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REVIEW ARTICLE

Role of Anti-CD38 Monoclonal Antibodies in the Treatment of Adult Immune Hematological Diseases

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Abstract

Daratumumab is a first-in-class human anti-CD38 IgG1 monoclonal antibody approved for treating newly diagnosed and relapsed refractory multiple myeloma. Pre-clinical data supported daratumumab's ability to deplete autoantibodies producing plasma cells, B-cells, and NK cells. Those reports showed promising results on using daratumumab in autoimmune disorders that are refractory to multiple lines of therapies, which encouraged using daratumumab in various autoimmune conditions that are refractory to standard therapies. This review aims to summarize the literature reporting experience using anti-CD38 antibodies in hematological autoimmune diseases, focusing on the most common autoimmune hematological diseases, including autoimmune hemolytic anemia, immune thrombocytopenia, post-transplant cytopenia, and pure red blood cell aplasia.

Keywords: Autoimmune diseases, CD38, Daratumumab

1. Introduction

CD38 is a glycoprotein expressed on hematopoietic cells, including plasma cells, B cells, monocytes, and natural killer cells [1]. Anti-CD38 monoclonal antibodies play an important role in treating newly diagnosed and refractory multiple myeloma. There are currently two approved anti-CD38 medications, daratumumab and isatuximab. The roles of these medications in multiple myeloma and plasma cell dyscrasias have been established through multiple phase III clinical trials [2,3].

Anti-CD38 monoclonal antibodies exert their toxic activity against cells expressing CD38, such as plasma cells, through several mechanisms, such as complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis. Plasma cells have very high CD38 expression and play an important role in the pathogenesis of antibody-mediated autoimmune diseases through antibody production [4]. They are also resistant to current commonly used immunomodulatory therapies. This role was highlighted by some studies; for example, using RNA sequencing, genes related to plasma cells and plasmablasts were upregulated in synovial biopsies in patient with rheumatoid arithritis and systemic lupus erythematosus [5]. Additionally, daratumumab could ex-vivo deplete plasma cells and plasmablasts in peripheral blood mononuclear cells from patients with rheumatoid arthritis and systemic lupus erythematosus (SLE). Thus, it has been hypothesized that using anti-CD38 antibodies might be able to control of refractory autoimmune diseases. Several other in-vivo animal pre-clinical data have highlighted this possible role of daratumumab in autoimmune diseases. Using TAK 079 (also known as Mezagitamab), a fully human monoclonal

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antibody targeting CD38, less joint damage was noted by radiological and histopathological evidence when used in Cynomolgus monkeys [6].

Using daratumumab in MM decreased autoantibody titers in 85% of patients receiving it [7]. Several case reports demonstrated the role of daratumumab in patients with SLE; for instance, Ostendorf et al. reported the use of daratumumab in two patients with refractory SLE who achieved significant and durable clinical responses [8]. Several other examples were reported in other non-hematological autoimmune diseases, such as autoimmune encephalitis and antiphospholipid syndrome.

This review aims to summarize the literature reporting experience using anti-CD38 antibodies in hematological autoimmune diseases, focusing on the most common autoimmune hematological diseases, including autoimmune hemolytic anemia, immune thrombocytopenia, post-transplant cytopenia, and pure red blood cell aplasia. Additionally, the ongoing clinical studies investigating the role of the different anti-CD38 monoclonal antibodies will be highlighted.

2. Methodology

This study aims to provide a comprehensive review of the literature. Thus, a systematic electronic search was performed using Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) from inception to the first week of March 2023. The search strategy utilized Boolean logic. The terms were included as both keywords and MeSH terminology. The following anti-CD38 antibodies were included in the search: Daratumumab and Isatuximab. Alternatively, diseases included in the search were: autoimmune hemolytic anemia (AIHA), autoimmune cytopenias, immune thrombocytopenia (ITP), thrombotic thrombocytopenic purpura (TTP), and pure red cell aplasia (PRCA). The references of the resulting studies were searched, and google scholar was screened for any additional results.

Two authors separately screened the titles and abstracts of the yielded studies and selected the articles to be included in the study based on prespecified selection criteria. This review was limited to primary data (review articles were excluded), human adult studies (pediatrics and pre-clinical studies were not included), and English language. A meta-analysis was not performed because of the limited quality of data investigating this topic, the lack of randomized controlled studies, cohort studies, and variability in reported responses. However, clinical data of interest were collected, including demographics, prior lines of therapy, duration of therapy, doses, route of administration, best response, and duration of responses.

While analyzing the data, the following definitions were used to better summarize the results of the included studies. For AIHA, a response was defined as an increase in 2 g/dl in hemoglobin level or being transfusion independent. In the case of ITP, complete response was defined as achieving a platelet count above 100×10^9 and having no bleeding. Conversely, partial response was defined as achieving a platelet count above 30×10^9 or a two-fold increase in platelet count, in addition to having no bleeding. Not achieving a count of 30×10^9 was reported as no response [9].

