Current Treatment Strategies: Collagen Vascular Diseases in Children

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Abstract

Of the various collagen vascular diseases seen in pediatric age group, discoid lupus erythematosus, systemic lupus erythematosus, neonatal lupus erythematosus, juvenile dermatomyositis and childhood scleroderma are common and of practical importance to clinicians. Various treatment modalities of these conditions have been discussed at length. Of these, some are conventional and routine,while others are used in challenging situations of these diseases. Autologous stem cell transplant, biological therapies, intravenous immunoglobulin and narrow band ultraviolet B are among the latest therapeutic options for these difficult-to-treat conditions in children.

Key words: *Children, collagen vascular diseases, lupus erythematosus*

Introduction

Collagen vascular disorders are multisystemic diseases with autoimmune etiology. This group of conditions requires prolonged therapeutic intervention because of chronic nature and relapsing course. Systemic corticosteroids are the mainstay of conventional therapeutic approach in most of these disorders.

Collagen vascular disorders are not infrequent during childhood. Commonest among these is systemic lupus erythematosus. In some cases of adult systemic lupus erythematosus (SLE), the disease onset is during childhood.[1] Idiopathic, inflammatory myopathies are rare in children, of which juvenile dermatomyositis is the commonest disorder encountered at this age. Neonatal lupus erythematosus, a unique disorder at this age occurs in a frequency of 1 in 20,000 live births.[2]

Recently there is a trend of transition in the therapeutic intervention of collagen vascular disorders from corticosteroid monotherapy to combination therapy with various immunosuppressive drugs and biologicals. This has brought a ray of hope in this field in terms of increased survival rate of affected patients and better quality of life. However, treatment of collagen vascular disorders in children is challenging as long-term use of both systemic steroids and immunosuppressive drugs are associated with high toxicities during the formative years of their life. Often, the side-effects related to the use of these drugs surpass the clinical features of the original illness.

Among the collagen vascular disorders, recent therapeutic approach to the following diseases in children will be discussed:

1. Discoid lupus erythematosus
2. Systemic lupus erythematosus
3. Neonatal lupus erythematosus
4. Juvenile dermatomyositis
5. Childhood scleroderma

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Discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is less frequent in the pediatric age group. Among adults with DLE, less than 5% patients develop the disease before 16 years and less than 3% develop it before 10 years of age.[3,4] Childhood onset DLE has a higher chance of developing systemic disease. The aim should be to treat lesions of DLE at an early stage to prevent scarring. This is more so if scalp is involved, as the sequela is scarring alopecia which may cause negative psychological impact upon the affected child.

For localized lesions of DLE, moderately potent topical or intralesional corticosteroid is the first line of treatment along with strict photoprotection. In limited skin lesions not responding to topical therapy, oral hydroxychloroquine should be started.[5]

In disseminated skin lesions systemic treatment is compulsory. These include hydroxychloroquine (4-6 mg/kg/day) and/or oral corticosteroid (1-2 mg/kg/day). In severe cases intravenous methylprednisolone pulse therapy may be given.[5] Children on hydroxychloroquine therapy need baseline and thereafter routine ophthalmic check up. Miettunen *et al*.[5] reported a 5-year-old girl with rapidly progressive scalp DLE with scarring, whom they treated with methylprednisolone pulse therapy (10 mg/kg/day for 3 days), single dose, followed by hydroxychloroquine, oral prednisolone, and topical amcinonide (0.1%) lotion. This treatment regimen resulted in complete regrowth of scalp hair without recurrence during follow up.

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Other therapeutic modalities for childhood DLE are calcineurin inhibitors, dapsone, and thalidomide.[5] Dapsone (50 mg/day) is a well tolerated drug used in childhood DLE.[6] Cherif *et al*.[3] used dapsone for 8 months in a child with complete remission. Moises-Alfaro *et al*.[7] used thalidomide alone or in combination with Chloroquine in eight patients. Children with DLE on systemic therapy need clinical evaluation every 4-6 months along with repetition of laboratory parameters every 6 months.

Systemic lupus erythematosus

SLE is a relatively common collagen vascular disorder during childhood and adolescence. In about 15% cases, clinical manifestations of SLE start during childhood.[1] Significant morbidity and mortality is associated with pediatric SLE because of underlying organ involvement, of which lupus nephritis is the commonest.

Childhood SLE deserves a rapid and aggressive treatment as renal and cerebral involvements are the main concern.[1] The goal of modern therapeutic approach is to prolong the survival rate of these patients by minimizing organ damage. Various therapeutic modalities in children suffering from SLE are as follows:

Corticosteroids

Corticosteroids remain the first-line therapy in childhood SLE. Various immunosuppressive drugs have been used along with corticosteroids. Oral prednisolone or intravenous pulse therapy with methyl prednisolone may be used. Long-term use of corticosteroids is associated with grave sequelae like iatrogenic Cushingoid features, recurrent infections and osteoporosis.

Hydroxychloroquine

Oral hydroxychloroquine (4-6 mg/kg/day) is used in children with SLE with marked cutaneous manifestation. It may improve other manifestations like arthritis, lethargy, pulmonary involvement, hyperlipidemia, and reduces the risk of cardiovascular and renal complications.[8]

Immunosuppressive Agents

So long cyclophosphamide had been the main drug to treat renal and cerebral lupus.[1] Risk of gonadal toxicity and drug-induced hair loss is worrisome for treated patients and their parents. In view of immediate and long-term toxicity of this drug, other drugs like azathioprine and mycophenolate mofetil (MMF) are gradually being preferred over cyclophosphamide.[8]

Some authors have used methotrexate successfully to treat cutaneous lesions and arthritis in children with SLE whereas others found this drug to be ineffective.[1,9]

Oral azathioprine (2-2.5 mg/kg/day) has been used in children without significant toxicity as compared with cyclophosphamide.[9]

