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ORIGINAL RESEARCH

Daratumumab for autoimmune diseases: a systematic review

Marie-Therese Holzer ,[1] Nikolas Ruffer,[1] Tobias B. Huber,[2] Ina Kötter,[1,3] Lennard Ostendorf ,[4,5] Martin Krusche [1]

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LO and MK contributed equally.

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[1]Division of Rheumatology and Systemic Inflammatory Diseases, III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2]III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[3]Department of Rheumatology and Immunology, Klinikum Bad Bramstedt, Bad Bramstedt, Germany
[4]Department of Nephrology and Medical Intensive Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany
[5]Deutsches Rheuma-Forschungszentrum (DRFZ), Berlin, Germany

Correspondence to
Dr Marie-Therese Holzer; m.holzer@uke.de

ABSTRACT

Objective Refractory autoimmune diseases remain a significant challenge in clinical practice and new therapeutic options are needed. This systematic review evaluates the existing reported data on the CD38-targeting antibody daratumumab as a new therapeutic approach in autoantibody-mediated autoimmune diseases.

Methods A protocolised systematic literature review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was performed. Two databases (Medline and Embase) were searched for suitable studies. Usage of daratumumab in non-oncological or non-transplantation associated diseases with autoimmune pathophysiology was analysed including patient characteristics, therapeutic regimen, adverse events and patient outcome.

Results 38 publications reporting the clinical course of 83 patients met the inclusion criteria. Daratumumab usage was reported in therapy-refractory cases (median of 5 different previous therapies) in 24 different autoimmune diseases. The median number of applications of daratumumab was 4, mainly via intravenous applications (87%). Concomitant treatment included glucocorticoids in 64% of patients, intravenous immunoglobulins (33%) and rituximab (17%). Remission or improvement of disease was reported in 81% of patients. Autoantibody depletion or reduction was stated in 52% of patients. Death occurred in three patients (3%). Adverse events were reported in 45% of patients including application-associated reaction (20%), infection (19%) and hypogammaglobulinaemia (33%).

Conclusion Targeting CD38 via daratumumab is a new promising therapeutic option in therapy refractory autoimmune diseases. Efficacy as well as optimal therapeutic regimen and management or prevention of adverse events require further investigation. Therefore, systematic clinical trials of this therapeutic approach are needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The anti-CD38 monoclonal antibody daratumumab is evolving as a new therapeutic approach in autoantibody-mediated autoimmune diseases.

WHAT THIS STUDY ADDS

⇒ Daratumumab may be an effective option for treatment in a variety of therapy refractory diseases after conventional therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Addressing CD38 is a promising target for autoantibody-mediated diseases. Nevertheless, safety, efficacy and the best therapeutic regimen need to be evaluated in prospective, controlled clinical trials.

INTRODUCTION

Daratumumab, a CD38-monoclonal antibody, is a well-established therapeutic agent in many haematooncological diseases. Best known is its effect in multiple myeloma (MM),[1–3] since the transmembrane protein CD38 is highly expressed on myeloma cells.[4] The effect of the anti-CD38 antibody on MM cells is based on cell-mediated cytotoxicity but also complement-mediated cytotoxicity and phagocytosis.[5] Apart from on malignant cells, CD38 is also expressed on many immune cell types such as lymphocytes (as plasma cells or T cells), macrophages, dendritic cells or other cells such as neurons.[6]

B-cells are an important cell population in autoimmunity, as they are involved in autoantibody production.[7 8] Therapeutic targeting includes B-cell depletion (via monoclonal antibodies or chimeric antigen receptor T cells),[9] plasmapheresis[10] or intravenous immunoglobulins (Ig).[11]

Apart from B-cells, long-lived plasma cells also contribute to humoral autoimmunity.[12 13] The long-lived plasma cells have been found to be resistant to many conventional therapeutic strategies including glucocorticoids, rituximab or cyclophosphamide.[14 15] They survive independently of antigenic stimulation in niches within the bone marrow or in inflamed tissue and are resistant to conventional immunosuppressive treatment like B-cell-depleting therapy.[16] Plasma cells express high levels of CD38 surface molecule and an ex vivo study could prove the depletion of circulating plasma blasts and plasma

cells by daratumumab in human peripheral blood mononuclear cells.[17]

While analysing the effect of daratumumab in MM patients, auxiliary findings showed autoantibody levels (eg, rheumatoid factor or antineutrophil cytoplasmic antibodies) decrease under daratumumab therapy.[18] Subsequently, the use of daratumumab has been reported as an experimental therapy in case reports and series of different autoantibody-mediated diseases.