3. Results

The search yielded 50 studies after removing duplications. Abstracts were screened for all included studies, and the full text was accessed when required. After excluding studies that did not meet inclusion criteria, 22 studies were included in the review. All included studies were case reports or case series, and all included studies reported daratumumab use. Fig. 1 shows the flow diagram of the systematic review.

Of the included studies: 6 studies (10 patients) discussed AIHA, 5 studies (11 patients) discussed ITP, 9 studies (10 patients) discussed PRCA, and 2 (7 patients) studies discussed immune TTP. We discuss the data and studies of each of the included diseases below.

3.1. Autoimmune hemolytic anemia (AIHA)

AIHA is an autoimmune disorder in which the immune system destroys red blood cells (RBCs). AIHA is classified as warm AIHA (WAIHA) and cold agglutinin disease (CAD). WAIHA is almost always mediated by Immunoglobulin type G [10]. WAIHA can rarely be mediated by IgA autoantibodies [11]. When exposed to low temperatures, CAD is mediated by IgM autoantibodies which fix complements and cause agglutination of RBCs. AIHA can be idiopathic or secondary to underlying conditions such as lymphoproliferative disorders, infections, neoplasms, or other autoimmune diseases [12].

Glucocorticoids are typically used first line for treating WAIHA, with response rates between 70% and 90%; less than half of these patients stay in remission for over one year [13]. Rituximab is frequently used as a first-line treatment along with glucocorticoids or in second-line settings. In

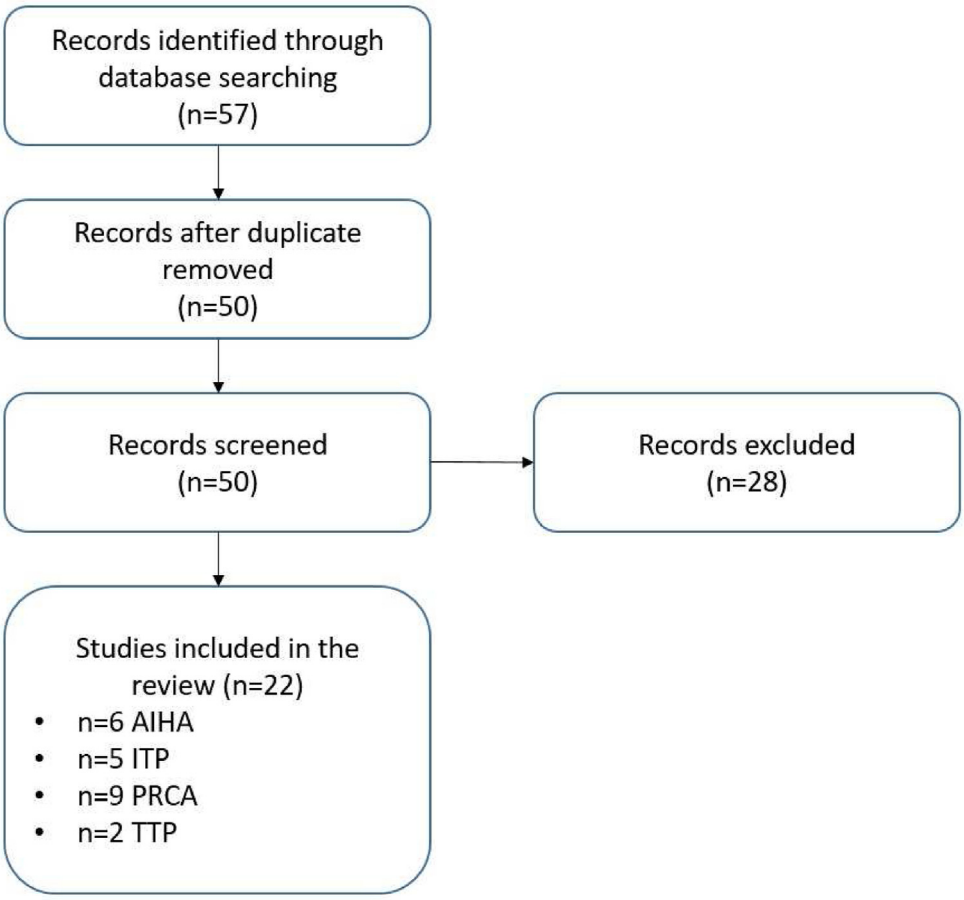

Fig. 1. The flow diagram of the systematic review.

refractory or persistent cases, various immunosuppressants such as cyclosporine, cyclophosphamide, azathioprine, mycophenolate mofetil, and bortezomib have been suggested in the literature [14]. Splenectomy is also occasionally considered in non-responders. No randomized trials have compared the efficacy of treatments in refractory cases.