MMF, a drug with comparable efficacy to cyclophosphamide but fewer side effects, has been used in adult SLE with advanced nephritis. Chances of intercurrent infection are lower with this drug as compared with cyclophosphamide. Some authors have used this drug in pediatric lupus nephritis but long-term follow up of these patients is notavailable.[1,10] Retrospective data analysis (from a multicenter study) of 26 patients with childhood LE treated with MMF showed that the drug was effective in controlling disease activity in 54% cases and disease stabilization in 31% cases.[11] Four patients (15%) with renal involvement were nonresponsive to the drug. Side effects like severe diarrhea and pain abdomen was seen in two children, in whom it was stopped. The authors have concluded that MMF is an effective and safe drug for pediatric LE, especially in patients without nephritis.[11]

The dose of MMF in children should be gradually built up to avoid gastrointestinal side effects, especially diarrhea. A maximum dose of 0.6-1.2 g/m^2/day (in two divided doses) may be used.[8]

Cyclosporin may help in tapering of corticosteroids but in patients with lupus nephritis it is difficult to use a nephrotoxic drug with risk of hypertension.[1]

Intravenous Immunoglobulin (IVIg)

Children with severe hematological disease associated with SLE can be treated with IVIg at a dose of 2 g/kg (maximum 70 g) at 4-6 weeks interval.[8] There is limited use of this agent in pediatric SLE, usually when associated with cerebral or pulmonary involvement.[12,13]

Plasma exchange

Plasma exchange has been used with some improvement in severe, refractory pediatric SLE with crescentic glomerulonephritis or cerebral involvement.[14]

Biological therapy

Rituximab is a mouse–human chimeric monoclonal anti-CD20 antibody, which targets B lymphocytes and prevents its pathogenic role of immune complex formation and complement activation in patients with SLE, thus preventing tissue injury. It has a favorable effect in the outcome of SLE patients with life-threatening disease activity. Refractory cases of pediatric SLE have been treated successfully with this agent with rapid reduction of disease activity.[15,16] The dose used for children was 750 mg/m^2, administered intravenously at the interval of 2 weeks. Occurrence of herpes zoster was noted in some patients. Repeated dosage of rituximab in children with SLE may be associated with severe side effects and hence not recommended.[8]

Autologous stem cell transplantation

Autologous stem cell transplantation (ASCT) has been tried in adolescents with SLE achieving prolonged disease remission, without any drug therapy.[17]

The usual presentation of SLE in childhood is systemic features along with renal involvement. These patients require early, aggressive management to prevent permanent renal damage. Marks *et al*.[8] suggested therapeutic protocol for children with SLE and lupus nephritis. It includes two phases, the *'induction phase'* and the *'maintenance phase'*. The aim of induction therapy is to control disease activity by aggressive treatment of life threatening organ involvement and to bring remission.

The choice of treatment is based on severity of the disease (International Society of Nephrology/Renal Pathology Society [ISN/RPS]). The recommendations for induction therapy are as follows:[8]

- For moderate to severe disease: injection methylprednisolone as pulse therapy (0.6-1 g/m^2/day, [maximum 1 g], for 3 days, each dose by intravenous infusion over 30 min). This may be repeated according to clinical severity, and thereafter followed by oral prednisolone (dose as mentioned below).
- For mild disease without lupus nephritis, prednisolone is the first drug to be initiated (1-2 mg/kg/day, orally, maximum 60-80 mg/ay), followed by rapid tapering.
- MMF (300-600 mg/m^2/dose, twice daily (maximum 3 g/day) OR
- Injection cyclophosphamide (intravenous, 0.5-1 g/m^2/dose monthly × 6 months, and thereafter 3 monthly (according to American National Institute of Health protocol; this dose may be reduced according to side effect profile).

In less severe cases, oral azathioprine (in patients with lupus nephritis) and methotrexate (in patients without lupus nephritis) may be used. In patients with severe disease not responding to the above drugs, or associated with rapidly progressive, crescentic nephritis, plasma exchange (daily for 5-10 days) or rituximab may be used.[8]

Maintenance therapy is started following achieving remission and aimed to avoid relapse by minimizing disease activity.[8] It should last for a period of minimum 2-3 years. The clinician may determine the duration of this phase by using some disease activity scale (e.g. The British Isles Lupus Assessment Group Index [BILAG]. Systemic corticosteroid with hydroxychloroquine or azathioprine/ MMF should be used during this period.

Marks *et al*.[8] recommended the following regimen for maintenance therapy of pediatric SLE:

- Oral prednisolone (10-15 mg) on alternate days.
- Oral hydroxychloroquine (200 mg/day)
- Oral azathioprine (2-2.5 mg/kg/day) OR
- Oral MMF (300-600 mg/m^2/dose, twice daily, [maximum daily dose of 3 g])

Cutaneous features of children with SLE resolve with systemic treatment but strict photoprotection with restriction of day time activity and use of opaque sunscreen is required to prevent recurrence. Hydroxychloroquine is effective in ameliorating cutaneous symptoms. These children are prone to develop hypertension and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers is the drug of choice.

Continuous monitoring for systemic involvement and drug-related side effects is mandatory for all children with SLE. Calcium and vitamin D supplementation is essential to maintain normal bone density and ensure adequate growth. Some patients may require psychiatric help and physiotherapy is helpful for debilitating joint involvement.

Neonatal lupus erythematosus

Neonatal lupus erythematosus (NLE) is an anti-Ro antibody mediated disorder comprised of cutaneous, cardiac, hepatic, and hematological manifestations.[2] Rarely neurological and pulmonary involvement may be present.[18] One or combination of more than one organ involvement is usual. Cutaneous and cardiac disorders are common than manifestations related to other organ involvement.

The cutaneous lesions of NLE may be present at birth or appear thereafter. These lesions are transitory and subside spontaneously within few weeks to months and rarely persist beyond 1 year of life. Morbidity of NLE is due to the cardiac involvement.

Photoprotection and low potency topical corticosteroids are the mainstay of therapy for cutaneous lesions of NLE.[2] Parents of the affected children must be thoroughly counseled regarding avoidance of sunlight, proper use of sunscreen, and protective clothing.