In this review, we systematically collected and analysed the current data on the use of daratumumab as a therapeutic option to evaluate the efficacy and safety of this new treatment approach in autoimmune diseases.

METHODS

A systematic review of the literature according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines[19] was conducted. Two databases (MEDLINE via PubMed, Embase via Ovid) were searched on the 16 March 2023 (updated search on 10 June 2023, on 9 September 2023 and 6 November 2023) to identify case reports and case series reporting the use of daratumumab in autoimmune diseases. A broad search strategy was developed: title and abstract were searched for 'daratumumab' with exclusion of the common haematological applications of 'leukemia', 'lymphoma', 'myeloma' or 'amyloidosis' in the title.

The retrieved publications were imported to Rayyan,[20] duplicates were deleted, and titles and abstracts were screened independently by two of the authors (M-TH and NR). Full text was reviewed if titles and abstracts lacked sufficient data for a decision. Disagreement was resolved by a third reviewer (MK).

The following criteria for inclusion were applied: (a) study published in a peer-reviewed journal; (b) publication in English language; (c) study type: case report or case series (individual data of reported cases available) as well as case-based reviews and (d) established diagnosis of an autoimmune disease. The following exclusion criteria were applied: (a) records: study result records; (b) language: other than English; (c) oncological diseases, monogenetic syndromes or associated paraneoplastic events (eg, POEMS syndrome (syndrome of polyneuropathy, organomegaly, endocrinopathy, myeloma protein and skin changes), myelodysplastic syndrome (MDS), monoclonal gammopathy of renal significance) and (d) usage of daratumumab pre (conditioning) or post-transplantation or in transplantation associated diseases (such as pure red cell aplasia after stem cell transplantation).

Microsoft Excel was used for data collection and data processing. Data extraction and analysation of patient and disease characteristics as well as of therapeutic regimen, treatment response and adverse events were performed. Plots were designed in GraphPad Prism V.10.

Due to the heterogeneity of data, a narrative synthesis was performed. Reported complete remission was recorded as remission. Description of clinical or laboratory improvement or partial remission was recorded as improvement. Adverse events were recorded as reported.

RESULTS

We identified 434 publications on MEDLINE and 430 publications on Embase. After deletion of duplications, 698 records were screened. Eventually, 38 studies (case reports and case series without controls) describing 83 different patients were included (figure 1). A detailed description of all extracted data is available in online supplemental table 1. Due to the heterogeneity of the data, no meta-analysis was performed. Instead, we performed a narrative synthesis of the available data.

Demographics

Of the 83 included patients, 50% (41/83) were male and 48% (40/83) were female (gender in two cases not reported). The median age was 34 (range 6–74) years. Daratumumab was used in 24 different conditions in neurology, haematology, nephrology and rheumatology (table 1). Most reported cases were haematological autoimmune diseases (40%), followed by the field of nephrology (25%), rheumatology and neurology (23% and 10%, respectively). All cases were refractory to standard-of-care therapy with a median of five different immunosuppressive treatments being applied before the start of daratumumab. Prior B-cell depletion with CD20-targeted therapy was used in 69 patients (83%).

Treatment regimen

The therapeutic regimen differed significantly between the reported cases: Concomitant treatment included mainly glucocorticoids (53/83, 64%), intravenous Ig (27/83, 33%), rituximab (14/83, 17%) or plasmapheresis (10/83, 12%) (online supplemental figure 1). Daratumumab was administered intravenously in most cases (73/83, 88%). The number of applications ranged from 1 to 24 with a median of 4. In 27 patients (33%) daratumumab was applied four times, in 19 patients (23%) only once (online supplemental figure 2). All cases in which daratumumab was administered multiple times, weekly application of daratumumab for up to the first eight applications was reported. The dosage of daratumumab applications varied. In most cases (41/83, 49%) daratumumab was dosed according to the current MM protocols for intravenously usage with 16 mg/kg.[1 21] Other therapeutic approaches were 1000 mg/1.73 m² body surface intravenously (20/83, 24%), 100 mg intravenously (5/83, 6%), 4 mg/kg intravenously (2/83, 2%) or 8 mg/kg intravenously (4/83, 5%) as well as the subcutaneous (sc) application of 1800 mg daratumumab (10/83, 12%). In one patient, the dosage from 8 mg/kg/week intravenously was elevated to 16 mg/kg/week as tolerated.