For CAD, rituximab is preferred because glucocorticoids and splenectomy are ineffective in such patients [15]. Rituximab can induce remission in up to 60% of CAD cases; however, the remission rate can increase by adding fludarabine and bendamustine. In general, the response rate of CAD to immunosuppressants is poor. There are promising data on treating CAD with complement inhibitors such as sutimlimab, a monoclonal antibody against C1s, which was recently approved for use in CAD [16].

The literature on the use of anti-CD38 monoclonal antibodies in managing AIHA is discussed below. Notably, all studies published in the literature have used daratumumab and are limited to case reports and case series.

3.2. Warm autoimmune hemolytic anemia (WAIHA)

Four case reports/series discuss eight patients who received daratumumab to treat WAIHA; these included seven females and one male. Despite having differing courses of their disease and different prior interventions, they were all treated with a median of 4.5 (range, 1–8) therapies. All eight patients received steroids, and six patients were refractory to rituximab. Crickx et al. did not discuss why the two patients with WAIHA in their study were not treated with rituximab [17]. Three of the eight patients had received allogeneic stem cell transplants; however, only two were thought to have developed WAIHA secondary to ABO incompatibility, and the other was thought to be related to the recurrence of chronic myelogenous leukemia.

All patients received the standard dose of 16 mg/kg per week (range, 3–11 week) of intravenous daratumumab. In some patients, the number of doses given was modeled after the schedule used

for multiple myeloma treatment; however, weekly re-evaluation and other constraints determined the number they ultimately received. Jain et al. reported a 60-year-old female who received four infusions of daratumumab and had 20 weeks of transfusion independence before she relapsed; in this case, daratumumab had to be stopped due to financial constraints [18]. Reiger et al. reported a 60-year-old female patient who showed such a good response that only three infusions had to be administered, and she was in remission over a year out of the last one [19]. However, it remains unclear what the optimal number of cycles is because the two patients who received the most doses (11) were the two who had no response [17,20].

Six of eight patients had a response, as measured by an increase in average hemoglobin of two units or any significant period of transfusion independence. The response duration was between two to six months for those who relapsed, and the hemoglobin increase from nadir to peak was an average of 4 g/dl. Adjunct therapies included steroids (n = 5), IVIG (n = 2), and Eltrombopag (n = 1). The 44-year-old patient who received the eltrombopag had Evan's syndrome with WAIHA and ITP; hemoglobin and platelets stabilized during her remission [19].

Several patients developed minor infusion reactions to daratumumab that resolved with premedication. Crickx et al. reported a 55-year-old patient who did not respond to daratumumab and had an adverse event; she developed COVID pneumonia requiring hospitalization and with subsequent chronic viremia [17]. One death was noted among the reports, related more to the severity of an underlying disease rather than daratumumab treatment. Schuetz et al. reported on a 19-year-old female with WAIHA after a stem cell transplant for acute lymphoblastic leukemia. She had attempted over eight different therapies in different combinations before receiving daratumumab. She then achieved transfusion independence for four weeks before relapsing and needing further treatments. She eventually died from refractory WAIHA a few months later [20].

It is unlikely that many conclusions will be drawn from the data presented above, including the expected response rate and duration of response, which remain unclear, as reported cases vary in terms of types of previous treatments, other comorbidities, durations of daratumumab treatment, intervals of follow up, and the metrics used to determine treatment success. Five of the eight patients were receiving steroids at different doses co-administered with daratumumab, which adds another variable to the comparison. Overall, daratumumab offered a transient improvement in average hemoglobin and decreased the need for blood transfusions in most reported cases.

3.3. Cold agglutinin disease (CAD)

There are two reported cases of CAD successfully treated with daratumumab [21,22]. Both patients had CAD for approximately eight years and had been treated with multiple lines of therapy with inevitable relapse and transfusion dependence. In a study by Zaninoni et al. a 59-year-old man was treated with daratumumab (every week for two weeks, every other week for three months, followed by monthly for almost a year) with progressive improvement of anemia and circulatory symptoms. At publication, the patient had been on daratumumab for approximately 1.5 years with a stable clinical picture [21]. Tomkins et al. reported another successful experience with utilizing daratumumab in a 48-year-old male patient with disabling CAD associated with an underlying lymphoproliferative disorder. Despite having a stable hemoglobin of 12, he was treated due to severe symptoms of acrocyanosis and cold intolerance, which substantially affected his daily life. His symptoms started to improve within two weeks of therapy, and by week eight of treatment, symptoms disappeared, and hemolysis labs stabilized [22].

Both patients were diagnosed with CAD for approximately eight years before receiving daratumumab. In both cases, outcomes included the qualitative improvement of symptoms and the quantitative decrease in serum immunoglobulins with an increase in average hemoglobin. However, the reported cases had a short follow-up after the last daratumumab infusion (1–2 years). This makes it difficult to assess whether the benefits of daratumumab can persist beyond these few months or whether relapse is inevitable in patients with these highly refractory hematologic diseases.

