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Daratumumab - New indications revolving around "off-targets"

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The IgG1k monoclonal anti-CD38 antibody daratumumab, approved only five years ago, became a principal agent in the treatment of patients with multiple myeloma. Evidence from multiple trials and real world experience proved its safety and effectiveness¹. 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 intra-cellular calcium signaling and energy metabolism². Normal human plasma cells, as well as myeloma cells, highly express CD38. 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, T and B cells, and erythrocytes leads to "off-target" effect as well as to some common side effects, such as the interference with blood products cross-match or potential immune-modulation through regulatory T cell elimination. Yet, the clinical significance of daratumumab "off-target" effect on CD38+ non-plasma cells is not fully characterized.

In this issue of *Haematologica*, Crickx and colleagues³ reported the outcome of eight patients treated with daratumumab for refractory immune thrombocytopenia (ITP) or warm autoimmune hemolytic anemia (wAIHA). Patients were struggling with a long-lasting disease duration, with a median of 84.5 months (range 18–174), refractory to multiple lines of standard therapies. The daratumumab administered protocol 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 wAIHA responded. A decrease in gamma-globulin levels was reported, but the autoimmune suppressive effect of daratumumab in these patients most probably goes beyond its effect on patients' normal plasma cells. Notably, in addition to plasma and mature B cells, CD38 is expressed also by T and NK cells, and can also be induced by interferon and other cytokines. These cells are considered "off-targets" and in MM patients treated with daratumumab, a reduction in regulatory T cell count and expansion of CD4+ and CD8+ T cells was reported⁴. 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.

Patients treated by Crickx and colleagues presented with long lasting ITP and wAIHA resistant to various lines of therapy. ITP and wAIHA are antibody mediated diseases and therefore one can speculate daratumumab targets mature B or plasma cells which survived previous lines of therapy. Such a mechanism may apply for 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 mismatches 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 immune thrombocytopenia was made through a comprehensive pathology evaluation of patients' spleens. CD38 was identified as a prominent marker specifically present in clinically severe cases⁵. However, despite broad-range staining for multiple markers, authors could not definitely confirm that the CD38+ cells were of B or plasma cell phenotype.

The potential activity of daratumumab in targeting T cells or early lymphoid precursors came from a preclinical study demonstrating its potential effect in T-ALL injected mice⁶. Next, came reports of successful treatment of patients with resistant cases of ALL with daratumumab⁷⁻⁹, with best and lasting responses achieved in patients treated for minimal residual disease eradication. Interestingly, daratumumab was recently reported active in diseases where the pathological immune response was complicated and involves multiple coordinating cells such as systemic lupus erythematosus, and proliferative glomerulonephritis (Table 1). The multiple aberrant immune mechanisms potentially involved in these diseases are a challenge for identifying the exact mechanism in which daratumumab is effective in such conditions. Notably, a recent alarming report described that COVID19 produces autoantibodies targeting CD38 that lead to exacerbation of immune response resulting in autoimmune thyroiditis, insulin dependent diabetes and even exacerbating cytokine storm and other deleterious response in COVID19¹⁰.

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

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Table 1 - List of conditions in which daratumumab was reported clinically beneficial

Condition	Reference	
Post-allogeneic stem cell transplantation hemolysis/cytopenia	Blood. 128 (2016):4819 Blood Advances, 2.19(2018), 2550-2553 British Journal of Haematology, 187.2(2019), e48-e51 Pediatric Blood & Cancer, 67.1(2020), e28010. Blood Advances, 4.5(2020), 815. Molecular and Cellular Pediatrics 8.1 (2021): 1-7. Frontiers in Immunology 12 (2021): 444..	
Post-allogeneic stem cell transplantation pure red cell aplasia	New England Journal of Medicine 379.19 (2018): 1846-1850 American Journal of Hematology 94.8 (2019): E216-E219. Bone Marrow Transplantation, 55.6(2020), 1191-1193. European Journal of Haematology 104.2 (2020): 145-147 Acta Haematologica (2021): 1-5.	
Autoimmune hemolysis	Transfusion. 59 (2019):3801–2. Am J Hematol. 2020 Jul 11 Ann Hematol. 100.5 (2021); 1351-1353	
Antibody mediated rejection of transplanted kidney	Case Reports in Nephrology and Dialysis 9.3 (2019): 149-157	
Antiphospholipid syndrome	Frontiers in Immunology 12 (2021): 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	