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SHORT COMMUNICATION

Daratumumab for treatment-refractory antibody-mediated diseases in neurology

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Abstract

Background and purpose: A fraction of patients with antibody-mediated autoimmune diseases remain unresponsive to first-/second-line and sometimes even to escalation immunotherapies. Because these patients are still affected by poor outcome and increased mortality, we investigated the safety and efficacy of the plasma cell-depleting anti-CD38 antibody daratumumab in life-threatening, antibody-mediated autoimmune diseases.

Methods: In this retrospective, single-center case series, seven patients with autoantibody-driven neurological autoimmune diseases (autoimmune encephalitis, $n = 5$; neurofascin antibody-associated chronic inflammatory demyelinating polyneuropathy associated with sporadic late onset nemaline myopathy, $n = 1$; seronegative myasthenia gravis, $n = 1$) unresponsive to a median of four (range = 4–9) immunotherapies were treated with four to 20 cycles of 16 mg/kg daratumumab.

Results: Daratumumab allowed a substantial clinical improvement in all patients, as measured by modified Rankin Scale (mRS; before treatment: mRS =5, $n = 7$; after treatment: median mRS =4, range = 0–5), Clinical Assessment Scale in Autoimmune Encephalitis (from median 21 to 3 points, $n = 5$), Inflammatory Neuropathy Cause and Treatment disability score (from 7 to 0 points, $n = 1$), and Quantitative Myasthenia Gravis score (from 16 to 8 points, $n = 1$). Daratumumab induced a substantial reduction of disease-specific autoreactive antibodies, total IgG (serum, 66%, $n = 7$; cerebrospinal fluid, 58%, $n = 5$),

and vaccine-induced titers for rubella (50%) and tetanus toxoid (74%). Treatment-related toxicities Grade 3 or higher occurred in five patients, including one death.

Conclusions: Our findings suggest that daratumumab provided a clinically relevant depletion of autoreactive long-lived plasma cells, identifying plasma cell-targeted therapies as promising escalation therapy for highly active, otherwise treatment-refractory autoantibody-mediated neurological diseases.

KEYWORDS
autoimmune encephalitis, CIDP, daratumumab, myasthenia gravis, sporadic late onset nemaline myopathy

INTRODUCTION

Antibody-mediated autoimmune diseases often share similar disease mechanisms. At acute disease stages, antibody-secreting B cells or short-lived plasmablasts secrete autoantibodies directed against surface epitopes that induce tissue malfunction and/or damage, often accompanied by a distinct T-cell or complement dysfunction. These patients usually show good response to standard immunotherapies [1]. Severe disease courses are often characterized by prolonged hospitalization at intensive care units (ICUs), artificial ventilation, and increased mortality [2,3]. In a fraction of these patients, autoreactive plasma cells terminally differentiate into long-lived plasma cells residing within the bone marrow or other inflamed tissues. They are resistant to first-/second-line and even sometimes to escalation therapies like the proteasome inhibitor bortezomib [4–6]. Novel drug developments like the humanized monoclonal anti-CD38 antibody daratumumab, approved for treatment of multiple myeloma [7], can target long-lived plasma cells and provided favorable responses in autoimmune hemolytic anemia [8], systemic lupus erythematosus [9] and autoimmune encephalitis [4,5]. As the conduction of randomized controlled trials for rare diseases is hampered by the limited number of available patients, knowledge of new treatment options often arises from experiences in single cases. Our case series aims to investigate the safety and efficacy of daratumumab in patients with treatment-refractory severe courses of neurological autoantibody-driven diseases by using a mechanism-based basket trial-like approach [10].

METHODS

Patients and daratumumab treatment protocol

In this retrospective case series, seven patients with antibody-mediated autoimmune disorders (autoimmune encephalitis $n = 5$ [anti-contactin-associated protein 2 (CASPR2), $n = 2$; anti-N-methyl-D-aspartate receptor (NMDAR), $n = 1$; autoantibodies against unknown epitopes $n = 2$], neurofascin antibody-associated chronic inflammatory demyelinating polyneuropathy [CIDP] with sporadic late onset nemaline myopathy [SLONM] and smoldering multiple myeloma, $n = 1$; seronegative generalized myasthenia gravis with excessive dependency on plasma exchange [3 times/week], $n = 1$) were treated with a median of nine cycles (range = 4–20) of 16 mg/kg intravenous daratumumab according to multiple myeloma protocols [11,12]. Up to eight cycles were always applied in weekly intervals. Thereafter, Patient #1 received daratumumab at 2-week intervals and Patient #7 obtained cycles nine to 12 at 2-week and thereafter at monthly intervals. Comorbidity of Patient #6 with smoldering multiple myeloma required treatment according to the MAIA protocol [12] for the first eight cycles followed by 12 further daratumumab cycles at monthly intervals. The varying number of applied daratumumab cycles was based on the individual disease severity, the clinical and serological response to daratumumab, and comorbidities.