3.4. Immune thrombocytopenic purpura (ITP)

ITP is an acquired antibody-mediated autoimmune disease resulting in increased destruction of platelets and impaired platelet production [23]. Mainstays of therapy for ITP include corticosteroids and IVIG in the first-line settings, with second-line options including rituximab, splenectomy, thrombopoietin receptor agonists, and other immunosuppressive therapies [24].

Eleven cases of refractory ITP treated with daratumumab were reported in the literature. There

were six males and five females, ages ranging from 20 to 82 years old. Some had symptoms of bleeding, including epistaxis, hemorrhagic cystitis, and petechial rashes. Many required weekly to bimonthly transfusions. All ten patients had received more than two lines of therapy, including steroids, IVIG, rituximab, eltrombopag, mycophenolate, and azathioprine; six had already had splenectomies [17,25–28].

Two cases involved 35-year-old and 60-year-old patients who developed refractory ITP after HCT [26,27]. Both patients had physical signs of bleeding and required many platelet transfusions. After receiving four daratumumab infusions (16 mg/kg weekly), their hemoglobin and platelet numbers stabilized, and they remained transfusion-free for a few months [26,27].

For all reported cases, daratumumab was given as a later line of therapy, and three to eight medications were used before daratumumab was initiated. All cases except one used the 16 mg/kg weekly intravenous dosing, and the treatment duration was between four to twelve cycles. Since there is no evidence-based recommendation for the number of cycles, this was determined on a case-by-case basis, sometimes limited by availability, financial constraints, or the development of adverse effects. Strussmann et al. reported on a case of ITP relapse in a 39-year-old man with a history of splenectomy 25 years prior to his presentation and multiple lines of therapy [29]. This is the only case where subcutaneous daratumumab (12 weekly doses of 1800 mg) was used for refractory ITP. The patient had a remarkable improvement in symptoms and achieved complete remission for 20 months and counting [29].

Steroids were used as an adjunct therapy n four patients. Vernava et al. reported an 82-year-old female who received daratumumab after her sixth relapse of ITP [28]. Prednisolone was added when she did not respond to the first few infusions. Thereafter, she achieved complete remission with stable platelets for the last year and could wean down the steroids. Crickx et al. reported on a 70-year-old patient who had no response to daratumumab in the first four weeks; however, after increasing his dose of co-administered steroids, he achieved long-lasting remission [17]. However, other cases did not respond to daratumumab despite receiving concomitant high-dose steroids and IVIG, and some patients achieved complete remission and did not receive any steroids with daratumumab [17].

Seven of the eleven patients had complete responses (platelets $>100 \times 10^9$), and one patient relapsed three months after daratumumab initiation. The other patients maintained their response for at least 6–20 months without relapse. Regarding side effects, there were a few minor reactions to daratumumab infusions reported across the case reports. Only one adverse event was reported in the 35-year-old patient who did not respond to daratumumab and was hospitalized for severe bacterial pneumonia approximately four weeks into treatment [17].

3.5. Pure red cell aplasia (PRCA)

In contrast to AIHAs which involve the destruction of circulating RBCs, PRCA is a production issue in which RBCs fail to mature, causing normocytic anemia [29]. In contrast to MDS and myeloid cancers, the bone marrows of these patients appear normal, suggesting an immunological impairment to erythropoiesis [30]. PRCA can happen idiopathically but can also be associated with several hematological disorders, including lymphoproliferative disorders and plasma cell dyscrasias, and it is also a common phenomenon after allogeneic hematopoietic cell transplant [31,32]. In allogeneic HCT, PRCA occurs in bidirectional or major ABO mismatched transplants. Treatment in cases of idiopathic PRCA involves immunosuppressive agents such as cyclophosphamide, corticosteroids, cytotoxic agents, and anti-thymocyte globulins [30]. In post-allogeneic HCT, PRCA has no established standard of care.

Our systematic review yielded nine case reports/series discussing ten adult patients who received daratumumab to treat PRCA. Only one study reported a case of idiopathich PRCA not post-HCT in a 74 year old patient with MGUS. The patient received nine different therapies for PRCA, including corticosteroids, immunosuppressive agents (cyclosporin, ATG, cyclophosphamide), anti-CD20 therapy (rituximab), and plasma cell-directed therapy (bortezomib). The patient had relapses or failure to respond after all of these lines. The patient was subsequently started on daratumumab weekly for eight weeks and continued it monthly. The patient achieved a partial response and was transfusion independent for more than 12 months; she was maintaining response by the time the report was published [33].

The other included studies ($n = 8$) discussed cases of post-HCT PRCA in patients who received ABO-incompatible transplants. The patients' ages ranged from 34 to 77 years old, and most were males. Indications for transplant included: Acute myeloblastic leukemia ($n = 4$), Myelodysplastic syndrome ($n = 3$), and aplastic anemia ($n = 1$). All patients had

PRCA at least 60 days after transplant with reported complete donor engraftment with positive high titer isohemagglutinin, and all patients had only PRCA as a sign of graft dysfunction [33–40] except for one case reported by Martino et al. where the patient also had thrombocytopenia [40].