Outcome

Complete remission was reported in 47/83 cases (57%), improvement or partial remission in 18 cases (22%),

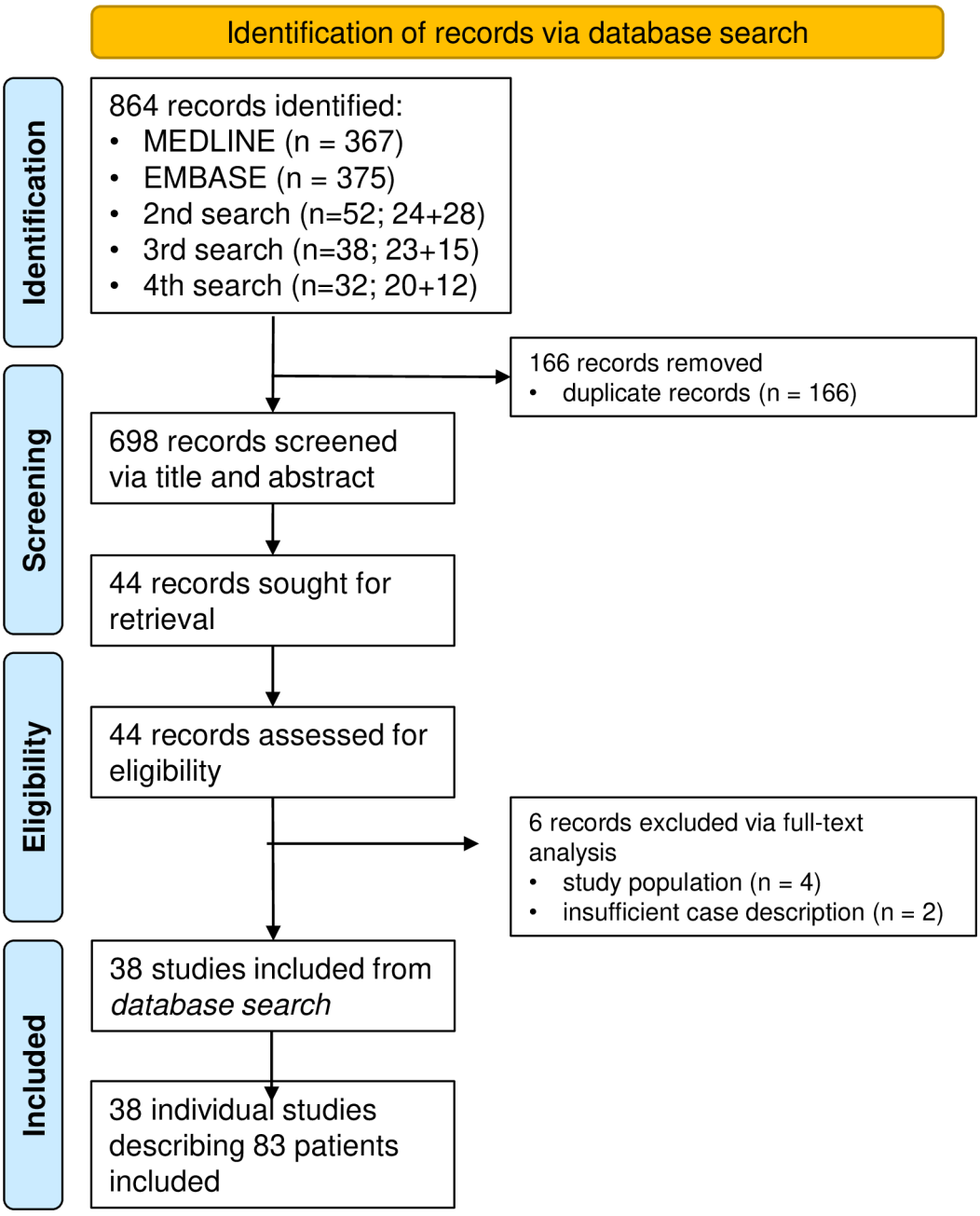

Figure 1 Flow chart showing the selection process of the systematic review.