Intravenous premedication 1 h before each daratumumab infusion included 100 mg methylprednisolone, 1 g paracetamol, and antihistamines. Twenty milligrams methylprednisolone per os was applied on Days 1 and 2 after each daratumumab infusion. Concomitant infection prophylaxis consisted of 200 mg/day aciclovir and 960 mg cotrimoxazole thrice weekly.

Ethical approval

The study was approved by the institutional ethics committee of Charité–Universitätsmedizin Berlin, Germany (EA2/096/21) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and/or their legal representatives.

Clinical, serological, and immunological outcome measures

Clinical outcome evaluation

Clinical outcomes were assessed by modified Rankin Scale (mRS), Clinical Assessment Scale in Autoimmune Encephalitis (CASAE) [13], Inflammatory Neuropathy Cause and Treatment (INCAT) disability score [14] or Quantitative Myasthenia Gravis (QMG) score [15].

Detection of autoreactive antibodies

Anti-CASPR2, anti-NMDAR, and antineurofascin antibodies (NF-155, NF-186) were determined by cell-based indirect immunofluorescence assays at Labor Berlin or Euroimmun, Germany. Autoantibodies directed against unknown neuronal epitopes were detected by indirect immunofluorescence on mouse brain slides as previously described [16].

Quantification of immunoglobulins, vaccine titers, and neurofilament light chain

Immunoglobulin levels were measured by nephelometry, tetanus toxoid (VaccZyme Tetanus-Toxoid IgG Kit; The Binding Site) and rubella (Elecsys Rubella IgG; Roche Diagnostics) vaccine titers by immunoassay, and neurofilament light chain in serum by the Simoa NF-light Advantage Kit on an HD-X analyzer (Quanterix).

Flow-activated cell sorting analysis

Peripheral blood mononuclear cells were isolated and stained using the following antibodies: CD3 (UCHT1), CD4 (RPA-T4), CD8 (REA734), CD45RA (T6D11), CCR7 (150503), HLA-DR (G46-6), CD19 (497), CD56 (HCD56), CD14 (HCD14), CD16 (3G8), CD38 (Cytognos), CD38 (IB6-clone, Miltenyi). Cells were analyzed using FACSCanto II Cytometer (BD Bioscience) or 10-color Navios flow cytometer. Data analysis was performed by FlowJo 10.5.3 for Mac OS (FlowJo) or Navios Software (Beckman Coulter).

Statistical analysis

Descriptive values are presented as median (minimum/maximum), and statistical analysis was performed by Wilcoxon matched-pairs signed rank test. Probability values < 0.05 were considered statistically significant.

RESULTS

Detailed patient information with demographic characteristics, clinical course, autoantibody titers, applied immunotherapies, and outcome evaluation is reported in Figure 1a, Table 1, and online in the Supplemental Case reports with Figures S1 and S2.

At daratumumab treatment initiation, the patients presented at a median age of 57 years (range = 16–69) and with a median disease duration of 9 months (range = 2–52). All patients suffered from life-threatening disease courses requiring treatment at neurological ICUs and were unresponsive to a median of four (range = 4–9) first- and second-line (prednisolone/methylprednisolone, intravenous immunoglobulins [IVIGs], plasma exchange, immunoadsorption, rituximab, mycophenolate mofetil, azathioprine, methotrexate) or even escalation immunotherapies (bortezomib, eculizumab). Treatment with daratumumab led to substantial clinical improvement, beginning within 2–4 weeks, except for Patients #1 and #7, with the most severe disease activity, who started to improve after 2 months. Before daratumumab therapy, all patients had an mRS of 5 and reached as best neurological outcome full or partial remission, with a median mRS of 4 (range = 0–5), during a median follow-up time of 13 months (range = 5–15) after daratumumab treatment initiation (Figure 1a, Table 1). At last follow-up, all patients with autoimmune encephalitis (#1–#5) showed a decrease in CASAE score from a median of 21 (range = 20–27) to 3 (range = 1–14) points (Figure 1b). The INCAT score of the CIDP patient (#6) dropped from 7 to 0 points, and the myasthenia gravis patient (#7) achieved a moderate decrease in QMG score from 16 to 8 points (Figure 1c), but became independent from high-frequent plasma exchange therapy and ventilation.

