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Review Article

The effectiveness of dapsone as refracterial therapy for juvenile dermatomyositis

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ABSTRACT

Juvenile dermatomyositis (JDM) is a rare autoimmune disease that affects mostly children's muscles and skin. The small number of patients with JDM, heterogeneous disease phenotype, and few clinical trials for JDM pose challenges for clinicians in developing standard treatment protocols. Although there has been some consensus, the obstacles to JDM therapy, especially in refractory cases, have not been resolved. Dapsone is one of the anti-inflammatory agents that can provide significant clinical improvement in patients with dermatomyositis. This aim of the study was to discuss various previous studies to determine the potential use of dapsone in cases of refractory JDM.

Keywords: Dapsone, Juvenile dermatomyositis, Idiopathic inflammatory myopathy, Refractory

INTRODUCTION

A rare immune disorder known as juvenile dermatomyositis (JDM) mostly affects the skin and skeletal muscles. JDM is a part of the idiopathic inflammatory myopathy (IIM) group, which is a diverse group of conditions defined by skeletal muscle inflammation, histological abnormalities, and muscle weakening.[1,2] Skin rashes on the hands and face, vasculopathy, and involvement of life-threatening organs like the lung, heart, and intestinal tract are just a few of the distinct characteristics of JDM.[3,4]

JDM is the most common type of inflammatory myopathy in children (75%), with an incidence reaching 2.3 cases/million people/year.[5] Although the underlying cause of JDM is still unknown, it is believed to be caused by a confluence of various hereditary and environmental variables.[1]

The Childhood arthritis and rheumatology research alliance (CARRA), the Single Hub and Access point for pediatric Rheumatology in Europe (SHARE), and the JDM working committee of the Society for Pediatric Rheumatology have all made suggestions for standardized JDM care.

In general, methotrexate and steroids are used as the first line of treatment for JDM, with dose adjustments or treatment modifications made if resistance develops.[3] Due to the small number of cases, the diverse nature of the disease pattern, and the paucity of randomized double-blind controlled clinical trials-particularly for refractory JDM-treatment for JDM cases remains challenging.[6,7]

Dapsone is a sulfone antibiotic used to treat leprosy but also has anti-inflammatory activity.[1] There are numerous accounts of people with dermatomyositis receiving dapsone medication showing clinically substantial improvement. Before using dapsone on a big scale, more study is required because up to this point, no extensive studies have been conducted to evaluate the benefits and drawbacks of doing so, particularly for refractory JDM. The aim of the study was to gather data from several earlier research to assess the potential role of dapsone in JDM that is refractory.

JUVENILE DERMATOMYOSITIS

JDM is a rare disease with an incidence in the UK of about 2-3 cases per one million children per year.[8] The average onset of JDM occurs at the age of 6.7 years for boys and 7.3 years for girls with a ratio of female to male sufferers. Male, namely 2,3:1.[5] Most patients with JDM are diagnosed between the ages of 4-14 years.[9]

JDM is thought to be caused by an autoimmune reaction in individuals who have special genetic susceptibility and are triggered by environmental factors. There is a hypothesis that JDM is an inflammatory process caused by interferon type 1, and triggered by environmental stimuli such as infection, exposure to cigarette smoke or UVB rays, targeting children who have genetic susceptibility. JDM, but one study found an association of infection with parvovirus B19, coxsackievirus B, enterovirus, hepatitis, influenza, group A streptococcus, Borrelia burgdorferi, and toxoplasma with JDM. Genetic susceptibility has been reported to occur in the human leukocyte antigen (HLA) allele, namely HLA DRB1*0301 with major risk, as well as non-HLA genes such as tumor necrosis factor-alpha (TNF-) and interleukin (IL)-1 receptor antagonist polymorphisms.[1,2] Autoantibodies are found in >60% of patients with JDM and have a role in the disease phenotype. There are two classifications of autoantibodies, namely myositis-specific antibodies (MSA) which are only found in myositis, and myositis-associated antibodies (MAA) which can be found in patients with myositis and other autoimmune diseases. Patients who have similar autoantibodies tend to have similar clinical manifestations and prognoses.[3,10] Characteristics in the pathogenesis of JDM, namely the occurrence of vasculopathic changes in the tissue accompanied by endothelial cell dysfunction that causes capillary damage and atrophy of muscle fibers.