stabilisation without improvement in one patient (1%) and remission after the first relapse with the help of a second cycle in two patients (2%). On the other hand, relapse, relapse after initial remission and complete failure occurred in six (7%), three (4%) and three (4%) patients, respectively (figure 2). Three patients died (4%): one patient due to septic shock, one death was caused due to ventilator-associated pneumonia after ventilation was necessary due to rituximab-induced pneumonitis and one patient died due to a ventilation cannula defect. Antibody depletion was reported in 20 patients (24%) and antibody reduction in 23 (28%) patients. Antibody reduction before relapse, as well as no effect on antibody titre, was measured in one (1%), respectively, three patients (4%). In all other cases, antibody levels were not reported (18 patients, 22%), not measured (1 patient, 1%) or not applicable (17 patients, 20%) (figure 3).

Adverse events

Notably, a significant proportion of the included case reports did not provide sufficient data on adverse events and 19 case descriptions (23%) lacked any statement. Reports of adverse events did not always comment on the most common events such as application-associated reaction, infection or hypogammaglobulinaemia. In the case of hypogammaglobulinaemia, not every publication included whether this adverse event was addressed with substitution of immunoglobulins. In total, adverse events were reported in 37 patients (45%). In 17 cases

Table 1 Included cases with the underlying disease

Autoimmune disease		No of patients
Haematological	Total	33 (40%)
	Idiopathic-acquired pure red cell aplasia	1
	Immune thrombocytopaenic purpura	8
	Acquired immune mediated thrombotic thrombocytopaenic purpura	9
	Autoimmune haemolytic anaemia	4
	Acquired haemophilia A	9
	Red blood cell antibodies (inducing haemolytic transfusion reaction in sickle cell disease)	1
	Idiopathic cold agglutinin disease	1
Rheumatological	Total	19 (23%)
	Idiopathic inflammatory myopathy	3 with: 2 MDA5-positive dermatomyositis with interstitial lung disease 1 SRP-positive immune mediated necrotising myopathy
	Systemic lupus erythematosus	10 with: 7 lupus nephritis 2 autoimmune haemolytic anaemia 1 cerebral vasculitis
	ANCA-associated vasculitis	4 with: 1 MPO-positive microscopic polyangiitis 3 PR3-positive granulomatosis with polyangiitis
	Primary Sjögren's disease	2 with: 1 cryoglobulinaemia 1 hyperchylomicronaemia
Nephrological	Total	21 (25%)
	Idiopathic nephrotic syndrome	14
	PLA2R-positive membranous nephropathy	1
	Focal segmental glomerulosclerosis	3
	Minimal change disease	3
Neurological	Total	8 (10%)
	Autoimmune encephalitis	6 with 2 NMDA-R-positive 2 CASPR2-positive 2 without antibody
	Chronic inflammatory demyelinating polyneuropathy	1
	Seronegative myasthenia gravis	1
Other	Total	2 (2%)
	Primary antiphospholipid syndrome	1
	Anti-IFNγ antibodies and severe mycobacterium avium infection	1

ANCA, anti-neutrophil cytoplasmic antibody; CASPR2, contactin associated protein-like 2; IFN, interferon; MDA5, melanoma differentiation-associated protein; MPO, myeloperoxidase; NMDA-R, N-methyl-D-aspartate receptor; PLA2R, phospholipase A2 receptor; PR3, proteinase 3; SRP, signal recognition particle.