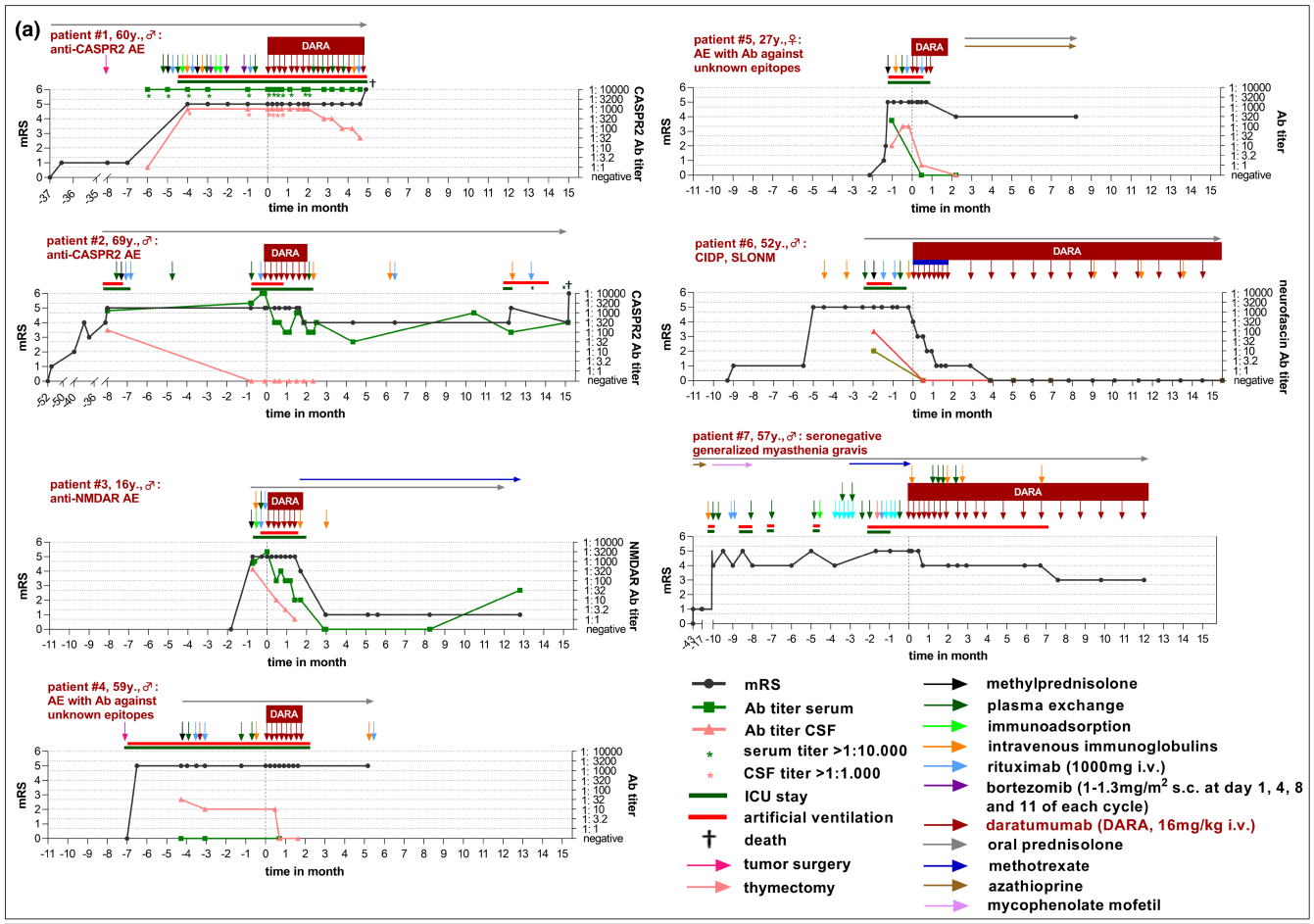
Daratumumab induced remarkable serologic responses, reflected by a reduction of autoantibodies that even became negative in four patients (Figure 1a, Table 1). Total IgG declined in serum (66%, $n = 7$) and cerebrospinal fluid (CSF; 58%, $n = 5$; Figure 1d,e), and rubella vaccine titer was reduced by 50% and tetanus toxoid titer by 74% (Figure 1f,g). Interestingly, the median value of the neurodegeneration marker neurofilament light chain decreased by 72% during daratumumab therapy (Figure 1h), which might act as an indirect surrogate marker for treatment responses.

Fluorescence activated cell sorting analysis of peripheral blood leukocytes (Figure 1i–l, Figure S3) demonstrated a large heterogeneity between the different patients concerning pretreatment state and treatment response. Immune alterations before daratumumab included B-cell depletion following rituximab therapy and T-cell lymphopenia in some patients. However, there was a general trend toward increased coexpression levels of CD38 and HLA-DR on both $CD4^+$ and $CD8^+$ memory T cells at baseline, and CD38-expressing T cells and NK cells significantly decreased during daratumumab treatment. At follow-up, no consistent changes in T-cell subsets were observed.