In addition, there is also overexpression of MHC-I in myocytes and endothelial damage that attracts immune cells and produces chemotractants such as plasmacytoid dendritic cells (pDC), memory CD4+ T cells, B cells, and increased activity of interferon type I and interferon α.[4] Myogenic precursor cells in JDM patients, it was found to be able to synthesize type I interferon and modulate muscle microvascular damage. NK cells are also thought to contribute to cell damage.[5] The deposition of the membrane attack terminal complex, C5b-9, in muscle microvasculature is associated with perifascicular atrophy underlying antibody (MSA).[5,11]

The clinical manifestations of JDM vary widely, but most patients experience varying degrees of muscle weakness (Table 1). The onset of the disease can be rapid or slow, with a median duration from the appearance of symptoms to diagnosis of about 3-7 months.[1] The familiar criteria for the diagnosis of JDM are the Bohan and Peter criteria published in 1975. At least there is a pathognomonic rash (heliotrope rash, Gottron papules) and three of the following four to establish the diagnosis: proximal muscle weakness, elevated serum muscle enzyme levels, electromyographic changes of chronic inflammatory myositis, and histopathological changes of inflammatory myositis.[12,13] Newer diagnostic criteria have been developed by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) in 2017. The sensitivity of the EULAR/ACR criteria is 93% and the specificity is 88% but it is still not widely applied.[14,15]

Table 1: Various clinical manifestations of JDM.[1]

Clinical manifestation	Frequency of symptoms at early onset (%)
Constitutional signs and symptoms	
Fatigue	82-100
Fever	21-53
Weight loss	20-61
Lymphadenopathy	23-25
Musculosceletal symptoms	
Muscle weakness	85-96
Muscle pain	48-75
Arthritis	26-45
Mucocutaneus symptoms	
Heliotrope rash	62-84
Papul Gottron	59-91
Photosensitive rash	51
Malar rash/facialis erythema	34-79
Periungual capillary changes	21-68
V sign/shawl sign	5
Raynaud phenomenon	5-28
Skin ulcer	6-23
Kalsinosis	0-11
Lipodystrophy	4

Continued.

Clinical manifestation	Frequency of symptoms at early onset (%)
Cardiopulmonary involvement	
Cardio involvement	2,5-25
Lung involvement	8-12
Gastrointestinal involvement	
Dysphagia/dysphonia	11-25
Gastrointestinal symptoms	8-25

Management of JDM requires multidisciplinary collaboration. The main goals of therapy are to control inflammation, prevent therapy-related complications and long-term disease sequelae, and improve the patient's quality of life.[1] There are several recommendations for standardized JDM therapy, including recommendations from the Childhood Arthritis and Rheumatology Research Alliance (CARRA), Single hub and access point for pediatric rheumatology in Europe (SHARE) (Figures 1 and 2), and JDM working group of the Society for pediatric rheumatology.

Initial therapy of JDM generally uses a combination of high-dose steroids and methotrexate, with dose escalation or treatment modification if resistance occurs.[1,3] A clinical trial showed combination steroid therapy with methotrexate or cyclosporine was more effective than steroid monotherapy.[16] Another therapy is intravenous immunoglobulin (IVIG) as adjuvant therapy with good efficacy for controlling disease in severe or refractory JDM.[17]*Mycophenolate mofetil* (MMF) is used as adjuvant therapy for resistant and refractory JDM because it has been shown to decrease disease activity in several retrospective studies, but there are no controlled clinical trials for it.[1,18] Cyclophosphamide also showed good efficacy without significant short-term side effects. Patients with severe and refractory JDM have improved skin, muscle, and global conditions.[19] Treatment recommendations by CARRA also include hydrocycloroquine for JDM with predominant skin manifestations.[20] Several case reports of tacharolimus have shown effectiveness in refractory JDM, but no large-scale studies have been conducted.[1,21] Agen The biologic agent rated less useful in refractory JDM, etanercept.[22] Anti-TNF therapy, adalimumab or infliximab, has shown promising clinical improvement in refractory JDM.[7]