Sometimes, though there is resolution of active skin lesions, pigmentary changes, atrophy, and telangiectasia may persist over face and other exposed body parts. In such cases cosmetic camouflage helps these children in social interaction. Persistent telangiectasia may be managed with vascular laser.[18]

Systemic corticosteroids or immunosuppressives are not recommended to treat cutaneous lesions of NLE.[2] In rare cases, if systemic therapy is indicated, hydroxychloroquine may be used.[2] Systemic corticosteroid is used in cases of severe thrombocytopenia and hepatic involvement.[19] Patients with thrombocytopenia may also require blood transfusion and/or IVIg.[19]

Cardiac screening must be performed in all patients with NLE. In a known high risk mother (suffering from any collagen vascular disorder/positive anti-Ro antibody/history of previous birth with NLE) intrapartum monitoring of the fetus by pediatric cardiologist is recommended for early detection of conduction defects; such deliveries are to be planned in a set up with facility of immediate postpartum pacemaker implantation.[19]

Prophylactic systemic corticosteroid maintenance therapy of high risk mothers during pregnancy has been found

to prevent occurrence of congenital heart block in theneonate.[20] It is administered as oral prednisolone 15-20 mg/day started before 16 weeks of gestation and tapered slowly beyond this period to ≤10 mg. Betamethasone, which crosses placenta more effectively, is a better alternative of prednisolone, started at 9-12 weeks of gestation.[20] However, when this treatment is started beyond 16 weeks, it does not provide such protection. Prophylactic corticosteroid therapy during pregnancy may not be effective to prevent occurrence of cutaneous NLE.[20]

Juvenile dermatomyositis

Dermatomyositis, an inflammatory myopathy; when occurs before 18 years of age, it is designated as Juvenile dermatomyositis (JDM).[21] Though rare, it is the commonest inflammatory myopathy in childhood. The 'amyopathic' variant of the disease is encountered still rarely in children.The onset of symptoms may be insidious or acute with fulminant clinical presentation.[22] The main aims of therapy in JDM are to reduce the morbid sequelae of myopathy and to prevent life threatening complications (cardiac, pulmonary, gastrointestinal hemorrhage, ulcerations, calcinosis).[23] Various therapeutic modalities in JDM has been discussed below.

Corticosteroids

The first line of therapy used for JDM is systemic corticosteroid, started at a dose of 1-2 mg/kg body weight, tapered slowly over several months or 1-2 years. In severe cases or during acute exacerbations, intravenous pulse of methyl prednisolone may be administered. Various immunosuppressive drugs are often combined withcorticosteroid.[22] Prolonged corticosteroid use is associated with profound therapy-related morbidity. However, till today corticosteroid remains the mainstay of therapy in JDM, because use of this drug has reduced JDM associated morbidity and mortality drastically (as compared with the pre-corticosteroid era) and there has been great decrease in the incidence of calcinosis.[23]

Hydroxychloroquine

Hydroxychloroquine (5-6 mg/kg/day) has been used in JDM and it may have a steroid-sparing effect. Available studies report improvement of cutaneous lesions as well as muscle disease with this therapy.[23] However, there may also be exacerbation of the cutaneous lesions with this drug.[22]

Plasmapheresis

Plasmapheresis was the conventional therapy for life-threatening JDM prior to the routine use of immunosuppressive drugs. Though found to be ineffective in adult disease, there are reports of improvement in JDM.[23]

Immunosuppressive drugs

Various immunosuppressive drugs used in JDM are methotrexate, cyclophosphamide, azathioprine, cyclosporine, and oral tacrolimus. These drugs are used as adjunct to corticosteroid therapy.

Fisler *et al*.[24] reported 'aggressive management' of 36 patients with JDM with corticosteroid and methotrexate. The treatment protocol consisted of high dose oral or intravenous corticosteroid, followed by administration of methotrexate (0.5-1 mg/kg/week, subcutaneous/intravenous) for 6 weeks. The authors have concluded that this mode of therapy resulted in rapid control of active disease and prevented long-term complications like calcinosis. Various therapeutic protocols involving methotrexate have been used by other authors and it has been found that early use of methotrexate may allow faster weaning of corticosteroids than usual.[25]

Cyclophosphamide pulse therapy has been used in a group of 12 children with JDM along with high dose corticosteroids.[26] The indications of cyclophosphamide in these patients were skin ulceration, severe muscle weakness, and severe systemic involvement (interstitial pneumonia, gastrointestinal tract ulcers, seizure).[26] Cyclophosphamide was administered at 500 mg/m^2/dose, increased upto 1000 mg/m^2/dose, according to patient's tolerance level. Each patient received 6-7 such monthly pulses followed by 3 monthly pulses till disease severity was decreased.[26] Nine of these patients received some other immunosuppressive drug along with the above therapy. Side effects related to this treatment were mild and transient. Ten patients showed stability or regression of disease activity and have been kept under long-term follow up.[26]

There are studies with small sample size, using azathioprine, cyclosporine, and oral tacrolimus, which report improvement of symptoms and achieving disease remission with these agents.[23,25] The published study reports on therapy of JDM with various immunosuppressive drugs are either uncontrolled or lack adequate follow up of patients hindering establishment of definitive therapeutic schedules using these agents.[25]

IVIg

The indication of IVIg in JDM is severe disease refractory to treatment with corticosteroid and immunosuppressive drugs. There are reports of using IVIg at the onset of the disease.[23] Long-term treatment with IVIg helps in ameliorating both cutaneous manifestations as well as myositis. It is administered at a dose of 2 g/kg body weight/day for a period of 3-5 days, administered every 4-6 weeks.[22]

Biological therapy

Several authors have treated cases of JDM using antitumor necrosis factor (TNF) agent etanercept (0.4 mg/kg, twice weekly, subcutaneously).[25] The basis of this treatment was

the postulation that TNF gene polymorphism (TNFα-308) is related to the human leukocyte antigen (HLA) associations (*HLA-B, HLA-DR3*) found in JDM.[25] Some studies have demonstrated that such polymorphism is associated with increased chances of disease chronicity, increased production of TNFα by peripheral blood mononuclear cells and myocytes in these patients and the finding of capillary occlusion in muscle biopsy.[25] However, the results of the preliminary studies on treatment of JDM with etanercept did not merit its routine use.[25]

In an open label study, infliximab, a monoclonal antibody against tumor necrosis factor has been tried in five children with progressive JDM and calcinosis refractory to conventional therapy.[27] The initial dose of infliximab was 3 mg/kg, repeated at 2nd and 6th weeks and every 8 weeks thereafter, subsequent dosage and treatment interval determined by clinical response of the patients.[27] The patients showed significant improvement in muscle strength and function; there was reduction in disease activity, joint contracture, and need for corticosteroid use with this therapy.[27] Further data on use of this agent in JDM is not available.