All patients received intravenous daratumumab formulation, and most patients had weekly dosing at 16 mg/kg. However, Bicsko et al. reported a flat dose of 400 mg [38]. The duration of daratumumab administration and the number of cycles varied between the different studies; for instance, Asawapanumas et al. showed sufficient improvement after a single dose and reported that the response lasted at least a month [41]. The number of cycles ranged between 1 and 6; however, the response, as evidenced by reticulocytosis and hemoglobin, was reported after 1–2 cycles, except in Salas et al. where it was reported after dose six [37]. All patients achieved at least a partial response and were transfusion independent by the end of administered doses. Most patients (at least 5) had complete responses and normal hemoglobin levels after daratumumab administration. All patients included in the analysis were maintaining their responses by the time of publication. The longest response duration was reported by Martino et al. for a 77-year-old patient with AML who received allogeneic HCT and subsequently developed PRCA. The patient received three cycles of daratumumab, after which she maintained a response for >30 months [40]. Most included studies reported no side effects; however, one reported low immunoglobulins levels necessitating IVIG infusions [40].

Earlier studies using daratumumab for post-HCT PRCA used it after multiple lines of therapy (generally 3–5), with corticosteroids and rituximab being the most frequently used after immunosuppression tapering. However, two studies published in 2022 used it as initial therapy and reported at least partial response in the three included patients [40,41]. Daratumumab and anti-CD38 therapy appear promising in post-transplant settings [31]. This has been reported to have similar effects to those of daratumumab on resistant CD38-positive recipient's plasma cells which play a crucial role in PRCA pathophysiology as opposed to CD-20-positive immune cells [32,42].

3.6. Thrombotic thrombocytopenic purpura

Immune TTP is an autoimmune disorder involving antibodies against ADAMSTS13, an important enzyme in hemostasis [43]. TTP is an emergency associated with unhindered thrombus formation accompanied by microvascular hemolytic anemia and thrombocytopenia [44]. Management of TTP includes PLEX, steroids, caplacizumab, rituximab, bortezomib, and other immunosuppressive agents; it is common to see different treatments used in rapid sequence or parallel due to the high relapse rate [45]. There are two published articles reporting the use of daratumumab in TTP. In contrast to most other case reports covered in previous sections, these cases describe the effects of daratumumab treatment in combination with PLEX and other co-therapies [46,47].

Van den Berg et al. published the first reported case series of daratumumab use (intravenous 16 mg/kg dosing) in TTP treatment. Both patients initially received PLEX, steroids, caplacizumab, and rituximab but did not respond [46]. The first patient was a 32-year-old male in his third clinical relapse who was successfully treated with a combination of steroids, caplacizumab, and four infusions of daratumumab. The second was a 31-year-old female who was pregnant and had been diagnosed with HELLP syndrome; after her delivery, she still had persisting TTP symptoms. She was treated with caplacizumab and six infusions of daratumumab. After their respective regiments with daratumumab, both had platelet stabilization, the disappearance of inhibitory antibiotics, and restoration of ADAMSTS13 activity to normal. The remission was ongoing for approximately 14 and 10 weeks for these patients, respectively, at publication.

Xie et al. reported on five patients with TTP, who were all in their first episode and presented with varying symptoms. They received a regimen of PLEX (between 6 and 12 sessions), 100 mg daratumumab (D1), 100 mg rituximab (D1, 8, 15, 22), and daily steroids (dexamethasone 15–20 mg/kg or methylprednisolone equivalent) [47]. All patients eventually achieved complete remission within a couple of months after treatment. Three patients recovered ADAMSTS13 levels, and all five had stabilization of platelet levels. Their remissions lasted between 4 and 12 months.

These two studies vary widely in how daratumumab was administered, namely concerning the timing with other therapies. Van der Berg et al. gave both patients caplacizumab, steroids, and rituximab soon after PLEX, which maintained platelet levels but did not restore ADAMSTS13 levels [46]. As the decision was made to start daratumumab, one patient continued corticosteroids, and the other continued caplacizumab as a co-therapy. In the study by Van der Berg et al. daratumumab was given in sequence after rituximab [46]. This was in contrast to Xie et al. where patients were given

Table 1. Summary of ongoing clinical trials of the role of anti-CD38 monoclonal antibodies in autoimmune hematological diseases