Abatacept is also a safe and effective option for calcinosis in JDM. however for cases of refractory JDM, clinical trials are still in progress.[1,23] The use of Rituximab showed clinical improvement in 83% of cases of refractory JDM, but there was no significant difference with other treatment groups.[24] A newer type of therapy with the Janus Kinase inhibitor class showed good results. effective in some case reports of refractory JDM , but there have been no large-scale studies on it.[8,25] JDM mortality has decreased from >30% to about 2-3% compared to the era before steroid use, but long-term morbidity and resistance to therapy remain challenges for clinicians..[8,15] In addition to pharmacological therapy, it is also necessary to carry out non-pharmacological therapies such as the use of sunscreens with SPF >30 on a regular basis because JDM exacerbations often occur due to exposure to UV rays.[20] Vitamin D and calcium supplementation is considered necessary due to prolonged exposure to corticosteroids and chronic inflammatory conditions.[1,26]

Physiotherapy and occupational therapy are also important to prevent contractures and increase muscle strength. However, it is necessary to pay attention to the portion of exercise as needed because JDM patients experience decreased exercise capacity due to lung and muscle dysfunction, especially in active disease.[27,28]

DAPSON PROFILE

Dapsone (4,4'-diaminodiphenylsulfone) is a sulfone antibiotic used to treat leprosy but also has anti-inflammatory activity.[29] Indications for the use of dapsone approved by the FDA are for leprosy, dermatitis herpetiformis, and acne vulgaris, while some indications are not approved by the FDA- (a) bullous dermatosis linear IgA, chronic bullous dermatosis in children, bullous SLE, erythema elevate diutinum; (b) bullous pemphigoid, cicatrical pemphigoid, IgA pemphigus, subcorneal pustular dermatosis, pemphigus vulgaris, pemphigus foliaceous, epidermolysis bullosa acquisita; (c) dermatotic vasculitis such as leukocytoclastic vasculitis, urticarial vasculitis; (d) neutrophilic dermatoses such as Sweet syndrome, pyoderma gangrenosum, Behcet syndrome; and (e) other dermatoses such as subacute cutaneous lupus erythematosus, relapse polychondritis, granuloma annulare, loxoscelism, granuloma faciale, rosacea, panniculitis, pustular psoriasis, nodulocystic acne, rhinosporidiosis.[30,31]

The exact mechanism of action of dapsone is still unknown, but several studies have revealed that dapsone is able to inhibit the migration of neutrophils to areas of inflammation by inhibiting neutrophil chemotaxis by signaling the chemoattractants F-met-leu-phe and leukotriene B4 (LTB_4). Dapsone also inhibits neutrophil attachment to IgA localized in the skin and endothelium and inhibits the release of inflammatory mediators, including interleukin (IL)-8, prostaglandin D2, and TNF-α. In addition, dapsone can also inhibit the H2O2-halide-mediated cytotoxic myeloperoxidase system, through inhibition of calcium flow.[31,32]

