Tacrolimus-Induced Remission in Drug Resistant Inflammatory Myopathy: A Case Series

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Abstract

Idiopathic inflammatory myopathies are rare autoimmune disorders characterized by proximal muscle weakness, elevation of muscle enzymes, abnormal electromyogram and imaging studies revealing areas of edema and inflammation. Initial approach to inflammatory myopathies includes steroids and immunosuppressive agents, with most individuals responding satisfactorily to therapy. However, treatment-refractory myopathies prompts clinicians to use second line agents to achieve remission. In this case series, we describe three patients with refractory idiopathic inflammatory myopathies who were treated with tacrolimus (TAC) added to mycophenolate mofetil (MMF) and steroid therapy, who achieved clinical and biochemical remission.

Keywords: Refractory idiopathic inflammatory myopathies; Necrotizing myopathy; Dermatomyositis; Tacrolimus; Mycophenolate mofetil

Introduction

Dermatomyositis (DM), inclusion-body myositis (IBM), polymyositis (PM) and necrotizing autoimmune myositis are classified among the idiopathic inflammatory myopathies. These rare myopathies have an incidence of 2 to 8 cases per million person per year, affecting adults between the ages of 40 to 60 with a female to male ratio of 2-3:1 [1-3]. These diseases share the common feature of immune-mediated muscle injury through presence autoantibodies and inflammatory cell infiltrates in the muscle tissue. The clinical features and the characteristics of the immune cell infiltrates on muscle biopsy allow subgrouping of the inflammatory myopathies. Most classically, immune cell infiltrates affecting the endomysium is seen with PM, infiltration of the perivascular, perimysial and perifascicular regions is characteristic of DM, basophilic granular inclusion bodies near rimmed vacuoles in IBM and scattered necrotic fiber with macrophages in necrotizing autoimmune myositis [3-6]. The specific cellular infiltrates found in the muscle tissue include macrophages, dendritic cells, B cells, plasma cells, and several subsets of T cells. T cells in the muscle tissue mediate damage via direct cytotoxicity as well as by secretion of inflammatory cytokines. Furthermore, the clinical response to T cell modulating drugs such as methotrexate, tacrolimus (TAC), and cyclosporine favors the implication of T cells in the immuno-pathogenesis of DM and PM [7,8].

Standardized treatment of idiopathic inflammatory myopathies has not been established due to the rarity of the diseases, the clinical heterogeneity, and the small number of completed randomized-controlled trials [9]. The goals of treatment for these diseases are to improve muscle strength while avoiding side effects. Glucocorticoids remain the mainstay of initial therapy for DM, PM and necrotizing autoimmune myositis [10]. Initial glucocorticoid therapy in DM or PM begins with prednisone (PDN) to a maximum daily dose of 100 mg which is maintained until signs of remission are evident by improvement in muscle strength and reduction in creatine kinase (CK) value [11]. Immuno-suppressants are usually administered early, as steroid sparing agents and also to help induce remission in those patients who fail to respond to glucocorticoids alone, an estimate of 50% of the cases [2,3,12]. Methotrexate (MTX), leflunomide, mycophenolate mofetil (MMF) and azathioprine (AZA) are initiated resulting in muscle strength recovery that is apparent after several months of therapy. MMF, cyclophosphamide and TAC might prove beneficial in myositis with interstitial lung disease [3,11,13,14]. For refractory cases, intravenous immunoglobulin, repository corticotropin, rituximab, anti-tumor necrosis factor inhibitors, alemtuzumab, eculizumab, tocilizumab and anakinra have been reported to be effective [3]. We present three patients with refractory myositis. These patients had received adequate doses of steroids in combination with one or more immunosuppressive agents. The introduction of TAC to the ongoing combination regimen led to muscle strength recovery, reductions in steroid dose and CK level overtime.

Cases

Patient 1

42-year-old man presented with proximal muscle weakness of 1.5 years duration. Muscle biopsy demonstrated polymyositis. High dose PDN and MTX were initiated; however, no significant improvement was appreciated. After a year on PDN and MTX, the patient developed worsening proximal muscle weakness and difficulty in swallowing. PDN dose was increased and azathioprine (AZA) commenced. Two doses of intravenous immunoglobulin (IVIG) were administered. Given the lack of response to the new regimen, the patient transferred his care to our hospital. Physical exam was notable for 2/5 strength for neck flexors, deltoid, biceps, hand grip, hip flexors and quadriceps. Hands appeared swollen with muscle wasting.

