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Severe ICI-associated Myocarditis resolution after treatment with Abatacept

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Disclosures:

JES has served on an advisory board at Bristol Myers Squibb and has received paid speaking from Bristol Myers Squibb. JJM has served on advisory boards at Bristol Myers, Pfizer, Novartis, Regeneron, Takeda, Deciphera and Myokardia and has received research funding from Pfizer and Bristol Myers Squibb. DBJ has served on advisory boards for Array Biopharma, BMS, Genoptix, Incyte, Merck, and Novartis, and has received research funding from BMS and Incyte. MK has received research grant from Federation Francaise de Cardiologie, Sanofi and, Institut Servier. JES, YA, DBJ, JJM, and MK have a pending patent related to immune-checkpoint inhibitors. The other authors have nothing to disclose.

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Letter.

Immune-checkpoint inhibitors (ICI) have revolutionized cancer treatment but can result in immune-related adverse events (irAE).¹ ICI-induced myocarditis occurs infrequently (<1%) but is the most fatal irAE (up to 50% mortality) and is often associated with concurrent myositis and myasthenia-gravis-like syndrome.^{2,3}

We present a case where abatacept (a cytotoxic lymphocyte antigen-4 [CTLA4] agonist) resolved severe, steroid-refractory ICI-myocarditis. A 66 year-old woman with metastatic lung cancer presented with ptosis, diplopia, and subacute, painful paresis affecting proximal muscles following three doses of nivolumab. Subsequently, she developed chest pain and electrocardiographic repolarization abnormalities with cardiac magnetic resonance imaging confirming myocarditis. Troponin-T (1616ng/L) and NT-proBNP (4172ng/L) were increased (Fig.A). Coronary angiogram revealed normal arteries. Diagnostic work-up was negative for anti-acetylcholine receptor and muscle-specific tyrosine kinase antibodies; electromyography showed myogenic syndrome without neuromuscular dysfunction. Muscle biopsy revealed myositis (Fig.B-E). Despite administration of high-dose intravenous methylprednisolone (500mg/day; 3days) and plasmapheresis, her troponin levels increased (~5000-6000ng/L) and she developed premature ventricular contractions (10-14,000/day, presence of triplets). Abatacept (intravenous, 500mg/2weeks, 5 doses) was administered; troponin rapidly decreased, and ventricular hyper-excitability resolved over weeks. Ejection fraction remained normal. Myocarditis (arrhythmias), and myositis (muscular weakness, facial paralysis) symptoms progressively improved. The patient was discharged 7.5 weeks after admission; cross-sectional imaging performed one month after abatacept showed no tumor progression.

While rigorous studies for irAE treatment have not been performed, consensus guidelines recommend high-dose corticosteroids with progressive tapering.¹ If symptoms and laboratory findings

fail to improve with steroids, other immunosuppressants (e.g. infliximab, rituximab, mycophenolate-mofetil) can be considered.¹ However, fatal irAEs such as myocarditis are increasingly reported,²⁻⁴ and present a significant clinical challenge.

Herein, a CTLA4 agonist (CTLA4-Immunoglobulin fusion protein abatacept; approved in rheumatic diseases)⁵ was used as an antidote for life-threatening, steroid-refractory ICI-myocarditis. Several preclinical studies suggest potential efficacy of abatacept for myocarditis, leading to an upcoming clinical trial (<https://clinicaltrials.gov/ct2/show/results/NCT03619876>) in patients with rheumatoid arthritis and subclinical myocarditis. Broad-spectrum immunosuppressants affect multiple immune cell types and have numerous adverse events; further these agents have a less clear relationship with the CTLA4 and PD1/PDL1 signaling cascades. In contrast, CTLA4 agonists (abatacept/belatacept) inhibit CD28-B7 mediated T-cell co-stimulation at the level of dendritic-cells, and thus abrogate T cell co-stimulation upstream of CTLA4 and PD1/PDL1 pathways.⁵ Thus, abatacept should lead to rapid global T-cell anergy with limited off-target effects, and specifically reverse pathways activated by ICI.⁵ Ultimately, the risk-benefit balance of using abatacept in ICI-myocarditis needs further evaluation given possible risks of infectious complications and pro-tumorigenicity.⁵

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Figure Legend

Figure. Main clinical and biological findings and therapeutic interventions of a women presenting a life-threatening fulminant myocarditis associated with a myositis three doses after nivolumab (anti-PD1) for a lung cancer (A). Skeletal muscle transverse frozen sections with hematoxylin-eosin coloration highlighting (B, C) dense focal inflammatory infiltrates with necrotic myofibers (white arrows). Muscular infiltrates are composed by both CD68-positive macrophages (CD68 immunostaining, D) CD3-positive T-lymphocytes (CD3 immunostaining, E). Electrocardiogram at admission showing appearance of a right bundle branch block associated with T-wave repolarization abnormalities including concave ST elevation in precordial leads (V4-V6) (F). Cardiac magnetic resonance imaging showing a positive intramural septal and infero-apical late gadolinium enhancement (white arrows, G).