Rituximab has been used in cases of JDM who are nonresponders to conventional therapy. The basis of using rituximab is to achieve B cell targeted therapy, as humoral immunity and auto-antibodies are the principal factors involved in the pathogenesis of JDM. In a recent review of rituximab use in JDM, 12 children who have received this treatment (so far published reports) have been analyzed.[21] These children were nonresponders to conventional therapy for JDM, including IVIg. Majority of the patients received a dose of 375 mg/m^2/week for 4 weeks. Cutaneous and muscular symptoms improved in nine patients (75%); five among them (42%) achieved remission with single course of rituximab. Two patients had relapse and required repeat administration of the drug along with maintenance therapy or had to switch over to other treatment modality. Follow up data of rest of the patients were not consistent. No major adverse effect was reported by any of the authors.[21]

Efficacy of rituximab has been studied in other diseases like lymphoproliferative disorders and rheumatoid arthritis. Infusion reactions, increased incidence of infections, and cytopenias are the important adverse effects of this drug and patients require monitoring for these.[21] However, it appears to be a well-tolerated drug as various clinical trials record only a low incidence of adverse effects.[21] Currently the major pitfall of rituximab therapy in inflammatory myopathies is substantial rate of relapse, as soon as there is B cell recovery without providing sustained remission.[28,29] A randomized, placebo-controlled, double-blind trial on efficacy of rituximab in patients (aged > 5 years) with inflammatory myopathies is ongoing. Results of this trial may provide more information on the use of rituximab in refractory cases of JDM.[21]

ASCT

Immunoablation followed by ASCT has been attempted in two children with JDM, who failed to respond to all therapeutic modalities including rituximab.[29] Immunoablation was achieved with fludarabine, cyclophosphamide, and antithymocyte globulin followed by ASCT using CD3/CD19-depleted graft.[29] Both the patients showed significant improvement of symptoms at 26 month (patient 1) and 13 month (patient 2) follow up period. There was significant decrease in disease activity and improvement of inflammation (evidenced by MRI study) and the patients could be maintained without any immunosuppressive therapy.[29]

Other models of ASCT have been tried in adult patients with inflammatory myopathies achieving persistent improvement.[29] Though the authors found this method an effective way to treat severe treatment refractory cases of JDM, with low risk of toxicity or complications, long-term follow up data in children is not available at present.[29]

Supportive therapy

All children with JDM must adopt photoprotective measures. Supplementation with calcium and vitamin D is necessary as they are prone to develop osteopenia resultingfrom the disease process, secondary joint contracture related immobility, as well as due to prolonged corticosteroid use. Active and passive physiotherapy must be performed routinely to prevent joint contractures. Calcinosis, a long-term complication of JDM has been treated with several agents like diltiazem, aluminium hydroxide, bisphosphonates, colchicines, etc.[23,30] Incision and drainage may be performed for painful areas of calcinosis cutis, restricting mobility.[30]

Childhood scleroderma

Both localized (morphea) and generalized scleroderma may occur in children, but morphea is the usual presentation at this age.[31] Solitary plaque morphea is a self-limiting condition. However, linear morphea, en coup de sabre, pansclerotic morphea, and generalized morphea may be quite disabling.

Morphea

Various therapeutic modalities for treatment of morphea in children have been discussed below.

Topical therapy

Corticosteroid

Topical potent corticosteroid ointment should be started at the early stage of single/few lesions of plaque morphea and should be applied till the lilac-colored border disappears.[31]

Tacrolimus

Topical tacrolimus ointment (0.1%) has been found to be

effective in the treatment of morphea.[32] Exact mechanism of action of tacrolimus in morpheais poorly understood. It may exert immunomodulatory and antiinflammatory actionby T lymphocyte inhibition and decreased production of inflammatory cytokines.[33] Mancuso *et al*.[33] used topical tacrolimus under plastic wrap occlusion in adultswith morphea refractory to topical and systemic steroids. It has been found to be aneffective treatment for morphea with good tolerability, least side effects, and with scopefor long-term use. The authors have found that occlusion enhances the efficacy oftacrolimus.[33]

Imiquimod

Imiquimod has been used with success in both adult and childhood morphea. Imiquimod (5%) cream was applied as a thin layer before bed time on 3 nonconsecutive days. It was gradually increased to daily application. In the series of patients with morphea treated with imiquimod by Dytoc *et al*.,[34] three were children. Significant improvement was found in induration, erythema, and dyspigmentation in all the patients during the 6-month evaluation period and there was histopathological evidence of reduction of fibrosis. No significant side effect was noted with this drug except mild irritation in few cases. The probable mechanism of action of imiquimod in morphea is through production of cytokines interferon (IFN) -α and -γ, which inhibit human fibroblast collagen production. IFN- γ also inhibits profibrotic interleukins (IL), IL-4 and IL-13.[34]

Vitamin D analogues

In an open-label study involving 12 adults and children with morphea or linear scleroderma, topical calcipotriol (0.005%) ointment, twice daily application under occlusion was found to be effective.[35] Calcipotriol (50 μg/g) and betamethasone dipropionate (0.5 mg/g) combination therapy (ointment) is a balanced approach in the treatment of localized morphea. Dytoc *et al*.[36] reported the first case series on use of this combination therapy in morphea; among the six patients recruited for this trial, one was an adolescent girl (15 years). Both corticosteroid and calcipotriol inhibit fibroblast proliferation preventing fibrosis and the former has antiinflammatory action in addition. The patients included in this study showed moderate to marked clinical and ultrasonographic improvement of the treated skin lesions.[36]