After comprehensive case review, PDN 75 mg/day and TAC 2 mg twice daily were started. Biologics could not be prescribed due to non-medical reasons. TAC dose was increased to 4 mg twice daily, based on
through goal of 6-10 ng/mL.[15]. After a month of initiating tacrolimus, mycophenolate mofetil (MMF) 1500 mg twice daily was added without complications. Six months after TAC and MMF combination had started, muscle enzymes decreased significantly (CK 4419 U/L to 732 U/L and LDH 1402 U/L to 513 U/L) and clinical improvement was appreciated. PDN was tapered to 30 mg/day. Blood pressure and glycemic levels were monitored at every clinic visit. Eleven months after TAC and MMF were started, LDH and CK normalized; patient had 3/5 strength on neck flexors and 4/5 strength on hip flexors and quadriceps. No adverse effects have been reported (Figure 1).

Patient 2

39-year-old man with history of dermatomyositis (DM) presented to our hospital. Six months before, patient had developed typical skin rash and proximal muscle weakness. Work-up including muscle biopsy led to a diagnosis of DM. Intravenous methylprednisolone had been administered. Patient was lost to follow-up. On presentation to our hospital the patient had worsening proximal muscle weakness, rash, dysphagia, an elevated CK of 389 5 U/L, and elevated liver enzymes (AST 242 U/L, ALT 191 U/L, ALP 146 U/L). The acute episode was treated with pulse steroids and IVIG. Patient was placed on MMF 2 g/day, PDN 70 mg/day with plans for rituximab infusions.

Three months after disease onset, the patient reported improvement of skin lesions on his hands but continued to have significant muscle weakness evidenced by difficulty standing from a seated position and inability to lift his arms above his head. CK was 1352 U/L and LDH was 617 U/L. Despite MMF was increased to 3 g/day, the patient continued to have little improvement. Rituximab was given in and PDN was slowly tapered.

Eleven months after presentation, proximal muscle weakness recurred. CK (1495 U/L), LDH (495 U/L), and ESR (42 mm/hr) remained elevated; TAC 2 mg/day was added to the existing regimen and PDN was slowly tapered.

Three months after tacrolimus had been started, the patient was able to stand from a seated position. Labs revealed down trending CK (806 U/L), LDH (459 U/L), ESR (27 mm/hr). At this point, TAC level was 2.5 ng/ml, so TAC was increased to 3 mg twice daily. Five months after TAC initiation, there was significant clinical and laboratory improvement. TAC dosage was adjusted to achieve therapeutic level and PDN was eventually tapered off. Eleven months after TAC initiated, muscle weakness had significantly improved and labs normalized (CK 102 U/L and LDH 183 U/L). Patient was able to return to work (Figure 2).

Patient 3

51-year-old woman with a history of hypertension, hyperlipidemia, and stroke presented with a two-month history of muscle weakness; she reported a remote exposure to statins. Examination revealed 2/5 strength on the left side and 4/5 on the right. CK was 28,885 U/L; necrotizing myositis was suspected. Patient was treated with IV methylprednisolone followed by PDN 60 mg/day. Extensive proximal muscle edema was seen on MRI. Vastus medialis biopsy showed necrotizing features without inflammation. Hydroxy-Methyl-Glutaryl Coenzyme A reductase (HMG CoA) antibodies were strongly positive. One month after presentation, there was a modest improvement in motor weakness; CK had dropped to 5,546 U/L. IVIG (5 days) was given and MMF 1 g/day was started. Patient continued to experience weakness and CK remained elevated. Two months after presentation, rituximab was added to the regimen of MMF (3 g/day) and prednisone (60 mg/day). Two doses of IVIG were given as a bridge therapy. After an initial response, the patient’s muscle weakness returned. Three months after presentation, CK remained elevated (3,178 U/L). TAC 4 mg/day was added to MMF (3 g/day) and PDN 40 mg/day. On follow up visits, TAC dose was increased to 6 mg/day and PDN was tapered slowly. Eight months after TAC was initiated, weakness improved markedly and labs normalized (CK 117 U/L, LDH 251 U/L). One year after tacrolimus and MMF, the physical exam was normal with full strength throughout. PDN had been reduced to 5 mg daily (Figure 3).

Discussion

During the management of idiopathic inflammatory myopathies, the clinician will encounter cases resistant to conventional approach. A thorough investigation should rule out endocrinopathies, dystrophies, metabolic or vacuolar myopathies and underlying malignancies. Comorbidities, extent of organ involvement and glucocorticoid side effects have a huge impact on the clinical decision for step up therapy. However, the rarity and varied presentations of these inflammatory diseases have not lent themselves to achieve established guidelines. Therefore, the management of recalcitrant myositis cases includes the use of ACTH, biologics such as rituximab, IVIG or drug combination of TAC added to MMF. The literature on the use of TAC in DM and PM is limited to retrospective case series and anecdotal reports [14,16-25]. The use of immunosuppressive therapies for several
autoimmune diseases stems from the clinical experience gained in transplant medicine. Initial maintenance therapy following renal transplantation includes a triple regimen consisting of a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate mofetil), and prednisone. These recommendations are based on several randomized controlled trials (RCT) and meta-analyses demonstrating improved survival and decreased rejection [26-28].