Several adverse events (Grade 1–5) occurred during multimodal immunotherapy including daratumumab: blood stream infections ($n = 4$), urinary tract infections ($n = 3$), tracheobronchitis ($n = 3$), fever ($n = 3$), dyspnea ($n = 3$), and tachycardia ($n = 2$; Table 1). Both patients with anti-CASPR2 encephalitis died; Patient #1 died after Gram-negative septic shock likely related to severe immunosuppression 9 days after last daratumumab infusion; Patient #2 died 13 months after last daratumumab infusion unrelated to previous immunotherapy.

DISCUSSION

Add-on treatment of daratumumab in seven neurological patients with treatment-refractory antibody-mediated autoimmune diseases resulted in a substantial clinical improvement, most likely mediated


(a)
patient #1, 60y.,♂: anti-CASPR2 AE
patient #2, 69y.,♂: anti-CASPR2 AE
patient #3, 16y.,♂: anti-NMDAR AE
patient #4, 59y.,♂: AE with Ab against unknown epitopes
patient #5, 27y.,♀: AE with Ab against unknown epitopes
patient #6, 52y.,♂: CIDP, SLONM
patient #7, 57y.,♂: seronegative generalized myasthenia gravis
DARA
mRS
time in month
CASPR2 Ab titer
NMDAR Ab titer
neurofascin Ab titer
Ab titer
negative
mRS
Ab titer serum
Ab titer CSF
serum titer >1:10.000
CSF titer >1:1.000
ICU stay
artificial ventilation
death
tumor surgery
thymectomy
methylprednisolone
plasma exchange
immunoadsorption
intravenous immunoglobulins
rituximab (1000mg i.v.)
bortezomib (1-1.3mg/m² s.c. at day 1, 4, 8 and 11 of each cycle)
daratumumab (DARA, 16mg/kg i.v.)
oral prednisolone
methotrexate
azathioprine
mycophenolate mofetil