Study title	ClinicalTrials.gov Identifier	Phase	Status	Locations
Safety, Pharmacokinetics, and Efficacy of Subcutaneous Isatuximab in Adults with Warm Autoimmune Hemolytic Anemia (wAIHA)	NCT04661033	I	Active, not recruiting	USA & Europe
The Safety of Repurposing Daratumumab for Relapsed or Refractory Autoimmune Antibody-Mediated Hemolytic Anemia (DARA-AIHA)	NCT05004259	I	Recruiting	USA
Efficacy of the antiCD38 Monoclonal Antibody Isatuximab in the Treatment of PCRA by Major ABO Mismatch After Allogeneic Hematopoietic Stem Cell Transplantation (ErythroSIM)	NCT05559827	II	Not yet recruiting	Europe
The DART Study- Daratumumab Treatment in ITP	NCT04703621	II	Recruiting	Europe
A Clinical Trial to Assess Safety and Efficacy of Daratumumab in the Treatment of Primary Immune Thrombocytopenia	NCT05562882	I	Not yet recruiting	China
A Prospective, One-arm, and Open Clinical Study of CM313 in the Treatment of Immune Thrombocytopenia (2022-CM313-ITP)	NCT05694767	II	Not yet recruiting	China
A Study of TAK-079 in Adults with Persistent/Chronic Primary Immune Thrombocytopenia	NCT04278924	II	Recruiting	USA & Europe

rituximab and daratumumab concurrently at 100 mg doses; rituximab was administered every week for four weeks, while daratumumab was only administered once after the first day of PLEX [47]. With the different doses and the varying permutations of co-therapies, it is difficult to conclude the true effects of daratumumab on TTP. More controlled studies will help clarify the ideal timing and dosing and any synergistic effects of daratumumab with other therapies.

4. Ongoing research

Three clinical trials registries (ClinicalTrials.gov, The European Union Clinical Trials Register, and International Standard Randomized Controlled Trial Number ISRCTN) were searched to evaluate the ongoing clinical trials investigating the role of anti-CD38 monoclonal antibodies in autoimmune hematological diseases. The search strategy was also limited to the diseases listed above; however, we also included experimental anti-CD38 antibodies, such as MOR202 (Felzartamab) and TAK-079.

Seven ongoing early phase studies (phase I and II) were identified. Four were single-group studies, and three had parallel groups. No phase III studies were identified. The studies are investigating the use of anti-CD38 antibodies in different diseases, including four on ITP, two on AIHA, and one on PRCA after transplant. Conversely, three studies utilized daratumumab, two used isatuximab, and two investigated two new anti-CD38 antibodies (CM313 and TAK-079). Of the four studies investigating daratumumab, two are investigating subcutaneous administration. Five studies are taking place in the United States (US) and/or Europe (one in the US alone, two in the US and Europe, one in multiple European countries, and one in France), and two are taking place in China. Four studies were recruiting at the time of the search, while the other three had not yet started recruiting. Studies are summarized in Table 1.

5. Conclusions

This study reviewed the current evidence on using daratumumab as a treatment option for autoimmune hematological disease, including AIHA, ITP, PRCA, and immune TTP. Given the crucial role that plasma cells play in the pathophysiology of these diseases, using plasma cell-directed therapy has been reported in the literature, including anti-CD38 monoclonal antibodies and proteasome inhibitors (Muhsen et al. 2019; Ostendorf et al. 2020). All studies included investigated the role of daratumumab.

The results showed promising results as most patients in the study responded, despite using daratumumab as a later-line therapy. However, it is difficult to conclude the overall quality of data assessing anti-CD38 monoclonal antibody use if poor and not using study designs that would allow

for a more accurate assessment of this role (e.g., interventional/experimental studies). However, many early-phase trials are being undertaken, as shown in Table 1.

Several limitations should be noted. First, the data reported here was driven from journal publications, which might indicate publication bias overestimating the efficacy of anti-CD38 monoclonal antibodies. The other limitation is the variability in reporting long-term follow-up data to assess the durability of the response. Regardless, daratumumab might be considered in refractory patients to the initial first and second line of therapy in different autoimmune conditions, given the results reported in the literature to date, along with a reasonable safety profile. Notably, the response was generally better in patients who develop these diseases after transplant, which might be explained by the role of resistant recipients' plasma cells in the pathophysiology of these diseases. More studies are needed to clarify this role and to investigate the efficacy of anti-CD38 monoclonal antibodies in such diseases.

Conflict of Interest

All authors have no conflicts of interest to declare. All co-authors have seen and agreed with the contents of the manuscript and there is no financial interest to report.

References

[1] Lin P, Owens R, Tricot G, Wilson CS. Flow cytometric immunophenotypic analysis of 306 cases of multiple myeloma. Am J Clin Pathol 2004;121(4):482–8.

[2] Gozzetti A, Ciofini S, Simoncelli M, Santoni A, Pacelli P, Raspadori D, et al. Anti CD38 monoclonal antibodies for multiple myeloma treatment. 18 Hum Vaccines Immunother 2022; 30(5):2052658. https://doi.org/10.1080/21645515.2022.2052658. Epub 2022 Apr 11.

[3] Kocoglu MH, Badros AZ. Newly diagnosed multiple myeloma: current treatment strategies, emerging therapeutic approaches and beyond. Expert Rev Hematol 2020;13(6): 669–86.

[4] Hofmann K, Clauder AK, Manz RA. Targeting B Cells and Plasma Cells in Autoimmune Diseases. Front Immunol 2018; 9:835.