Oral dapsone is available in tablets of 25 mg and 100 mg, with therapeutic doses varying from 25 to 400 mg. After oral administration, dapsone is absorbed from the gut with a bioavailability of >86%. Peak serum concentrations are reached in 2-8 hours. Then dapsone is metabolized through

the enterohepatic circulation by the liver, PMNs, and mononuclear cells. Metabolites are distributed throughout the organs and are retained in the skin, muscles, kidneys, and liver.[33] Drugs can still be detected up to 3 weeks after discontinuation of therapy. Dapsone is also distributed in sweat, saliva, sputum, tears, bile, and can cross the blood-brain barrier, placenta, and is detected in breast milk. There are no reports of teratogenicity, but for pregnant women dapsone is classified as category C. About 50-90% of dapsone molecules are bound to plasma proteins. Excretion of dapsone and its metabolites is carried out by the kidneys, so it should be avoided in patients with severe renal impairment.[32] The side effects of dapsone can affect various systems such as the hematological, liver, skin, gastrointestinal, and neurologic systems. Life-threatening side effects include dapsone hypersensitivity syndrome, hemolysis, methemoglobinemia, agranulocytosis, aplastic anemia, hemophagocytic syndrome, and SJS/TEN.[32] The use of dapsone needs to be more careful in patients with G6PD deficiency, Met-Hb-reductase deficiency, severe hepatopathy, heart failure, lung disease, and co-medication with drugs that trigger met-Hb. Before starting treatment, it is advisable to evaluate bilirubin, ALT, AST, GGT, creatinine, Met-Hb, G6PD, hepatitis serological tests, and urinalysis.[33]

