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Daratumumab: new indications revolving around "off-targets"

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The IgG1κ monoclonal anti-CD38 antibody daratumumab, approved only 5 years ago, has become a principal agent in the treatment of patients with multiple myeloma. Evidence from multiple trials and real-world experience proved its safety and effectiveness.[1] Daratumumab targets CD38, a membrane glycoprotein with various functions. Binding of CD38 to its ligand (CD31) enables plasma cells to interact with surrounding immune and endothelial cells. Additionally, CD38 serves as a dual active enzyme involved in generating and hydrolyzing ADP-ribosyl cyclase and, therefore, affects intracellular calcium signaling and energy metabolism.[2] Normal human plasma cells, as well as myeloma cells, express CD38 highly. The anti-myeloma effect of daratumumab is mediated through the elimination of CD38-expressing plasma cells. During anti-myeloma therapy, binding of daratumumab to $CD38^+$ natural killer (NK), T and B cells, and erythrocytes leads to "off-target" effects as well as to some common side effects, such as interference with blood product cross-matching or potential immunemodulation through regulatory T-cell elimination. However, the clinical significance of "off-target" effects of daratumumab on $CD38^+$ non-plasma cells is not yet fully characterized.

In this issue of *Haematologica*, Crickx and colleagues[3] reported the outcome of eight patients treated with daratumumab for refractory immune thrombocytopenia (ITP) or warm autoimmune hemolytic anemia (AIHA). Patients were struggling with long-lasting diseases, with a median duration of 84.5 months (range, 18–174), refractory to multiple lines of standard therapies. The protocol of daratumumab administration was weekly infusions of 16 mg/kg combined with oral dexamethasone for at least four doses. Three out of five ITP patients and one of two patients with warm AIHA responded. A decrease in gammaglobulin levels was reported, but the autoimmune suppressive effect of daratumumab in these patients most probably went beyond its effect on patients' normal plasma cells. Notably, in addition to plasma and mature B cells, CD38 is also expressed by T and NK cells, and can also be induced by interferon and other cytokines. These cells are considered "off-targets" and in multiple myeloma patients treated with daratumumab, a reduction in regulatory T-cell count and expansion of $CD4^+$ and $CD8^+$ T cells were reported.[4] Therefore, caution is required with co-administration of daratumumab and checkpoint inhibitors or other immune therapies. Studies are ongoing to confirm the safety of such combinations. Given its multiple targets, predicting which patients with autoimmune diseases will benefit from daratumumab is a challenge.

The patients treated by Crickx and colleagues had long-lasting ITP or warm AIHA resistant to various lines of therapy. ITP and warm AIHA are antibody-mediated diseases and therefore one can speculate that daratumumab targeted mature B or plasma cells which survived previous lines of therapy. Such a mechanism may apply in other antibody-mediated refractory diseases. Indeed, reports of successful treatments in similar situations are accumulating (Table 1), including daratumumab as a therapeutic option in ABO mismatch-derived post-allogeneic stem cell transplantation hemolysis/cytopenia or pure red cell aplasia, antibody-mediated rejection of transplanted kidney, and even in a refractory case of antiphospholipid syndrome. An attempt to investigate the immune pathophysiology of ITP was made through a comprehensive pathology evaluation of patients' spleens. CD38 was identified as a prominent marker specifically present in clinically severe cases.[5] However, despite broad-range staining for multiple markers, the authors could not definitely confirm that the $CD38^+$ cells were of B-cell or plasma-cell phenotype.

The potential activity of daratumumab in targeting T cells or early lymphoid precursors was demonstrated in a preclinical study in mice injected with T-cell acute lymphoblastic leukemia.[6] Next came reports of successful treatment of patients with resistant cases of acute lymphoblastic leukemia with daratumumab,[7-9] with best and lasting responses achieved in patients treated for minimal residual disease eradication. Interestingly, daratumumab was recently reported to be active in diseases in which the pathological immune response was complicated and

Table 1. List of conditions in which daratumumab has been reported to be clinically beneficial.

Condition	Reference
Post-allogeneic stem cell transplantation hemolysis/ cytopenia	Blood. 2016;128:4819 Blood Advances 2018;2(19):2550-2553 British Journal of Haematology 2019;187(2): e48-e51 Pediatric Blood & Cancer 2021;67(1):e28010. Blood Advances 2020;4(5): 815. Molecular and Cellular Pediatrics 2021;8(1):1-7. Frontiers in Immunology 2021;12:444..
Post-allogeneic stem cell transplantation pure red cell aplasia	New England Journal of Medicine 2018;379(19):1846-1850 American Journal of Hematology 2019;94(8):E216-E219. Bone Marrow Transplantation 2020;55(6):1191-1193. European Journal of Haematology 2020;104(2):145-147 Acta Haematologica 2021;Apr 22;1-5 [Online ahead of print]
Autoimmune hemolysis	Transfusion 2019;59:3801-3802 American Journal of Hematology 2020 Jul 11 Annals of Hematology 2021;100(5);1351-1353
Antibody-mediated rejection of transplanted kidney	Case Reports in Nephrology and Dialysis 2019;9(3): 149-157
Antiphospholipid syndrome	Frontiers in Immunology 2021;12:1133
Systemic lupus erythematosus	New England Journal of Medicine 2020;383(12):1149-1155.
Proliferative glomerulonephritis	Journal of the American Society of Nephrology 2021;32 (5): 1163-1173

involved multiple coordinating cells such as systemic lupus erythematous, and proliferative glomerulonephritis (Table 1). The multiple aberrant immune mechanisms potentially involved make it difficult to identify the exact mechanisms of action of daratumumab in such conditions. Notably, a recent alarming report described that patients with COVID-19 can produce autoantibodies targeting CD38 which lead to exacerbation of immune responses resulting in autoimmune thyroiditis, insulin-dependent diabetes and even exacerbating the cytokine storm and other deleterious responses in COVID-19.[10]

Daratumumab is an effective anti-myeloma agent with a low toxicity profile. Its prominent effect is elimination of CD38-bearing cells, and in myeloma patients it targets mostly malignant plasma cells. The current report by Crickx *et al.* suggests that it should be considered as a therapeutic option in refractory cases of ITP and warm AIHA. A proposed mechanism of action is similar to that in myeloma, i.e., elimination of antibody-producing cells, but since CD38 is presented by many other immune cells, potential 'off-target' effects cannot be ruled out. Daratumumab's potential effectiveness against T-cell acute lymphoblastic leukemia is to be investigated in a future, planned, prospective study. The work by Crickx *et al.* is a step forwards in recognizing the potential role of daratumumab in autoimmune conditions. However, this treatment should be used with caution because its effect on multiple arms of the immune system may lead to paradoxical responses.

Disclosures

No conflicts of interest to disclose.

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