Phototherapy

Phototherapy is an effective mode of therapy for localized scleroderma. Various modalities have been used in both adults and children; psoralen and ultraviolet A (PUVA), bath-PUVA,[37] broadband ultraviolet A (UVA) therapy, UVA1 phototherapy and narrowband ultraviolet B (UVB) (NB-UVB) phototherapy. Of these UVA1 phototherapy has been found to be the most effective and is considered as the most recent advance in the treatment of morphea.[38]

Stege *et al*.[39] first reported (1997) effectiveness of high dose UVA1 phototherapy in the treatment of morphea. UVA1 has deeper penetrability and affects all the three main pathomechanisms of morphea, that is, disturbance in collagen metabolism, autoimmunity, and alteration in blood vessels.[38] UVA1 phototherapy in morphea helps in upregulation of specific messenger RNA of matrix metalloproteinases, depletion of locally infiltrating T cells, and proinflammatory cytokines, like IL-1 and IL-6 and modulation of endothelial regulation or transformation.[38] In addition, it induces a shift of the balance between proto-oncogenes and tumor suppressor genes by induction of apoptosis.[38] There are several uncontrolled trials on smaller sample size, proving efficacy of UVA1 phototherapy in morphea.

Medium dose UVA1 phototherapy has been found to be significantly superior to low dose and equipotent to high dose.[40] In a retrospective and prospective study in adult patients with morphea, short- and long-term efficacy of moderate cumulative dose of UVA1 phototherapy has been shown.[40] In an intrapatient comparative trial to determine optimum dose of UVA1 phototherapy in 16 patients (>14 years) with morphea, authors have irradiated different lesional sites of the same patient with varying dose, and a nonirradiated lesion was taken as control.[41] The authors have concluded that UVA1 phototherapy in morphea is a highly effective treatment modality, with medium dose schedules being more effective than low dose.[41] On follow-up for 1 year, good tolerability among patients, halt of disease progression and reversal of sclerosis were observed. The authors have proposed that medium dose UVA1 phototherapy can be considered as first line treatment for morphea.[41] However, facility of UVA1 phototherapy is available only at specific centers and it is costlier.[41]

In a randomized controlled study, Kreuter *et al*.[38] compared the efficacy and safety of low dose UVA1 (20 J/cm^2, 5 times/week × 8 weeks, cumulative dose 800 J/cm^2), medium dose UVA1 (50 J/cm^2, 5 times/week × 8 weeks, cumulative dose 2000 J/cm^2), and NB-UVB (starting dose of 0.1-0.2 J/cm^2, 5 times/week × 8 weeks, gradually increasing dose) in a sample of 64 patients comprised of both adults and children with localized scleroderma. The study results have shown that though medium dose UVA1 was significantly more effective, efficacy of NB-UVB was comparable to that of low dose UVA1.[38] The authors have proposed that in case of nonavailability of UVA1 phototherapy, NB-UVB may be used to treat morphea.[38]

Use of phototherapy alone may not give complete response. Hence, synergistic combination therapy with other agents may also be used. In an open prospective study, Kreuter *et al*.[42] studied the efficacy of combination treatment of calcipotriol ointment and low-dose UVA1 phototherapy in 19 children (3-13 years) with morphea

and found it to be an effective combination. Mid-potent topical corticosteroid may be combined in early, active stage of the lesions[38] and topical calcineurin inhibitorsmay also be used.[33]

Extracorporeal photochemotherapy has been used with success in adults with generalized deep morphea.[43]

Systemic therapy

Progressive lesions of morphea can be treated with systemic steroid along with methotrexate. The following protocol may be used for progressive plaque morphea, linear morphea, and en coup de sabre.[31,44]

Induction phase

- Intravenous injection of methylprednisolone (30 mg/kg/day, [maximum dose of 500mg/day], on days 1-3). The same pulse is to be repeated after 7 days (on days 8-10).

Maintenance phase

- Oral prednisolone (0.5-1 mg/kg/day) to be started after first pulse of methyl prednisolone (on days 4-7, again from day 11 onwards), to be continued for a minimum period of 4 weeks and thereafter gradually tapered over a period of 3-6 months.
- Oral/subcutaneous methotrexate to be started (o day 15) after 2nd pulse of methylprednisolone (10 mg/m^2/week). Dose may be reduced when the disease activity is stopped but it should be continued till 1 year thereafter.

Various other systemic treatments have been tried in progressive morphea. These include azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil,[45] hydroxychloroquine, colchicines, IVIg, photodynamic therapy, etc., with variable results.[46]

Strauss *et al*.[47] treated a 12-year-old girl with progressive linear morphea refractory to topical steroid, with cyclosporine (3 mg/kg/day). Improvement was recorded in 3 weeks with clearance of lesion by 4 months without recurrence up to 1 year of follow up.

Based on the above report, Crespo *et al*.[48] treated a case of progressive en coup de sabre in a 7-year-old girl with oral cyclosporine (3 mg/kg/day) with significant improvement by 3 months and showing stability for 18 months. Thereafter, on recurrence of the lesion, patient was restarted with cyclosporine (2.5 mg/kg/day) along with topical calcipotriol. After 4 months of this 'induction therapy,' as the lesion became inactive, patient was started on methotrexate (10 mg/week × 6 months) with folic acid supplementation. There was no relapse of the disease during 1 year of follow up.[48]

Oral calcitriol has been used in generalized morphea with success.[46] Diab *et al*.[49] reported successful treatment of an adult patient of recalcitrant generalized morphea with infliximab.

Martini *et al*.[45] retrospectively analyzed the data regarding effectiveness of MMF in the treatment of 10 children with severe form of morphea. All these children were refractory to treatment with corticosteroids and methotrexate. There was arrest of disease activity with MMF therapy allowing withdrawal of the previous drugs. Side effects of MMF in these children were minimal and the authors have concluded that it is an effective and well tolerated drug for the treatment of childhood morphea.