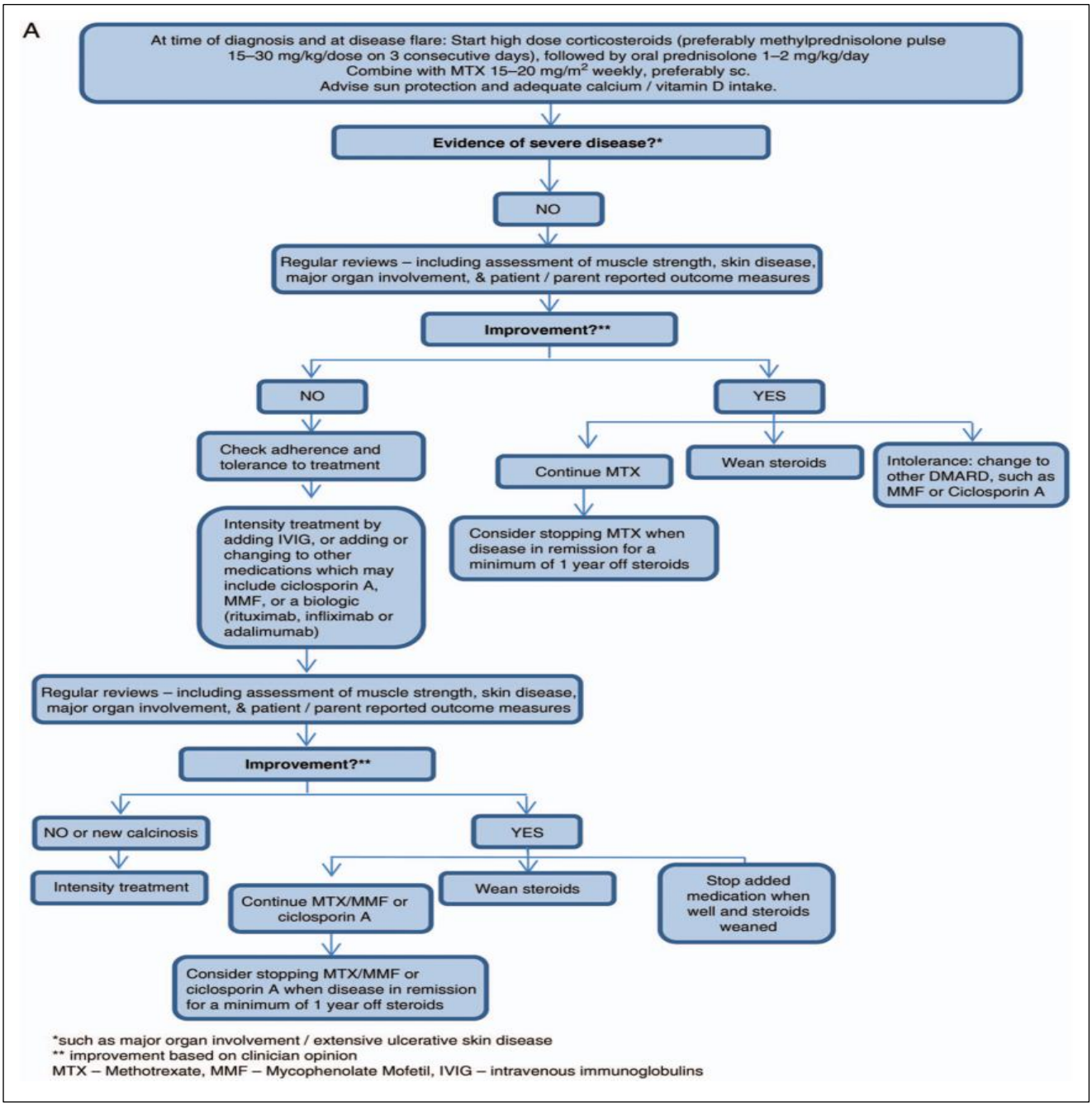

Figure 1: Algorithm for mild/moderate JDM therapy in new and refractory patients by SHARE.[6]

