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Case Study
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Lack of Efficacy of Daratumumab in a Patient with Severe Refractory Rheumatoid Arthritis

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Rheumatoid arthritis; Refractory; Daratumumab

Case Study

Genuine refractory Rheumatoid Arthritis (RA) is considered to exist when all potentially useful available therapeutic options have been exhausted [1]. Furthermore, the persistence of joint inflammation together with the presence of a brisk acute phase reaction and progression of structural damage might support the concept of a true refractory disease. In an attempt to look for a novel therapeutic strategy in a patient with refractory RA, and based on previous success in other autoimmune disorders [2,3] and *in vitro* experiments with RA samples [4], we used daratumumab, a human monoclonal antibody that targets CD38.

A 29 years old woman with a 10-year history of RA was first attended on 7/2011 because of a 5-months history of polyarthritis affecting small and large joints. At the initial visit, DAS 28 was 5.99 and she already had erosive disease. At diagnosis, ESR was 120 mm/1st h and she had a high autoantibody burden (RF: 632, ACCP: 632, ANA+ 1/1280).

She was started on methotrexate (20 mg/w) together with corticosteroids with a limited response. Three months later, she started etanercept combined with methotrexate, and due to the lack of response, 3 months later rituximab was added to methotrexate. Despite treatment, RA remained active (always moderate-high DAS28 activity and high acute phase reactants) and during the following years she subsequently received (added to methotrexate), tocilizumab, abatacept, adalimumab, tofacitinib, certolizumab, baricitinib and leflunomide without appropriate response. Furthermore, she was not able to reduce the dose of oral methyl-prednisolone below 8 mg/day, and had a clear deformity progression associated with new erosions on X-rays.

Due to the lack of clinical response and the progression of the structural damage, daratumumab therapy was proposed as a compassionate therapy. The patient signed an informed consent and the treatment was approved by the hospital Pharmacy Committee. The treatment schedule was as follows: daratumumab 1800 mg sc (weekly during 1 month, be weekly for 2 months, and monthly for 3 months), in combination with prednisone 20 mg/day during 2 days after injection and aciclovir 400 mg/12 h daily. Premedication consisted on acetaminophen, diphenhydramine, montelukast and prednisone (100 mg).

Daratumumab was well tolerated, and the patient reported only mild discomfort at the injection site and a vaginal mycosis resolved with topical treatment. After 6 months of treatment, the patient reported an absence of subjective improvement. As shown in Figure 1, DAS28 and ESR/CRP did not show an objective improvement. Although, the gray scale evaluation showed a slight improvement on feet joints, the overall ultrasound evaluation showed a stabilization of joint inflammation.

Here we report a lack of response to daratumumab treatment in a patient with severe refractory RA. There might be several explanations for this finding. First of all, daratumumab is not effective in RA. However, based on only one case, we cannot definitively support this conclusion. Second, daratumumab dosing schedule and/or as monotherapy is not appropriate [5]. Although, the right

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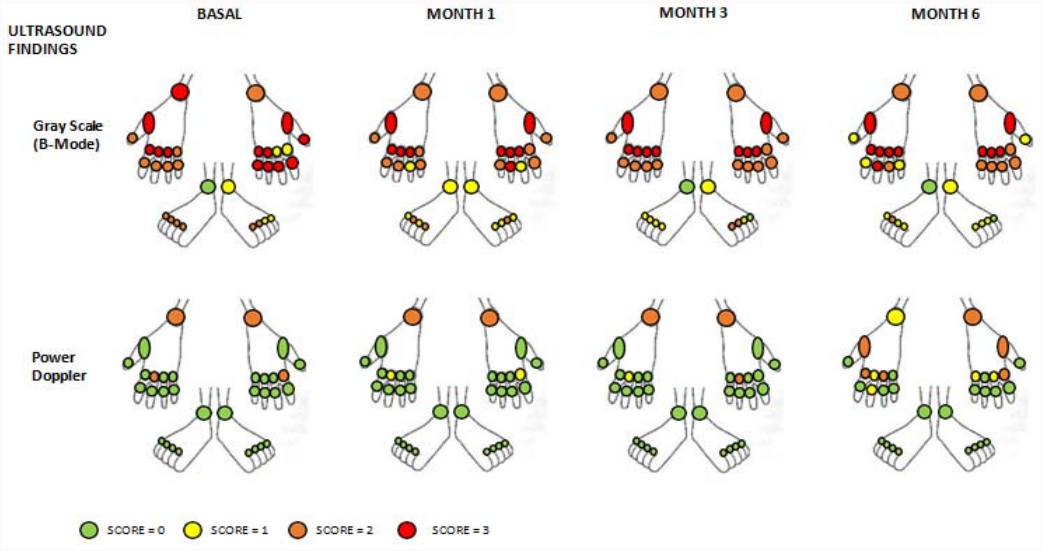

Figure 1A: Upper panel: Doppler-US, both gray scale and power Doppler, before and at different time points after daratumumab therapy.

LABORATORY FINDINGS	BASAL	MONTH 1	MONTH 3	MONTH 6
DAS28	5,89	5,52	5,74	6,47
CPR (mg/dL)	1,3	1,6	2	1,8
ESR (mm / 1h)	42	51	51	66
RF (IU/ml)	77,56	59,28	86,29	82,24
ACPA (UC)	32,6	10	14,2	43
CD19 (%)	2,47	3,8	2,91	2,26
IgG (mg/dL)	1605,65	855,39	828,49	852,89
IgM (mg/dL)	192,71	84,54	82,4	106,96
Plasmablasts (cells/ml)	280,18	0	0	0

Figure 1B: Lower panel: Clinical disease activity (DAS28), acute phase reactants (ESR and CRP), and immunological parameters assessed at different time points after daratumumab therapy.

therapeutic schedule in RA needs to be determined, we considered that looking at the previous history of this patient, the addition of methotrexate would not add much benefit. Furthermore, a longer duration of therapy might be considered, but previous data on treatments directed to the B cell pathway, suggest that a 6 months period is reasonable. Third, daratumumab therapy should be used at early stages of the disease. It is possible, that in this type of RA patients, the role of stromal cells might be dominant [1], and the response to plasma cell depletion has not the expected efficacy.

Although relatively infrequent, patients with difficult to treat RA does exist, and new therapeutic options should be explored [6].

Author Contributions

EO and VMT designed the research. VMT, IGM, and MAB were involved in patient management. IGM and MLH collected clinical and laboratory data. JLH. VMT and IGM wrote the manuscript. EO, MAB and MLH critically revised the manuscript. All authors discussed the results and contributed to the final paper.

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