloidosis were excluded from the study. Multiorgan dysfunction was present in the majority of patients. At a median follow-up of 11.4 months, 91.8% of patients achieved an overall response. VGPR was achieved by 78.5% of patients, and 53.3% achieved CR. Almost three quarters (70.5%) of patients achieved a difference in free light chain levels less than 20mg/L. Median time on treatment was 9.6 months, but median duration of response was not reached at the time of presentation. Time to best hematologic response was 60 days. Hazard ratio for major organ deterioration, hematologic progression, or death was 0.58 (95% CI: 0.36–0.93), favoring SC daratumumab-VCd. Time to next treatment was significantly prolonged as well (HR 0.39, 95% CI 0.27–0.56). Overall survival data were immature at time of publication. Only 9.8% of patients were eligible for ASCT; there was no noticeable difference in overall survival post-transplant. A notable proportion of patients who achieved hematologic complete remission with SC daratumumab-VCd ultimately exhibited cardiac response (41.5%) and renal response (53%) at six months. These findings suggest that SC daratumumab is at least as effective as IV daratumumab in newly diagnosed AL amyloidosis, though there has been no head-to-head trial.

Real world data on SC daratumumab in AL amyloidosis remain sparse, due to the recent introduction of the SC formulation into the treatment space. A recent retrospective cohort study of 22 patients with Mayo IIIB AL amyloidosis treated with SC daratumumab is, at the time of this review's writing, the sole instance of clear and validated SC daratumumab deployment in a non-trial setting which investigated survival outcomes.⁵⁷ Patients achieved hematologic at least VGPR at a rate of 88.2% in one month, 93.8% at three months, and 86.7% at six months from initiation of treatment. Sixty-three percent of evaluable patients reached an involved free light chain level below 20mg/L and a difference in free light chain levels below 10mg/L at three months from treatment initiation. Though further study is needed, such results suggest that SC daratumumab achieves efficacy comparable to rates reported in ANDROMEDA in an expanded AL amyloidosis population. Prospective investigations of SC daratumumab efficacy in Mayo 2004 stage IIIB patients are currently underway.

Patients treated with either SC or IV daratumumab may ultimately become refractory to treatment; a small minority do not respond at all. Data regarding potential mechanisms of delayed or upfront resistance are sparse in AL amyloidosis and remain vexed in the multiple myeloma space. In multiple myeloma, the recent discovery of XBP1 loss driving decreased CD38 expression suggests simple decreased target antigen expression as a pathway for tumor escape from daratumumab.⁵⁸ A separate molecular study of a combined cohort of multiple myeloma and AL amyloidosis patients found that upfront resistance did not, however, depend on CD38 expression levels.⁵⁹ Evidence otherwise exists to suggest that cytogenetics and the inflammatory profile of the bone marrow milieu play key roles in mediating anti-CD38 agent resistance.^{58,60} Research continues regarding mechanisms of daratumumab resistance in AL amyloidosis specifically.

Safety

AEs associated with SC daratumumab in large part mirror those seen with IV daratumumab, with one notable exception in later-phase investigations: the rate of IRRs.

SC daratumumab-related AEs reported in the PAVO study in relapsed/refractory multiple myeloma included anemia at 33%, upper respiratory tract infection (27%), pyrexia (27%), and diarrhea (27%).⁵⁴ Neutropenia occurred at 15.6% incidence in the 1800mg dosing group. Seven of 45 (15.6%) experienced grade 3–4 anemia; 6.7% experienced grade 3–4 neutropenia and thrombocytopenia. Two patients experienced grade 3 influenza infections. Eleven of 45 patients (24.4%)

experienced IRRs; all were grade 1–2 and occurred with the first administration of drug. No patients discontinued therapy due to AE. Pre- or post-administration medication regimens were not discussed.

SC daratumumab was shown to be at least equally well-tolerated compared to IV daratumumab in patients with relapsed/refractory multiple myeloma by the COLUMBA noninferiority trial.⁵⁵ IRR rate was significantly decreased for SC (33 of 260 patients, 13%) vs. IV daratumumab (89 of 258 patients, 34%; OR 0.28 95% CI 0.18–0.44). Most IRRs occurred after the first dose: one patient in the SC arm and two in the IV arm had at least one delayed-onset IRR, all grade 1–2. Grade 3 IRRs occurred in only four patients due to SC daratumumab but 14 patients due to IV daratumumab; there were no higher-grade reactions. IRRs manifested as chills, pyrexia, and dyspnea. Median time to onset of IRR was 3.4 hours for the SC daratumumab group, significantly longer than that for the IV daratumumab group (1.5 hours). IRRs in IV daratumumab interrupted dosing for 79 of 258 patients (31%) and led to treatment discontinuation in two patients. There were no dosing interruptions or discontinuations associated with IRRs in the SC daratumumab arm. Grade 1–2 injection site reactions were noted in 18 patients in the SC arm. AE profiles were otherwise similar between SC and IV daratumumab: 13–14% of patients experienced grade 3–4 anemia; 8–13% experienced neutropenia; and 14% experienced thrombocytopenia. Three to four percent of patients developed grade 3–4 pneumonia. Pharmacokinetic evidence suggesting that patients with less body mass had about 60% higher mean maximum systemic concentrations of daratumumab with SC formulation than with IV formulation correlated with a slightly higher incidence of any AEs in the SC daratumumab arm vs. IV daratumumab arm (95% vs. 89%). Treatment discontinuations due to AEs were equivalent.