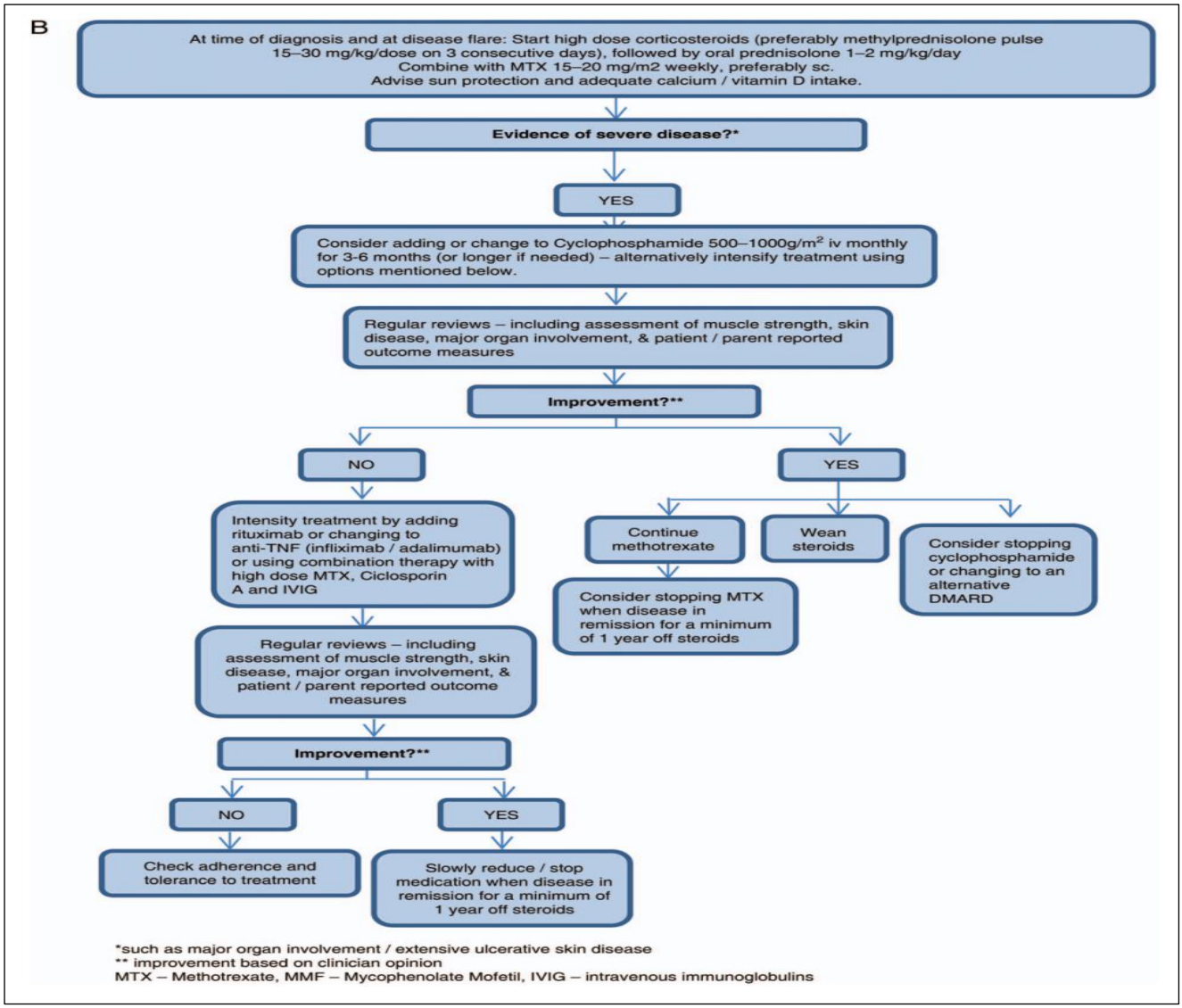

Figure 2: Algorithm for therapy of severe JDM in new and refractory patients by SHARE.[6]

EFFECTIVENESS OF DAPSONE IN REFRACTER JUVENILE DERMATOMYOSITIS

There haven't been any specific studies or clinical trials on dapsone's use for dermatomyositis in juvenile patients up until today, however there are a number of case reports showing its positive effects in dermatomyositis cases (Table 2). To the best of the authors' knowledge, Konohana et al. in Japan in 1994 reported the first reported use of dapsone for dermatomyositis. A 51-year-old male patient with newly diagnosed dermatomyositis received dapsone 75 mg/day; the results revealed a significant improvement within 2 weeks and no recurrence was discovered.[34] A case report by Cohen et al. in the United States in 2002 also showed improvement in the clinical condition of 2 cutaneous dermatomyositis patients aged 88 and 43 years who had not previously responded to prednisone, hydroxychloroquine, quinacrine, and other immunosuppressants. The dose of dapsone used in patient A was 25 mg twice a day, while in patient B the dose was 50 mg per day which was increased to 100 mg per day and added cimetidine 400 mg twice a day.[29] Similar results in Brazil were also reported in 2 refractory amyopathic dermatomyositis patients aged 55 and 43 years who did not respond to chloroquine diphosphate, prednisone, and hydroxychloroquine therapy. The initial dose of dapsone 50 mg per day, but was increased to 100 mg per day after 2 months there was no good clinical response.[35]The only report of the use of dapsone for JDM was in Brazil in 2010. An 8-year-old boy diagnosed with juvenile SLE and JDM underwent standard therapy and had clinically significant improvement. However, 2 years later the patient developed new-onset urticarial vasculitis which was thought to be related to juvenile SLE and JDM. The patient was then given MP 1 g/day for 3 days, deflazacort 30 mg/day, dapsone 50 mg/day, and MMF 2 g/day and experienced significant clinical improvement and returned to stability.[36] A 37-year-old Japanese patient who was initially diagnosed with dermatomyositis and treated with prednisolone 50 mg per day until remission developed pruritic poikiloderma symptoms after the prednisolone dose was reduced to 10 mg per day. Finally, additional

therapy with 50 mg of dapsone per day was given and there was rapid resolution without increasing the steroid dose.[37] In Japan also reported a case of a woman aged 40 years with erythema on the face and neck that did not improve for 4 years and received only topical corticosteroid therapy and tacrolimus. After further examination, the patient was diagnosed with amyopathic dermatomyositis and was given dapsone 50 mg per day. As a result, there was a clinically significant improvement within 3 weeks and no side effects were found.[38] Dapsone has previously been widely utilized as a primary therapy and an adjuvant therapy for autoimmune conditions. Dapsone has a broad spectrum of anti-inflammatory properties, including the ability to suppress neutrophil chemotaxis, the release of inflammatory mediators (IL-8, prostaglandin D2, and TNF-), and the inhibition of myeloperoxidase, which may help to lessen inflammation in dermatomyositis skin lesions. Dapsone is hypothesized to be able to prevent complement-mediated vascular damage in the etiology of dermatomyositis because it can inhibit the alternative pathway of complement activatio.[1,38] From several studies above, it can be seen that the results of using dapsone in various types of dermatomyositis resulted in significant clinical improvement and there were no reports of serious side effects. However, until now there has been no specific study for juvenile dermatomyositis cases. In addition, large-scale clinical trials are still needed to see the safety of using dapsone in JDM because dapsone also has some fatal side effects such as hemolysis and methemoglobinemia.[38,39]