(20%), an infusion reaction was reported, in 10 of these cases (12%) the patients suffered from dyspnoea, bronchospasm or tracheobronchitis. Interestingly, all reported application-associated reactions occurred in intravenously application. Hypogammaglobulinaemia was reported in 27 patients (33%) and infection in 15 patients (18%), respectively. Sepsis or bloodstream infection was reported in six cases (7%) (table 2). In six

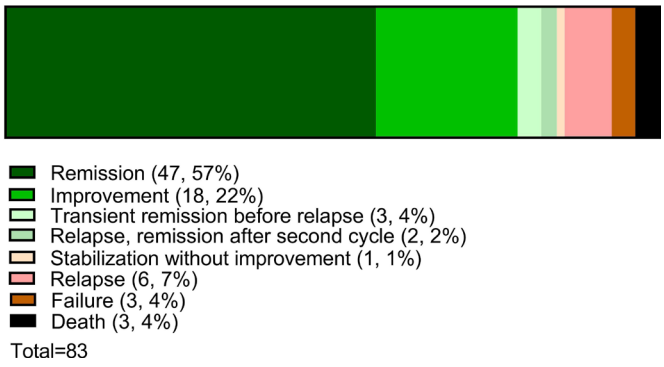

Figure 2 Clinical outcome of patients with autoimmune disease treated with daratumumab (number of patients).

cases (7%) infections occurred concomitant to hypogammaglobulinaemia (this corresponds to 40% of the reported 15 cases with infections). All other reports of infections did not state hypogammaglobulinaemia. The substitution of hypogammaglobulinaemia with immunoglobulins was reported in 24 patients (29% of all patients, respectively, 89% of patients with hypogammaglobulinaemia). There was no correlation between numbers of daratumumab applications and occurrence of hypogammaglobulinaemia (online supplemental figure 3). Deaths occurred in two patients with CASPR2-encephalitis and one patient with acquired haemophilia A.

Rheumatological diseases

The evaluation of the 19 patients with rheumatological diseases (three inflammatory idiopathic myopathies, ten systemic lupus erythematosus (SLE) including seven lupus nephritis, four ANCA-associated vasculitis patients and two primary Sjögren's disease) showed remission or disease improvement in 95% of the patients (18/19). Antibody depletion was reported in four cases (21%) and a reduction in 13 cases (68%). Two cases did not report antibody titres. A median of 5 therapies (minimum 1, maximum 9) was applied before treatment with daratumumab was initiated. In three patients (16%), hypogammaglobulinaemia was reported, these three patients received intravenous Ig substitution. Five patients (26%) developed a mild/asymptomatic infection or upper respiratory tract infection.

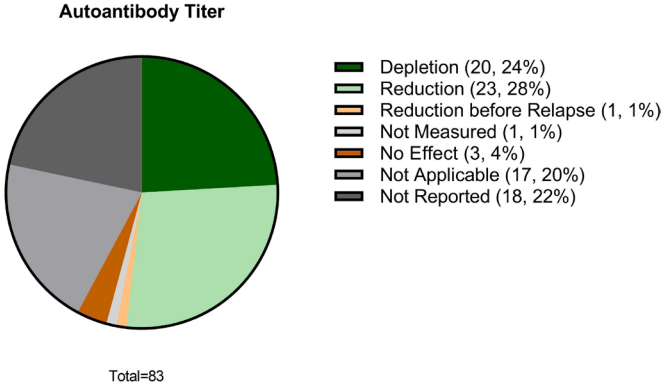

Figure 3 Autoantibody titre after daratumumab treatment (number of patients). Not applicable=cases without presence of known autoantibody.

Table 2 Reported adverse events

Reported adverse event	No of patients (% of all)
Any	37 (45)
Hypogammaglobulinaemia	27 (33)
Application-associated reaction	17 (20)
Dyspnoea, bronchospasm or tracheobronchitis	10 (12)
Urticaria, itching, flush, labial oedema	5 (6)
Vomiting, diarrhoea	3 (4)
Fever	2 (2)
Fatigue	1 (1)
Stated as mild without description	1 (1)
Infection	15 (18)
Upper respiratory or mild infection without description or asymptomatic SARS-CoV2 infection	7 (8)
Sepsis or bloodstream infection	6 (7)
Oral soor	1 (1)
Laboratory inflammation without clinical infection	1 (1)
Neutropenia	2 (2)
Aseptic meningitis*	1 (1)
Not reported	19 (23)
None	27 (33)

*With concomitant intravenous Ig treatment.