TAC is a second-generation calcineurin inhibitor that binds to an intracellular protein FKBP-12, to inhibit the phosphatase activity of calcineurin, resulting in the inhibition of T cell proliferation in response to antigens [26]. The use of TAC in transplant patients is effective based on its ability to selectively inhibit calcineurin, thereby impairing the transcription of Interleukin-2 (IL-2). By doing so, TAC suppresses T cell and T cell-dependent B cell activation. In transplant medicine, TAC is preferred over cyclosporine because of increased efficacy and better tolerability [28,29]. TAC toxicity includes tremor, headache, new onset diabetes, gastrointestinal symptoms, alopecia, hirsutism, hypertension and gingival hyperplasia. TAC has been shown to be particularly effective in cases of inflammatory myopathy complicated by ILD [16,30,31]. In a small group of patients with refractory PM (most with anti-Jo1 positive antibodies), TAC was given at a dose of 0.075 mg/kg/day, in two divided doses. The results showed an improvement in manual muscle strength, serum CK levels, pulmonary function tests, and extra-muscular manifestations such as fever and polyarthritides [32]. In one case series, eight patients with refractory PM were treated with TAC, resulting in improved strength and decline in CK levels, as well as improvement in pulmonary function. A second series, included 13 patients followed for 51 months showed similar results and allowed for a taper in the prednisone dose [33]. Another observational clinical study including both DM and PM patients demonstrated an improvement in muscle strength and CK levels 2-4 months after initiation of TAC [24].

Anti-metabolic agents like MMF and AZA interfere with the synthesis of nucleic acids and inhibit proliferation of T and B cells [34,35]. MMF works as an inhibitor of inosine-5’-monophosphate dehydrogenase, the rate-limiting enzyme in the de novo purine synthesis pathway, ultimately preventing DNA generation and cell replication [34]. In addition to suppressing cell-mediated immune responses and antibody formation, MMF also affects the expression of adhesion receptors on the vascular endothelium interfering with the recruitment of lymphocytes and monocytes to sites of inflammation [26,36]. Despite its increased cost, MMF is well tolerated and used much more frequently than AZA due to its superior ability to prevent acute rejection although it has slow onset of action [37]. Its side effects include cytoxenias, gastrointestinal upset, infection risk, and teratogenicity [32,38]. MMF has been used with success in some retrospective series of patients with inflammatory myopathy. In one report, ten DM patients with refractory disease were treated with MMF resulting in improved manual muscle testing scores and decreased corticosteroid doses [39]. In a second report, six patients with treatment-resistant myositis were treated for 22 months, resulting in improved muscle strength and serum CK levels [30].

TAC and MMF were first introduced for immunosuppression in renal transplantation in the mid-1990s, and since then their efficacy as a combination therapy have been validated by several clinical trials [26]. The widespread use of TAC and MMF in combination is partly supported by the effect of TAC on the metabolism of MMF. Plasma trough levels of mycophenolic acid (the active component of MMF) appear to be lowered by the concurrent administration of cyclosporine, which is not observed with TAC [40]. In fact, TAC inhibits UDP-glucuronosyltransferase, the enzyme that metabolizes mycophenolic acid, thereby increasing its concentration and increasing the efficacy of immune tolerance in kidney transplant [41]. Although generally well-tolerated, side effects of MMF include gastrointestinal effects, anemia, leukopenia, and invasive CMV infection. It is understood the GI toxicity of MMF can be ameliorated by dividing doses [42] which could suggest that the MMF has some direct toxicity with relationship to GI tolerability (independent of the mycophenolic acid levels). As such, concurrent use of TAC with MMF, which has been shown to increase plasma levels of the active mycophenolic acid allows a reduction in MMF dose, while achieving efficacy, and ultimately a reduction in adverse effects [40]. MMF dosing can be reduced up to 50% when administered concurrently with TAC [43].

Limited data is available in support of the use of individual or combination therapies in inflammatory myopathies. Drawing from the experience in renal transplantation and refractory inflammatory myopathies case series in which TAC was added to immunosuppressants resulting in clinical improvement, we have decided to apply the same approach in the management of our patients [14,21-25,43]. Consistent with the published reports, time to recovery observed in our patients was 6 to 11 months.

Conclusion

Refractory myopathies are observed in clinical practice. Given the lack of established guidelines and the lessons learned in transplant medicine supporting the addition of TAC to background MMF and steroids, the addition of this agent appears to be an attractive therapeutic strategy at this time pending the availability of randomized controlled trials and the establishment of guidelines for management of these rare disorders. It is important to note that TAC levels and adverse effects should be routinely monitored, aiming for a trough level of 6-10 ng/mL. Clinical and laboratory remission is expected to occur between 6-11 months after the initiation of TAC therapy.

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References