No new safety concerns with SC daratumumab were seen in the phase II PLEIADES trial, focused on multiple myeloma.⁵² Rates of grade 3–4 treatment-emergent AEs were comparable to those cited in prior studies. Grade 3–4 neutropenia occurred at 28–32% incidence (D-VRd, D-Rd arms); grade 3–4 thrombocytopenia occurred at maximum 43.3% rate (D-VMP arm). Grade 3–4 pneumonia occurred in 3–12.3% of cases. IRRs occurred in 7.5% of patients overall, with most occurring with the first administration of SC daratumumab. Only one incident of grade 3 IRR, decreased oxygen saturation, occurred. Median time to IRR was 4.4–6.9 hours across the three cohorts. Grade 1–2 injection-site reactions occurred in 7.5% of patients.

The SC daratumumab-related AE profile reported by the ANDROMEDA trial for newly diagnosed AL amyloidosis was consistent with the profile seen in prior studies across plasma cell dyscrasias.⁵⁶ Clinically significant respiratory infections of any grade were increased in the SC daratumumab-VCd arm, occurring at 10.9% incidence compared to 6.4% in the control VCd arm. Grade 3–4 pneumonia occurred in 7.8% of SC daratumumab-VCd patients. Neutropenia of any grade also occurred in 10.9% of patients who received daratumumab-containing regimen, with 5.2% incidence of grade 3–4 toxicity. There was no other significant hematologic toxicity recorded. Diarrhea, peripheral edema, and lymphopenia were otherwise common, in line with prior reported AEs. Only 4.1% of patients who received SC daratumumab-VCd discontinued treatment due to AEs, similar to the 4.3% rate in the control arm. Grade 1–2 injection site reactions occurred in 7.2% of patients receiving SC daratumumab; there were no severe reactions.

No significantly different SC daratumumab-related AEs in AL amyloidosis patients were noted in the report by Chakraborty et al.⁵⁷ There is one other instance of SC daratumumab use in real-world populations, which investigated short-term safety outcomes.⁶¹ Patients in this recently published multicenter Italian retrospective cohort study had either AL amyloidosis or multiple myeloma. After premedication with glucocorticoids, antihistamines, acetaminophen, and variably montelukast, 4% of the 189 subjects experienced mostly grade 1–2 IRRs. All clinically significant AEs occurred at less than 5% incidence in a comparison population of multiple myeloma patients with more frailty. At the time of manuscript writing, no cost-effectiveness or cost-comparison studies of SC vs. IV daratumumab have been published.

Summary and Conclusions

Systemic AL amyloidosis is a subset of plasma cell dyscrasias most prominently marked by the production of misfolded light chain immunoglobulins which aggregate and deposit as amyloid fibrils into bodily tissues, causing widespread organ dysfunction. It is an ultimately fatal disease and remains underdiagnosed. The standard-of-care therapeutic approach focuses on prevention of fibril generation by eliminating the plasma cell clone. Until recently, this has been accomplished with chemotherapy and, if the patient is healthy enough, ASCT.

The advent of the anti-CD38 monoclonal antibody, daratumumab, has fundamentally altered the treatment landscape for plasma cell dyscrasias and AL amyloidosis in particular. Daratumumab has swiftly been integrated into first-line combination regimens for AL amyloidosis: first as an IV infusion, and more recently as an SC injection. Daratumumab has been associated with an increased risk of sinopulmonary infections and increased risk of hematologic toxicities. IV daratumumab has been associated with long infusion times and grade 1–2 IRRs. These reactions, while typically easily managed with supportive medications, can cause distress to the patient and can cause delays in delivery of drug.

SC daratumumab appears to be as effective as IV daratumumab in plasma cell dyscrasias generally, with decreased IRRs, decreased time spent administering drug, decreased administered volume in patients who may not develop frank acute heart failure but who may have difficulty with diuresis, and no other new safety signals. From our clinical practice, the SC adipose layer in patients with AL amyloidosis can be so thin that SC injections are either too painful or indeed impossible; conversely, SC edema can be so significant that absorption and dispersal of drug is theoretically impaired. There are currently no published findings regarding cost effectiveness of SC vs. IV daratumumab. We note that given the findings presented, SC daratumumab appears likely to correlate with decreased time spent by patients in infusion centers, increased patient exposure to drug, and potentially increased treatment capacity in infusion centers. Overall, we find that SC daratumumab should be preferred over IV daratumumab, but the clinical situation should determine the route of administration. Further prospective investigations into cost-effectiveness, “real-world” experiences in non-trial populations, and patient-reported outcomes with SC daratumumab are warranted.

Disclosure

S.L. is a Consultant and/or Advisor for Adaptive Biotechnologies, Alexion Therapeutics, Bristol-Meyers-Squibb, Caelum Biosciences, Janssen Pharmaceuticals, Karyopharm Therapeutics, Oncopeptides AB, GSK, Abbvie, Janssen, Pfizer, and Takeda Pharmaceutical Company; receives research funding from Celgene, Inc., Sanofi, Zentali; received honoraria from Clinical Care Options and Regeneron Pharmaceuticals; and has Royalties/Patents with Caelum Biosciences. In addition, S.L. has a patent CAEL-101 with royalties paid to Columbia University. The authors report no other disclosures or conflicts of interest in this work.

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