Autoantibody mediated diseases

Seventeen cases were reported without current autoantibodies: 14 cases with idiopathic nephrotic syndrome, one case with idiopathic pure red cell aplasia, one case with autoimmune encephalitis with autoantibodies against an unknown epitope and one case of seronegative myasthenia gravis. Though it is discussed, that in idiopathic nephrotic syndrome, idiopathic pure red cell aplasia and also seronegative myasthenia gravis so far unknown autoantibodies are present and could contribute to pathogenesis,[22–24] we analysed all cases with known autoantibody-mediation separately. In cases with autoantibody-mediated diseases remission was reported in 37/66 patients (56%), improvement in 16/66 patients (24%) and remission after initial relapse in 2/66 patients (3%). Therefore, remission or improvement was achieved in 83% of the autoantibody-mediated diseases. In the autoimmune diseases without autoantibodies, remission was stated in 10/17 (58%) and improvement in 2/17 (12%) patients respectively. The rate of remission or improvement in this subgroup remained at 71%.

Daratumumab after CD20-targeting therapy

We compared cases with (n=69) and without (n=14) previous CD20-targeting therapy. Positive treatment effects (remission, remission after initial relapse or improvement) occurred in 80% (55/69) and 86% (12/14), respectively. Autoantibody depletion or reduction was reported in 46% (32/69) and 79% (11/14), respectively.

DISCUSSION

To the best of our knowledge, this is the first systematic review of the literature to analyse and summarise the existing literature regarding the underlying disease, therapeutic regimen and adverse events for daratumumab in autoimmune disease. We found only reports of individual cases or case series without controls. Overall, these reported a high rate of positive outcomes despite treatment-refractory disease. In the reported rheumatological diseases,[25–35] 18 out of 19 patients achieved improvement or complete remission of the disease with good manageable adverse events and reduction or depletion of autoantibodies in 17 of the 19 cases.

In the existing reports, daratumumab was almost exclusively used in patients with treatment-refractory diseases and mostly was used as part of a combination therapy. Details on adverse events, prophylactic treatment during daratumumab therapy and the exact treatment regimen were not stated in all reports. Furthermore, a publication bias is possible, as negative outcomes after daratumumab application are less likely to be published.

The best therapeutic regimen for daratumumab in autoimmune diseases is currently unknown and varied widely in the analysed reports. For most patients, a protocol adapted to the MM regimen was used, which comprises a weekly application in the first eight weeks. The frequency of daratumumab applications ranged from 1 to 24 and did not correlate with the outcome (online supplemental table 1) nor with the risk of hypogammaglobulinaemia (online supplemental figure 3). Eight of the latest case reports, including ten patients[25 26 29 30 34–37] published in 2023, used daratumumab as sc application. Whereas in 17/73 (23%) patients with intravenously application infusion reaction occurred, none of the patients with sc application had a reported injection reaction. Results of a trial in MM showed significantly fewer application-related reactions such as chills and dyspnoea but more fever in sc application compared with intravenously application of daratumumab.[38] Combined with reported higher patient satisfaction but similar safety profiles and non-inferiority regarding the outcome,[38] sc use of daratumumab seems therefore preferable.

The ideal patient population for the use of daratumumab also needs further investigation. While the reports collected here almost exclusively deal with treatment-refractory cases, early depletion of pathogenic plasma cells could prevent the accrual of organ damage over time. On the other hand, depletion of (also protective) humoral immunity in patients without significant disease activity could lead to 'overimmunosuppression'. Similarly, higher total doses of daratumumab likely lead to a more complete depletion of pathogenic plasma cells but at the price of a probable higher risk of hypogammaglobulinaemia and infectious complications. In the reported cases, the number of applications did not correlate with the reported occurrence of hypogammaglobulinaemia, though it is to remark, that total dosages of daratumumab were mainly unknown and previous, lately applied medication should be taken into account as well.