Currently, the evidence-based treatment protocol for treatment of morphea in various scenarios is as follows:[50]

a) Limited plaque morphea

Topical tacrolimus ointment (0.1%) is the first line of treatment. In absence of response after 8 weeks, any of the following modalities may be used:

- Lesional phototherapy, according to availability (NB-UVB/PUVA/UVA/UVA1)
- Topical calcipotriol under occlusion
- Topical imiquimod
- Topical calcipotriol + betamethasone dipropionate

b) Linear morphea (face or across a joint)

Combination of methotrexate and systemic steroid remains the first therapeutic choice in such situation. In absence of response after 8 weeks, any of the following modalities may be used:

- Lesional phototherapy, according to availability (NB-UVB/PUVA/UVA/UVA1)
- Mycophenolate mofetil

c) Generalized morphea without joint contracture

Phototherapy has to be started, according to availability (NB-UVB/PUVA/UVA/UVA1). Phototherapy has a better side effect profile, hence preferred over methotrexate as first line of treatment. If there is no response after 8 weeks of phototherapy, combination therapy of systemic corticosteroid, and methotrexate is administered. If the patient does not respond in further 8 weeks, mycophenolate mofetil has to be started.

Generalized scleroderma (systemic sclerosis [SSc])

SSc is rarer in children as compared with morphea, less than 3% of the adult cases starting during childhood.[51] Unlike in adults, the limited cutaneous variant (CREST syndrome) of the disease is very rare in children.[51]

Currently available treatment modalities provide symptomatic relief to patients suffering from SSc. Since this condition is rare in children organ specific therapeutic protocol, as for adults, is not available. Various therapeutic agents those have been used in childhood SSc are as follows:

Immunosuppressive drugs

Systemic therapy for childhood SSc consists of

immunosuppressive drugs. However, the decision on use of such therapy must be weighed carefully against the benefit to be achieved. The specific indications of immunosuppressive therapy are limited to:[51]

- Early stage of diffuse cutaneous sclerosis,
- Active muscle disease
- Pulmonary fibrosis.

The commonly used drugs are methotrexate, cyclophosphamide, azathioprine and cyclosporine, but there is no therapeutic trial of these drugs in childhood SSc.[51] Early stage of cutaneous disease may be treated effectively with methotrexate.[52]

Methotrexate has been used at a dose of 5-10 mg/m^2/week, but higher doses may also be used as children tolerate this drug better than adults.[51]

Cyclosporine has been reported to be used in childhood SSc but the patients require close monitoring.[52]

Cyclophosphamide may be used in children with SSc in presence of interstitial lung disease, as intravenous pulse therapy (0.5-1 mg/m^2/month × 6 months).[53]

Systemic corticosteroids

Systemic corticosteroids (oral prednisolone, 0.3-0.5 mg/kg/day) may be used in presence of myositis, arthritis or tenosynovitis.[51,52] Otherwise, role of steroids in childhood SSc is unproven and may be associated with high adverse effects.[51] Moreover, in the background of SSc use of even modest doses of corticosteroid may precipitate hypertensive renal crisis.[51,52]

UVA1 phototherapy, IVIg, various biologicals (infliximab, etanercept, rituximab) have been used in treating adult SSc but experience regarding their use in childhood SSc is limited.[52] d-Penicillamine, though widely used earlier, present consensus is not to use this drug in SSc because of its questionable efficacy and high side effect profile.[51]

Symptomatic treatment

Following suggestions are given in presence of Raynaud's phenomenon;

- Ensuring a warm environment with additional heating device during winter.
- Woolen gloves and socks to keep the extremities warm.
- Oral vasodilator therapy (calcium channel blocker/ACE inhibitor/angiotensin receptor blocker).[51] In severe cases of Raynaud's phenomenon, with or without digital ulcers, intravenous administration of prostacyclin analogue (iloprost) is helpful.[51,52,54]

Gastrointestinal involvement is common in patients with SSc. Proton pump inhibitors are used for gastroesophageal reflux, prokinetic agents are used for symptomatic dysmotility and prophylactic antibiotics may be administered in presence of intestinal bacterial overgrowth.[52] Early and regular physiotherapy is of immense importance in these children to prevent contracture of limbs.

Summary

Topical or systemic corticosteroids remain the first-line therapy in all types of collagen vascular diseases in children. In fact, use of corticosteroids has significantly brought down the mortality and morbidity associated with these disorders. However, prolonged use of corticosteroids is associated with side effects and there are cases refractory to this drug. Immunosuppressive drugs have been introduced as steroid-sparing agents and some of these have been found to serve this purpose and may also be continued as maintenance therapy during steroid-free period. Some of these immunosuppressive drugs have been specifically used to combat systemic manifestations, for example, cyclophosphamide for lupus nephritis, methotrexate for arthritis, etc. Hence, combination of treatment should be individualized according to given clinical scenario and patient need. Most of these drugs have significant adverse effects (immediate and long-term) and regular monitoring is required for all of them. Intercurrent infections, carcinogenicity, and infertility are some of the grave long-term complications.

Recently, in severe refractory situations various treatment modalities have been tried. These include IVIg, biologicals, and ASCT and the efficacy of some of these therapies is encouraging. Lack of long-term follow up and controlled studies on use of these agents in children are the current issues hindering widespread use of these agents. Moreover, requirement for specialized set up, high cost, and nonavailability are the other limiting factors.

The complex, multisystemic nature of these disorders requires a multidisciplinary approach. While managing one such patient, systemic involvements are to be identified early and specialist care should be sought.

Whichever treatment is being decided for a child with collagen vascular disorder, the main concern remains the long-term safety of the therapy. The aim should be to reduce disease activity to a minimum level and to allow treatment free intervals, so that the growth, development, and fertility of these children are ensured.