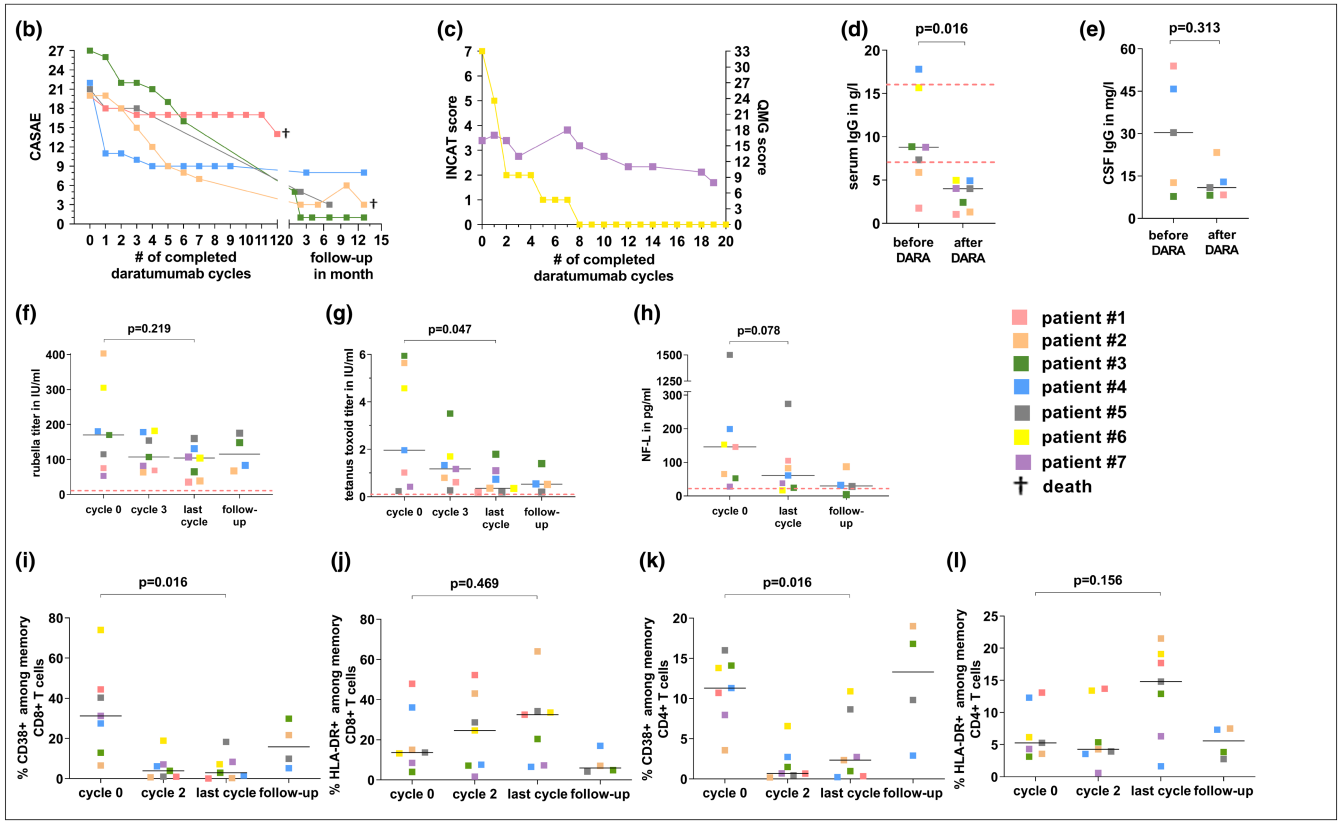

(b)
CASAE
# of completed daratumumab cycles
follow-up in month
(c)
INCAT score
QMG score
# of completed daratumumab cycles
(d)
p=0.016
serum IgG in g/l
before DARA
after DARA
(e)
p=0.313
CSF IgG in mg/l
before DARA
after DARA
(f)
p=0.219
rubella titer in IU/ml
cycle 0
cycle 3
last cycle
follow-up
(g)
p=0.047
tetanus toxoid titer in IU/ml
(h)
p=0.078
NF-L in pg/ml
patient #1
patient #2
patient #3
patient #4
patient #5
patient #6
patient #7
death
(i)
p=0.016
% CD38+ among memory CD8+ T cells
cycle 0
cycle 2
last cycle
follow-up
(j)
p=0.469
% HLA-DR+ among memory CD8+ T cells
(k)
p=0.016
% CD38+ among memory CD4+ T cells
(l)
p=0.156
% HLA-DR+ among memory CD4+ T cells

FIGURE 1 Overview of patients' clinical history with disease severity, applied treatments, and clinical and immunological outcome parameters before and after treatment with daratumumab. (a) The graphic illustration depicts patients' clinical course with modified Rankin Scale (mRS), duration of intensive care unit (ICU) stay and mechanical ventilation, history of antibody titers, and applied immunotherapies. Patients #1 and #2 were diagnosed with anti-contactin-associated protein 2 (CASPR2) encephalitis, Patient #3 with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, Patients #4 and #5 with autoimmune encephalitis mediated by autoantibodies directed against unknown epitopes (detected by indirect immunofluorescence of serum and cerebrospinal fluid [CSF] on mouse brain slides), Patient #6 with neurofascin antibody-associated chronic inflammatory demyelinating polyneuropathy (CIDP) with sporadic late onset nemaline myopathy (SLONM) and smoldering multiple myeloma, and Patient #7 with seronegative generalized myasthenia gravis with severe dependency on continuous plasma exchange therapy. All patients have in common that they received pretreatment with at least steroids, plasma exchange, and rituximab before daratumumab treatment initiation. (b) Patients with antibody-mediated autoimmune encephalitis (#1–#5) presented remarkable clinical improvement after treatment with daratumumab and during follow-up as measured by the Clinical Assessment Scale in Autoimmune Encephalitis (CASAE). (c) Patient #6 with neurofascin antibody-associated CIDP with SLONM and smoldering multiple myeloma and Patient #7 with seronegative myasthenia gravis also had relevant clinical benefit during ongoing daratumumab therapy as highlighted by decreases in Inflammatory Neuropathy Cause and Treatment (INCAT) score and Quantitative Myasthenia Gravis (QMG) score (without handgrip test). As an indirect marker of immunological response with relevant depletion of long-lived plasma cells, patients treated with daratumumab reached a considerable decrease of IgG levels in serum (d) and CSF (e) and reduction of long-lived vaccine titers like rubella IgG (f) and tetanus toxoid IgG (g). Interestingly, patients showed a trend toward a decrease of the neurodegeneration marker neurofilament light chain in serum after daratumumab treatment (h), which might serve as an indirect surrogate marker for treatment response. (i–l) Daratumumab treatment resulted in dramatic decrease of CD38 expression on $CD8^+$ and $CD4^+$ memory T cells ($CD45RA^-CCR7^-$) and increase of HLA-DR expression among memory $CD8^+$ and $CD4^+$ T cells ($CD45RA^-$ $CCR7^-$) that partly recovered after discontinuation of daratumumab administration (Patients #2–#5). Dashed lines (d, f–h) indicate normal ranges. Statistical analysis: (d–l) Wilcoxon matched-pairs signed rank test of $n = 7$. Significance: $p < 0.05$. Ab, antibody; AE, autoimmune encephalitis; DARA, daratumumab; i.v., intravenously; s.c., subcutaneously. (a) *Anti-CASPR2 antibody titers were much higher, but methodological limitations prevented exact titer quantification. [Colour figure can be viewed at wileyonlinelibrary.com]

by a relevant depletion of long-lived plasma cells, as indicated by reductions of autoreactive antibodies, immunoglobulin levels, and vaccine titers. Moreover, daratumumab induced a rapid decline of $CD38^+$ T lymphocytes and NK cells, which may have contributed to its disease-modifying immunomodulatory effects.