Daratumumab showed a promising effect in the depletion or reduction of autoantibodies in 43 cases (91% of cases, in which autoantibody titre was reported). The relevance of autoantibodies in autoimmune diseases, especially in autoantibody-mediated rheumatic diseases, is discussed widely.[39] The findings on autoantibody reduction and concomitant disease improvement might, therefore, hint once more towards the importance of autoantibodies in the pathogenesis of many autoimmune diseases as well as towards a possible individualised biomarker-guided therapy.[26]

Interestingly, both subgroups (autoantibody-mediated diseases and diseases without stated autoantibody) had similar rates of disease remission and improvement (83% and 71%, respectively). Whether this is due to the antibody-depleting effect on so far not known autoantibodies in these diseases[22–24] or due to pleiotropic effects of daratumumab on the immune system[28 40] remains uncertain.

Based on the published literature, the use of daratumumab in autoimmune diseases seems to be relatively safe. The most often reported adverse event was hypogammaglobulinaemia (27/83, 33%), followed by infusion reaction in 17/83 (20%) and infection in 15/83 (18%). However, the absence of common adverse events associated with daratumumab (like infection, infusion/injection reaction, hypogammaglobulinaemia) was often not explicitly stated—therefore, the data on the frequency of side effects need to be interpreted with caution.

In addition, the use of prophylactic anti-infective treatment was often not reported. We, therefore, recommend a standardised reporting system of adverse events and comedication for future studies. For instance, if infectious complications were reported, only in six cases hypogammaglobulinaemia was explicitly mentioned. Therefore, it remains unclear, whether secondary hypogammaglobulinaemia played a role in other patients with infection. Recommendations for screening and monitoring secondary hypogammaglobulinaemia in B-cell-targeted therapy have been published.[41] According to several guidelines,[41 42] intravenous Ig replacement therapy can be evaluated especially in case of hypogammaglobulinaemia and recurrent infections. For MM, there is evidence that intravenous Ig replacement therapy for hypogammaglobulinaemia after CD38-targeted therapy can decrease infection risk.[43]

To systematically evaluate the efficacy and safety of daratumumab in autoimmune diseases, there are ongoing trials conducted for primary antiphospholipid syndrome, systemic lupus erythematosus and lupus nephritis, immune thrombocytopaenia, neuromyelitis optica spectrum disorder, Alzheimer's disease, light-chain amyloidosis, autoantibody-mediated haemolytic anaemia, haemophilia A or nephrotic syndrome (ClinicalTrials.gov on 25 June 2023, online supplemental table 2).

Data from experimental studies suggest that CD38 inhibition might be effective in other autoimmune diseases not reported in this study. For instance, CD38 was found to be upregulated in synovial biopsies from patients with rheumatoid arthritis and daratumumab application lead to depletion of plasmablasts in rheumatoid arthritis samples ex vivo.[17]

In addition to the effect on long-lived plasma cells, daratumumab might also influence other cells in autoimmune diseases as CD38 is widely expressed on diverse immune cell subsets. In SLE, a correlation between CD8+CD38+HLADR+ T cells and disease activity was seen[44] and data from an SLE patient treated with daratumumab suggest a modulation of CD38+ T cells with downregulation of proinflammatory genes without significant depletion.[28] Moreover, in vitro experiments of NK cells from SLE patients with disturbed cytotoxicity treated with daratumumab showed restoration of NK cell function.[45]

CONCLUSION

This systematic review shows promising effects of daratumumab as a new therapeutic option in refractory autoimmune diseases including haematological, nephrological, neurological and rheumatological diseases. All 19 rheumatological cases were autoantibody-mediated diseases with sometimes life-threatening courses, 18 of them showed improvement or remission of the disease as well as autoantibody depletion or reduction in response to daratumumab therapy in 17 cases. The therapeutic regimen used varied widely between cases and diseases. The main adverse events included hypogammaglobulinaemia, infections and infusion reactions in intravenous application with the latter possibly favouring the future use of sc daratumumab.

We, therefore, recommend systematically to analyse treatment effect, best therapeutic regimen, treatment duration and adverse events in prospective randomised trials or standardised larger cohorts.

Twitter Marie-Therese Holzer @holzer_mt and Martin Krusche @kruschemartin

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ORCID iDs
Marie-Therese Holzer http://orcid.org/0000-0002-2064-6728
Lennard Ostendorf http://orcid.org/0000-0003-3553-6406
Martin Krusche http://orcid.org/0000-0002-0582-7790

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