References

1. Falcini F. Vascular and connective tissue diseases in the paediatric world. Lupus 2004;13:77-84.
2. Lee LA. Cutaneous lupus in infancy and childhood. Lupus 2010;19:1112-7.
3. Cherif F, Mebazaa A, Mokni M, El Euch D, Azaiz MI, Dhahri AB. Childhood discoid lupus erythematosus: A Tunisian retrospective study of 16 cases. Pediatr Dermatol 2003;20:295-8.
4. Sampaio MC, de Oliveira ZN, Machado MC, dos Reis VM, Vilela MA. Discoid lupus erythematosus in children – a retrospective study of 34 patients. Pediatr Dermatol 2008;25:163-7.

5. Miettunen PM, Bruecks A, Remington T. Dramatic response of scarring scalp discoid lupus erythematosus (DLE) to intravenous methylprednisolone, oral corticosteroids and hydroxychloroquine in a 5-year-old child. Pediatr Dermatol 2009;26:338-41.
6. Abe M, Ishikawa O, Miyachi Y. Linear cutaneous lupus erythematosus following the lines of Blaschko. Br J Dermatol 1998;139:307-10.
7. Moises-Alfaro C, Berron-Perez R, Carrasco-Daza D, Gutiérrez-Castrellón P, Ruiz- Maldonado R. Discoid lupus erythematosus in children: Clinical, histopathologic, and follow-up features in 27 cases. Pediatr Dermatol 2003;20:103-7.
8. Marks SD, Tullus K. Modern therapeutic strategies for paediatric systemic lupus erythematosus and lupus nephritis. Acta Paediatrica 2010;99:967-74.
9. Silverman E. What's new in the treatment of pediatric SLE. J Rheumatol 1996;23:1657-60.
10. Buratti S, Szer IS, Spencer CH, Bartosh S, Reiff A. Mycophenolate mofetil treatment of severe renal disease in pediatric onset systemic lupus erythematosus. J Rheumatol 2001;28:2103-8.
11. Falcini F, Capannini S, Martini G, La Torre F, Vitale F, Mangiantini F, *et al*. Mycophenolate mofetil for the treatment of juvenile onset SLE: A multicenter study. Lupus 2009;18:139-43.
12. Bichile LS, Pruthi MS, Zarkar A, Sabnis SA. Favourable outcome in a patient with central nervous system lupus. J Assoc Physicians India 1999;47:1201-2.
13. Chetan G, Mahadevan S, Sulanthang K, Narayanan P. Intravenous immunoglobulin therapy of lupus pneumonitis. Indian J Pediatr 2007;74:1032-3.
14. Wright EC, Tullus K, Dillon MJ. Retrospective study of plasma exchange in children with systemic lupus erythematosus. Pediatr Nephrol 2004;19:1108-14.
15. Marks SD, Tullus K. Successful outcomes with rituximab therapy in refractory childhood systemic lupus erythematosus. Pediatr Nephrol 2006;21:598-9.
16. Podolskaya A, Stadermann M, Pilkington C, Marks SD, Tullus K. B cell depletion therapy for 19 patients with refractory systemic lupus erythematosus. Arch Dis Child 2008;93:401-6.
17. Wulffraat NM, Sanders EA, Kamphuis SS, Rigkers GT, Kuis W, Lilien M, *et al*. Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. Arthritis Rheum 2001;44:728-31.
18. Wisuthsarewong W, Soongswang J, Chantorn R. Neonatal lupus erythematosus: Clinical character, investigation, and outcome. Pediatr Dermatol 2011;28:115-21.
19. McCauliffe DP. Neonatal lupus erythematosus. In: Harper J, Oranje A, Prose N, editors. Textbook of pediatric Dermatology. 2nd ed. Oxford: Blackwell Publishing Ltd; 2006. P. 126-33.
20. Shinohara K, Miyagawa S, Fujita T, Aono T, Kidoguchi K. Lupus erythematosus: Results of maternal corticosteroid therapy. Obstet Gynecol 1999;93:952-7.
21. Chiu YE, Co DO. Juvenile dermatomyositis: Immunopathogenesis, role of myositis-specific autoantibodies, and review of rituximab use. Pediatr Dermatol 2011;28:357-67.
22. Halbert AR. Juvenile dermatomyositis. Australas J Dermatol 1996;37:106-8.
23. Reed AM, Lopez M. Juvenile dermatomyositis. Recognition and treatment. Pediatr Drugs 2002;4:315-21.
24. Fisler RE, Liang MG, Fuhlbrigge RC, Yalcindaq A, Sundel RP. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. J Am Acad Dermatol 2002;47:505-11.
25. Huber AM. Juvenile dermatomyositis. Advances in pathogenesis, evaluation, and treatment. Pediatr Drugs 2009;11:361-74.
26. Riley P, Maillard SM, Wedderburn LR, Woo P, Murray KJ, Pilkington CA. Intravenous cyclophosphamide pulse therapy in juvenile dermatomyositis: A review of efficacy and safety. Rheumatology (Oxford) 2004;43:491-6.
27. Riley P, McCann LJ, Maillard SM, Woo P, Murray KJ, Pilkington CA. Effectiveness of infliximab in the treatment of refractory juvenile dermatomyositis with calcinosis. Rheumatology (Oxford) 2008;47:877-80.
28. Levine TD. Rituximab in the treatment of dermatomyositis: An open-label pilot study. Arthritis Rheum 2005;52:601-7.
29. Holzer U, van Royen-Kerkhof A, van der Torre P, Kuemmerle-Deschner J, Well C, Handgretinger R, *et al*. Successful autologous stem cell transplantation in two patients with juvenile dermatomyositis. Scand J Rheumatol 2010;39:88-92.
30. Wu JJ, Metz BJ. Calcinosis cutis of juvenile dermatomyositis treated with incision and drainage. Dermatol Surg 2008;35:575-7.
31. Sampaio C, Visentin MT, Howel K, Woo P, Harper J. Morphoea (Synonym: Localized Scleroderma). In: Harper J, Oranje A, Prose N, editors. Textbook of Pediatric Dermatology. 2nd ed. Oxford: Blackwell Publishing Ltd; 2006. P. 2020-9.
32. Mancuso G, Berdondini RM. Topical tacrolimus in the treatment of localized scleroderma. Eur J Dermatol 2003;13;290-2.
33. Mancuso G, Berdondini RM. Localized scleroderma: Response to occlusive treatment with tacrolimus ointment. Br J Dermatol 2005;152:180-2.
34. Dytoc MT, Ting PT, Man J, Sawyer D, Fiorillo L. First case series on the use of imiquimod for morphea. Br J Dermatol 2005;153:815-20.
35. Cunningham BB, Landells ID, Langman C, Sailer DE, Paller AS. Topical calcipotriene for morphea/linear scleroderma. J Am Acad Dermatol 1998;39:211-5.
36. Dytoc MT, Kossintseva I, Ting PT. First case series on the use of calcipotriol- betamethasone dipropionate for morphea. Br J Dermatol 2007;157:615-8.
37. Kerscher M, Meurer M, Sander C, Volkenandt M, Lehmann P, Plewig G, *et al.* PUVA bath photochemotherapy for localized scleroderma. Evaluation of 17 consecutive patients. Arch Dermatol 1996;132:1280-2.
38. Kreuter A, Hyun J, Stucker M, Sommer A, Altmeyer P, Gambichler T. A randomized controlled study of low-dose UVA1, medium-dose UVA1 and narrowband UVB phototherapy in the treatment of localized scleroderma. J Am Acad Dermatol 2006;54:440-7.
39. Stege H, Berneburg M, Humke S, Klammer M, Grewe M, Grether-Beck S, *et al*. High-dose UVA1 radiation therapy for localized scleroderma. J Am Acad Dermatol 1997;36:938-44.
40. Andres C, Kollmar A, Mempel M, Hein R, Ring J, Eberlein B. Successful ultraviolet A1 phototherapy in the treatment of localized scleroderma: A retrospective and prospective study. Br J Dermatol 2010;162:445-7.
41. Sator PG, Radakovic S, Schulmeister K, Hönigsmann H, Tanew A. Medium- dose is more effective than low-dose ultraviolet A1 phototherapy for localized scleroderma as shown by 20-MHz ultrasound assessment. J Am Acad Dermatol 2009;60:786-91.
42. Kreuter A, Gambichler T, Avermaete A, Jansen T, Hoffmann M, Hoffmann K, *et al*. Combined treatment with calcipotriol ointment and low-dose ultraviolet A1 phototherapy in childhood morphea. Pediatr Dermatol 2001;18:241-5.
43. Neustadter JH, Samarin F, Carlson KR, Giradi M. Extracorporeal photochemotherapy for generalized deep morphea. Arch Dermatol 2009;145:127-30.