Our data suggest that daratumumab depleted long-lived plasma cells more efficiently than bortezomib (50%–80% vs. 30%) [3,17]. Notably, in patients with autoimmune encephalitis, (auto)antibody titers declined in serum and CSF. Regarding the limited capacity of daratumumab to cross the blood–brain barrier, it remains open whether daratumumab targets (autoreactive) plasma cells in the central nervous system or only in the periphery. The combinational approach of rituximab with daratumumab induced depletion of peripheral B cells, and short-lived and long-lived plasma cells, and might have limited antibody-trafficking and immigration of autoreactive B cells and plasma cells into the brain. Currently, it remains to be explored whether daratumumab can also affect other interactions between B and T cells and/or the expression of costimulatory/coinhibitory checkpoint molecules to modify chronic autoimmune disorders.

Previous studies for multiple myeloma reported a reasonable safety profile of daratumumab [11]. In our study, the observed side effects of daratumumab might appear more severe, but considering the high disease severity at ICU, age, comorbidities, and the frequency of infectious complications of other immunotherapies, the spectrum of side effects appears acceptable, especially because ultima ratio decisions to use daratumumab were partly made as an alternative to palliative care, as in Patient #1.

The investigated patients received a number of different pretreatments according to generally accepted standards (guidelines) on a variable time frame and with varying intensity before daratumumab treatment was initiated. We consider it likely that these therapies influenced the immune system and thus contributed to the effects and adverse events. We would like to emphasize that most of the patients were largely unsuccessfully pretreated with these therapies for many months and only showed improvements after starting daratumumab treatment.

As a practical recommendation, daratumumab treatment should be initiated after an appropriate interval from previous immunotherapies, as the use of too many immunosuppressive drugs in a short period of time may favor the occurrence of life-threatening infections. We recommend the application of six to eight cycles of 16 mg/kg daratumumab in patients with sufficient clinical remission and decrease of autoantibody titers. In patients not sufficiently improving, a longer and individualized daratumumab treatment scheme can be chosen based on the rate of symptom remission and decline in laboratory surrogate markers of plasma cell depletion such as autoantibody titers, immunoglobulin levels, and IgG titers of specific vaccines (e.g., tetanus toxoid or rubella).

Of note, six patients in our study receiving ≥6 cycles of daratumumab required IVIGs to substitute treatment-related hypogammaglobulinemia.

Limitations of this uncontrolled retrospective study include its small sample size, disease heterogeneity, variable pretreatments, and different numbers of applied daratumumab cycles and durations of follow-up. The coapplied immunotherapies were confounders when attributing clinical improvement and antibody titer decrease to daratumumab.

In conclusion, our data suggest that daratumumab might serve as promising escalation therapy for highly active and treatment-refractory antibody-mediated neurological diseases. This is of clinical relevance, because these bedridden, ICU-dependent patients have barely a chance to survive alternative high-risk interventions

TABLE 1 Characteristics of patients treated with daratumumab ($n = 3$ with paraneoplastic disease variant)

Characteristic	Patient #1, M	Patient #2, M	Patient #3, M
Age at disease onset, years	57	66	16
Age at DARA initiation, years	60	69	16
DARA cycles	13	8	6
Autoimmune disease	Anti-CASPR2 autoimmune encephalitis	Anti-CASPR2 autoimmune encephalitis	Anti-NMDAR encephalitis
Tumor association	Tongue carcinoma	None	None
Symptoms	Seizures, cerebellar ataxia, neuromyotonia, aggressive behavior, coma, central breathing disorder	Focal seizures, cognitive deficits, coma, anarthria, dysphagia, neuropathic pain, tetraparesis, dyskinesia, myoclonus, central breathing disorder	Status epilepticus, psychosis with hallucinations, anxiety and aggressive behavior, hyperkinetic movement disorder
Antibody titer before DARA	Anti-CASPR2 CSF: >1:1000 Serum: >1:10,000	Anti-CASPR2 CSF: negative Serum: 1:10.000	Anti-NMDAR CSF: 1:400 Serum: 1:3200
Antibody titer after DARA	Anti-CASPR2 CSF: 1:32 Serum: 1:10,000	Anti-CASPR2 CSF: negative Serum: 1:32	Anti-NMDAR CSF: 1:1 Serum: negative
MRI results	Slight edema bilateral amygdala, minimal hippocampal atrophy, focal cytotoxic edema right cerebellum	Bilateral putaminal lesions after cardiac arrest, otherwise normal	Diffuse ictal edema in wide areas of the cerebral cortex and caudate nuclei
CSF results	Normal except positive OCB and intrathecal IgG synthesis (51%)	Normal except intrathecal IgG synthesis (10%)	16/µl leukocytes, intrathecal IgM (47%) and IgA (13%) synthesis
Immunotherapy before DARA	OS, MP, PE, IA, IVIG, RTX, BTZ	OS, MP, PE, RTX	OS, MP, PE, IA, IVIG, RTX
DARA-related adverse events	2 urinary tract infections, death after septic shock	Tracheobronchitis, urinary tract and blood stream infection	Fever (after first DTM infusion), tracheobronchitis
Scores before DARA	mRS: 5 CASAE: 20	mRS: 5 CASAE: 20	mRS: 5 CASAE: 27
Best neurological outcome after DARA	mRS: 5 CASAE: 14	mRS: 4 CASAE: 3	mRS: 1 CASAE: 1
Final outcome	mRS: 6 (death: septic shock after multimodal immunotherapy)	mRS: 6 (death: cardiac arrest after incident with tracheal cannula)	mRS: 1 CASAE: 1
Time of follow-up (since DARA initiation)	5 months	15 months	13 months