Table 2: Previous studies on dapsone's efficacy for treating dermatomyositis.[29,34,35,37,38]

Study	Methods	Participants	Intervention	Outcomes	Result
Konohana et al (1994)[34]	Case report (Japan)	1 dermatomyositis patient	Dapsone 75 mg/day	There was a significant clinical improvement, no recurrence	Dapsone therapy can be an option to treat dermatomyositis skin and muscular lesions
Cohen et al (2002)[29]	Case report (United State of America)	2 patients with cutaneous dermatomyositis unresponsive to prednisone, hydroxychloroquine, quinacrine, and other immunosuppressants	• Dapsone 25 mg 2×1 • Dapsone 50 mg/day →100 mg/day, and Cimetidine 400 mg 2×1	There was a significant clinical improvement in both patients	Dapsone therapy for cutaneous dermatomyositis may have a role in the treatment of patient's refractory to prednisone and antimalarial therapy.
Galrao et al (2006)[35]	Case report (Brazil)	2 patients with amyopathic dermatomyositis refractory to chloroquine diphosphate, prednisone, and hydroxychloroquine therapy	Dapsone 50 mg/day →100 mg/day	There was significant clinical improvement and did not relapse	Dapsone can be used for the treatment of skin manifestations of dermatomyositis unresponsive to chloroquine
Macedo et al (2010)[36]	Case report (Brazil)	1 juvenile SLE and JDM patient who developed urticarial vasculitis 2 years after clinical improvement	• MP 1 g/day for 3 days •Deflazacort 30 mg/day •Dapsone 50 mg/day • MMF 2g/day	Complete resolution of skin and systemic lesions occurs	Combination therapy of MP, deflazacort, dapsone, and MMF may be the treatment of choice for the urticarial vasculitis syndrome associated with juvenile SLE and JDM.
Kawachi et al (2012)[37]	Case report (Japan)	1 patient with dermatomyositis-associated	Prednisolone 10 mg/day and	There was a significant clinical	Dapsone may be the treatment of choice for

Continued.

Study	Methods	Participants	Intervention	Outcomes	Result
		poikiloderma with a history of prednisone and topical steroid therapy	Dapsone 50 mg/day	improvement and there were no side effects	dermatomyositis skin lesions to avoid the serious side effects of high-dose systemic corticosteroid therapy
Ishibuchi et al (2015)[38]	Case report (Japan)	1 patient with amyopathic dermatomyositis with a history of topical corticosteroid therapy and tacrolimus	Dapsone 50 mg/day	There was a significant improvement of skin lesions, no side effects	Dapsone may be a safe option for dermatomyositis skin lesions, thereby avoiding the serious side effects of systemic corticosteroids

CONCLUSION

JDM is a rare autoimmune disorder that typically affects the skin and muscles in children. Autoantibodies, genetic variables such IFN-I dysregulation, and environmental factors are considered to be the causes of JDM. Steroids and methotrexate are the main treatments for JDM, but research on the recommended course of treatment is currently ongoing. Additionally, there are numerous potential new biologic treatments for JDM. One prospective anti-inflammatory drug, dapsone, has been shown to have minimal side effects while improving the clinical condition of people with dermatomyositis. There haven't been many studies done on dapsone for dermatomyositis, particularly refractory JDM.

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