44. Weibel L, Sampaio MC, Visentin MT, Howell KJ, Woo P, Harper JI. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphea) in children. Br J Dermatol 2006;155:1013-20.
45. Martini G, Ramanan AV, Falcini F, Girschik H, Goldsmith DP, Zulian F. Successful treatment of severe or methotrexate resistant juvenile localized scleroderma with mycophenolate mofetil. Rheumatology (Oxford) 2009;48:1410-3.
46. Humbert P, Aubin F, Dupond JL, Delaporte E. Oral calcitriol as a new therapeutic agent in localized and systemic scleroderma. Arch Dermatol 1995;131:850-1.
47. Strauss RM, Bhushan M, Goodfield MJ. Good response of linear scleroderma in a child to ciclosporin. Br J Dermatol 2004;150:790-2.
48. Crespo MP, Betlloch IM, Mataix JD, Costa AL, Nortes IB. Rapid response to cyclosporine and maintenance with methotrexate in linear scleroderma in a young girl. Pediatr Dermatol 2009;26:118-20.
49. Diab M, Coloe JR, Magro C, Bechtel MA. Treatment of recalcitrant generalized morphea with infliximab. Arch Dermatol 2010;146:601-4.
50. Fett NM. Morphea: Evidence based recommendations for treatment. Indian J Dermatol Venereol Leprol 2012;78:135-41.
51. Denton CP, Black CM. Systemic sclerosis in childhood. In: Harper J, Oranje A, Prose N, editors. Textbook of pediatric Dermatology. 2nd ed. Oxford: Blackwell Publishing Ltd; 2006. p. 2030-40.
52. Panda S. Scleroderma in children: Emerging management issues. Indian J Dermatol Venereol Leprol 2010;76:348-56.
53. Zulian F. Systemic sclerosis and localized scleroderma in childhood. Rheum Dis Clin North Am 2008;34:239-55.
54. Zulian F, Corona F, Gerloni V, Falcini F, Buoncompagni A, Scarazatti M, *et al*. Safety and efficacy of iloprost for the treatment of ischaemic digits in paediatric connective tissue diseases. Rheumatology (Oxford) 2004;43:229-33.

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Announcement

New Rules of Submitting Clinical Trial Reports in Indian Journal of Dermatology

The process of submitting clinical trial reports in the Indian Journal of Dermatology that will undergo some important changes in the near future.

We have recently incorporated the hyperlink to the most recent CONSORT Statement in our 'Instruction to Authors'(http://www.e-ijd.org/contributors.asp) and have advised all prospective trial report authors to adhere to the same. And that includes this recently introduced paragraph.

Original article (2500 words): Original, in-depth clinical studies or surveys. Please write a structured abstract and add statistical methods. Authors of randomized control trials are requested to follow the guidelines presented in the CONSORT statement (http://www.consort-statement.org/). For authors of epidemiologic studies the STROBE statement (http://www.strobe-statement.org/Checklist.html) guideline to be followed. Systemic review and meta analysis may be submitted under this section. Citation of levels of evidence is appreciated for any article when needed. Permission of ethics committee/IRB, statement of sources of support and conflict of interest are mandatory.

To extend the fast-improving quality of articles being published in this journal to the area of clinical trial reports, we shall be making it mandatory for all clinical trial reports to follow the most recent CONSORT Statement in totality. The authors will be asked to complete a checklist containing the various CONSORT criteria once you submit a clinical report.

This step is entirely in sync with current global standards of clinical trial reporting. It is expected that the visibility and citation of this journal and that of your own clinical trial reports are going to get a great boost once this system is in place.

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