[5] Cole S, Walsh A, Yin X, Wechalekar MD, Smith MD, Proudman SM, et al. Integrative analysis reveals CD38 as a therapeutic target for plasma cell-rich pre-disease and established rheumatoid arthritis and systemic lupus erythematosus. Arthritis Res Ther 2018;20(1):85.

[6] Korver W, Carsillo M, Yuan J, Idamakanti N, Wagoner M, Shi P, et al. A Reduction in B, T, and Natural Killer Cells Expressing CD38 by TAK-079 Inhibits the Induction and Progression of Collagen-Induced Arthritis in Cynomolgus Monkeys. J Pharmacol Exp Therapeut 2019;370(2):182–96.

[7] Frerichs KA, Verkleij CPM, Bosman PWC, Zweegman S, Otten H, van de Donk NWCJ. CD38-targeted therapy with daratumumab reduces autoantibody levels in multiple myeloma patients. J Transl Autoimmun 2019;2:100022.

[8] Ostendorf L, Burns M, Durek P, Heinz GA, Heinrich F, Garantziotis P, et al. Targeting CD38 with Daratumumab in Refractory Systemic Lupus Erythematosus. N Engl J Med 2020;383(12):1149–55.

[9] Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113(11):2386–93.

[10] Brodsky RA. Warm Autoimmune Hemolytic Anemia. N Engl J Med 2019;381(7):647.

[11] Sokol RJ, Booker DJ, Stamps R, Booth JR, Hook V. IgA red cell autoantibodies and autoimmune hemolysis. Transfusion 1997;37(2):175.

[12] Berentsen S, Barcellini W. Autoimmune Hemolytic Anemias. N Engl J Med 2021;385:1407.

[13] Michel M, Terriou L, Roudot-Thoraval F, Hamidou M, Ebbo M, Le Guenno G, et al. A randomized and double-blind controlled trial evaluating the safety and efficacy of rituximab for warm auto-immune hemolytic anemia in adults (the RAIHA study). Am J Hematol 2017;92:23–7.

[14] Muhsen IN, Alahmari A, Alnahedh M, Alkhudair NA, Samarkandi H, El Fakih R. Bortezomib for immune thrombocytopenia and autoimmune hemolytic anemia. Hematol Oncol Stem Cell Ther 2020;13(4):251–4.

[15] Berentsen S. How I treat cold agglutinin disease. Blood 2021; 137:1295.

[16] Röth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Sutimlimab in Cold Agglutinin Disease. N Engl J Med 2021;384(14):1323–34.

[17] Crickx E, Audia S, Robbins A, Boutboul D, Comont T, Cheminant M, et al. Daratumumab, an original approach for treating multi-refractory autoimmune cytopenia. Haematologica 2021;106(12):3198–201.

[18] Jain A, Gupta DK. Daratumumab for refractory warm autoimmune hemolytic anemia. Ann Hematol 2021;100(5): 1351–3.

[19] Rieger MJ, Stolz SM, Ludwig S, Benoit TM, Bissig M, Widmer CC, et al. Daratumumab in rituximab-refractory autoimmune haemolytic anaemia. Br J Haematol 2021;194(5): 931–4.

[20] Schuetz C, Hoenig M, Moshous D, Weinstock C, Castelle M, Bendavid M, et al. Daratumumab in life-threatening autoimmune hemolytic anemia following hematopoietic stem cell transplantation. Blood Adv 2018;2(19):2550–3.

[21] Zaninoni A, Giannotta JA, Gallì A, Artuso R, Bianchi P, Malcovati L, et al. The Immunomodulatory Effect and Clinical Efficacy of Daratumumab in a Patient with Cold Agglutinin Disease. Front Immunol 2021;12:649441.

[22] Tomkins O, Berentsen S, Arulogun S, Sekhar M, D'Sa S. Daratumumab for disabling cold agglutinin disease refractory to B-cell directed therapy. Am J Hematol 2020 Jul 11. https://doi.org/10.1002/ajh.25932.

[23] Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med 2002;346(13):995–1008.

[24] Miltiadous O, Hou M, Bussel JB. Identifying and treating refractory ITP: difficulty in diagnosis and role of combination treatment. Blood 2020;135(7):472–90.

[25] Blennerhassett R, Sudini L, Gottlieb D, Bhattacharyya A. Post-allogeneic transplant Evans syndrome successfully treated with daratumumab. Br J Haematol 2019;187(2): e48–51.

[26] Migdady Y, Ediriwickrema A, Jackson RP, Kadi W, Gupta R, Socola F, et al. Successful treatment of thrombocytopenia with daratumumab after allogeneic transplant: a case report and literature review. Blood Adv 2020;4(5):815–8.

[27] Vernava I, Schmitt CA. Daratumumab as a novel treatment option in refractory ITP. Blood Cells Mol Dis 2023;99:102724. https://doi.org/10.1016/j.bcmd.2023.102724. Epub 2023 Jan 13.