Abbreviations: AZA, azathioprine; BTZ, bortezomib; CASAE, Clinical Assessment Scale in Autoimmune Encephalitis; CASPR2, contactin-associated protein 2; CRP, C-reactive protein; CSF, cerebrospinal fluid; DARA, daratumumab; ECU, eculizumab; F, female; IA, immunoadsorption; INCAT, Inflammatory Neuropathy Cause and Treatment; IVIG, intravenous immunoglobulins; M, male; MMF, mycophenolate mofetil; MP, methylprednisolone; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; MTX, methotrexate; n.d., not determined; NMDAR, N-methyl-D-aspartate receptor; OCB, oligoclonal bands; OS, oral steroids; PCT, procalcitonin; PE, plasma exchange; QMG, Quantitative Myasthenia Gravis score (without handgrip test); RTX, rituximab.

Patient #4, M	Patient #5, F	Patient #6, M	Patient #7, M
59	27	52	54
59	27	52	57
9	4	20	20
Autoimmune encephalitis with antibody against unknown epitope	Autoimmune encephalitis with antibody against unknown epitope (differential diagnosis: Neuro-Behçet disease)	Acute onset CIDP with neurofascin antibodies, sporadic late onset nemaline myopathy	Seronegative myasthenia gravis
Non-small cell lung cancer	None	Smoldering multiple myeloma	None (thymectomy: normal histology)
Focal seizures, orofacial dyskinesia/myokymia, autonomous dysregulation, cerebellar ataxia, dysphagia, tetraparesis, central breathing disorder	Fever, headache, lymphadenopathy, hypesthesia, left hemiparesis, delirium, coma, autonomous dysregulation, hyperkinetic movement disorder, hydrocephalus occlusus	Sensorimotor tetraplegia with atrophy, respiratory insufficiency, areflexia, cranial nerve involvement with dysarthria, dysphagia, facial diplegia	Generalized muscle weakness, dysarthria, dysphagia, diplopia, bilateral ptosis, facial diplegia, vocal cord paralysis, respiratory insufficiency
Unknown epitope CSF: 1:10 Serum: negative	Unknown epitope CSF: 1:100 Serum: 1:200	Serum: NF-186: 1:100 NF-155: 1:10	None
Unknown epitope CSF: negative Serum: negative	Unknown epitope CSF: negative Serum: negative	Serum: NF-186: negative NF 155: negative	None
Normal	Hyperintensities and contrast-enhancing lesions in basal ganglia/thalamus, mesencephalon, pons, corpus callosum and caudae hippocampi	Contrast enhancement of cauda equine and lumbar spinal roots; inflammatory changes of back, pelvic girdle, and thigh muscles	n.d.
Normal	514/µl leukocytes, glucose 50 mg/dl, lactate 33 mg/dl, protein 1517 mg/dl, intrathecal IgG (4%), IgM (54%), and IgA (19%) synthesis	Normal except elevated protein of 1165 mg/dl	n.d.
OS, MP, PE, IVIG, RTX	MP, PE, IVIG, RTX	OS, MP, PE, IVIG, RTX	OS, IVIG, PE, IA, AZA, MMF, MTX, RTX, ECU
Tracheobronchitis, fungemia, fever, tachycardia, tachypnea	Transient increase of leukocytes, CRP, and PCT without infection	Dyspnea, night sweat, fever, blood stream infection	Dyspnea, tachycardia, fatigue, muscle pain
mRS: 5 CASAE: 22	mRS: 5 CASAE: 21	mRS: 4 INCAT: 7	mRS: 5 QMG: 16/33
mRS: 5 CASAE: 8	mRS: 4 CASAE: 3	mRS: 0 INCAT: 0	mRS: 3 QMG: 8/33
mRS: 5 CASAE: 8	mRS: 4 CASAE: 3	mRS: 0 INCAT: 0	mRS: 3 QMG: 8/33
13 months	8 months	15 months	12 months

such as autologous stem cell transplantation. Anti-CD38 therapy seemed to provide its beneficial responses by depleting autoreactive plasma cells and potentially further immunomodulatory effects, disrupting the chronic autoimmune process. However, to investigate its safety and efficacy further, randomized clinical trials are required.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Franziska Scheibe: Conceptualization (lead), data curation (lead), formal analysis (lead), funding acquisition (equal), investigation (lead), methodology (lead), project administration (lead), resources (lead), supervision (lead), validation (lead), visualization (lead), writing–original draft (lead). **Lennard Ostendorf:** Conceptualization (supporting), data curation (supporting), formal analysis (supporting), investigation (supporting), writing–original draft (supporting). **Harald Prüss:** Data curation (supporting), formal analysis (supporting), writing–review and editing (supporting). **Helena Radbruch:** Conceptualization (supporting), data curation (supporting), formal analysis (supporting), investigation (supporting), methodology (supporting), visualization (supporting), writing–original draft (supporting). **Tom Aschman:** Conceptualization (supporting), data curation (supporting), formal analysis (supporting), methodology (supporting), resources (supporting), visualization (supporting), writing–original draft (supporting). **Sarah Hoffmann:** Data curation (supporting), formal analysis (supporting), writing–review and editing (supporting). **Igor-Wolfgang Blau:** Data curation (supporting), supervision (supporting), writing–review and editing (supporting). **Christian Meisel:** Conceptualization (supporting), data curation (supporting), formal analysis (supporting), investigation (supporting), writing–review and editing (supporting). **Tobias Alexander:** Conceptualization (supporting), data curation (supporting), formal analysis (supporting), supervision (supporting), writing–original draft (supporting). **Andreas Meisel:** Conceptualization (supporting), data curation (supporting), formal analysis (supporting), funding acquisition (equal), investigation (supporting), methodology (supporting), resources (supporting), supervision (supporting), validation (supporting), visualization (supporting), writing–original draft (supporting), writing–review and editing (supporting).

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol*. 2013;12:157-165.
2. Hiepe F, Dorner T, Hauser AE, Hoyer BF, Mei H, Radbruch A. Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. *Nat Rev Rheumatol*. 2011;7:170-178.
3. Scheibe F, Pruss H, Mengel AM, et al. Bortezomib for treatment of therapy-refractory anti-NMDA receptor encephalitis. *Neurology*. 2017;88:366-370.
4. Ratuszny D, Skripuletz T, Wegner F, et al. Case report: daratumumab in a patient with severe refractory anti-NMDA receptor encephalitis. *Front Neurol*. 2020;11:602102.
5. Scheibe F, Ostendorf L, Reincke SM, et al. Daratumumab treatment for therapy-refractory anti-CASPR2 encephalitis. *J Neurol*. 2020;267:317-323.
6. Pitarokoili K, Yoon MS, Kroger I, Reinacher-Schick A, Gold R, Schneider-Gold C. Severe refractory CIDP: a case series of 10 patients treated with bortezomib. *J Neurol*. 2017;264:2010-2020.
7. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood*. 2016;128:384-394.
8. Schuetz C, Hoenig M, Moshous D, et al. Daratumumab in life-threatening autoimmune hemolytic anemia following hematopoietic stem cell transplantation. *Blood Adv*. 2018;2:2550-2553.
9. Ostendorf L, Burns M, Durek P, et al. Targeting CD38 with daratumumab in refractory systemic lupus erythematosus. *N Engl J Med*. 2020;383:1149-1155.
10. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med*. 2017;377:62-70.
11. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *New Engl J Med*. 2015;373:1207-1219.
12. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380:2104-2115.
13. Lim JA, Lee ST, Moon J, et al. Development of the clinical assessment scale in autoimmune encephalitis. *Ann Neurol*. 2019;85:352-358.
14. Breiner A, Barnett C, Bril V. INCAT disability score: a critical analysis of its measurement properties. *Muscle Nerve*. 2014;50:164-169.
15. Bedlack RS, Simel DL, Bosworth H, Samsa G, Tucker-Lipscomb B, Sanders DB. Quantitative myasthenia gravis score: assessment of responsiveness and longitudinal validity. *Neurology*. 2005;64:1968-1970.
16. Kreye J, Reincke SM, Kornau H-C, et al. A therapeutic non-self-reactive SARS-CoV-2 antibody protects from lung pathology in a COVID-19 Hamster Model. *Cell*. 2020;183:1058-1069.e19.
17. Alexander T, Sarfert R, Klotsche J, et al. The proteasome inhibitior bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. *Ann Rheum Dis*. 2015;74:1474-1478.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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