[28] Strüßmann T, Jung J, Heinz J, Duque Afonso J, Wäsch R, Engelhardt M, et al. Long-term complete remission of

refractory severe idiopathic immune thrombocytopenia (ITP) treated with daratumumab. Ann Hematol 2023;102(1):245−7.
[29] Means Jr RT. Update on pure red cell aplasia: etiology, diagnosis, and treatment. Clin Adv Hematol Oncol 2022; 20(1):18−21.
[30] Sawada K, Fujishima N, Hirokawa M. Acquired pure red cell aplasia: updated review of treatment. Br J Haematol 2008; 142(4):505−14.
[31] Marco-Ayala J, Gómez-Seguí I, Sanz G, Solves P. Pure red cell aplasia after major or bidirectional ABO incompatible hematopoietic stem cell transplantation: to treat or not to treat, that is the question. Bone Marrow Transplant 2021; 56(4):769−78.
[32] Longval T, Galimard JE, Leprêtre AC, Suarez F, Amiranoff D, Cazaux M, et al. Treatment for pure red cell aplasia after major ABO-incompatible allogeneic stem cell transplantation: a multicentre study. Br J Haematol 2021;193(4):814−26.
[33] Gangat N, Bleeker J, Lynch D, Olteanu H, Letendre L, Tefferi A. Daratumumab for treatment-refractory acquired idiopathic pure red cell aplasia. Haematologica 2022;107(10): 2523−6.
[34] Bathini S, Holtzman NG, Koka R, Singh Z, Wilding E, Zou Y, et al. Refractory postallogeneic stem cell transplant pure red cell aplasia in remission after treatment with daratumumab. Am J Hematol 2019;94(8):E216−9.
[35] Chapuy CI, Kaufman RM, Alyea EP, Connors JM. Daratumumab for Delayed Red-Cell Engraftment after Allogeneic Transplantation. N Engl J Med 2018;379(19):1846−50.
[36] Rautenberg C, Kaivers J, Germing U, Haas R, Ackerstaff S, Hoffmann T, et al. Daratumumab for treatment of pure red cell aplasia after allogeneic stem cell transplantation. Bone Marrow Transplant 2020;55(6):1191−3.
[37] Salas MQ, Alahmari A, Lipton JH. Successful treatment of refractory red cell aplasia after allogeneic hematopoietic cell transplantation with daratumumab. Eur J Haematol 2020; 104(2):145−7.
[38] Bicsko RR, Magyari F, Szasz R, Illes A, Gergely L. Administration of daratumumab in the case of severe pure red cell aplasia after allogeneic transplantation. Ann Hematol Oncol 2021;8:1331−2.
[39] Henig I, Yehudai-Ofir D, Zohar Y, Zuckerman T. Pure Red Cell Aplasia following ABO-Mismatched Allogeneic Hematopoietic Stem Cell Transplantation: Resolution with Daratumumab Treatment. Acta Haematol 2021;144(6):683−7.
[40] Martino R, García-Cadenas I, Esquirol A. Daratumumab may be the most effective treatment for post-engraftment pure red cell aplasia due to persistent anti-donor isohemagglutinins after major ABO-mismatched allogeneic transplantation. Bone Marrow Transplant 2022;57(2):282−5.
[41] Asawapanumas T, Chanswangphuwana C, Watanaboonyongcharoen P, Rojnuckarin P, Bunworasate U. Daratumumab as a Frontline Immunosuppression for Pure Red Cell Aplasia after Major ABO-mismatched Allogeneic Hematopoietic Stem Cell Transplantation. Leuk Res Rep 2022;17:100314.
[42] Bolan CD, Leitman SF, Griffith LM, Wesley RA, Procter JL, Stroncek DF, et al. Delayed donor red cell chimerism and pure red cell aplasia following major ABO-incompatible nonmyeloablative hematopoietic stem cell transplantation. Blood 2001;98(6):1687−94.
[43] Furlan M, Robles R, Solenthaler M, Lämmle B. Acquired deficiency of von Willebrand factor-cleaving protease in a patient with thrombotic thrombocytopenic purpura. Blood 1998;91(8):2839−46.
[44] Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. Blood 2017;129(21):2836−46.
[45] Sukumar S, Lämmle B, Cataland SR. Thrombotic Thrombocytopenic Purpura: Pathophysiology, Diagnosis, and Management. J Clin Med 2021;10(3):536.
[46] van den Berg J, Kremer Hovinga JA, Pfleger C, Hegemann I, Stehle G, Holbro A, et al. Daratumumab for immune thrombotic thrombocytopenic purpura. Blood Adv 2022;6(3):993−7.
[47] Xie XT, Xiao YY, Zhang Y, Luo ZM, Luo Y. Combination regimens containing daratumumab for initial diagnosed acquired thrombotic thrombocytopenic purpura. J Thromb Thrombolysis 2023;55(2):399−405.