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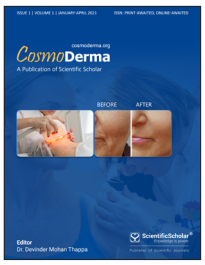

Brief Report

Clinicoimmunologic pattern, therapeutic response, and outcomes in connective tissue disease patients receiving steroid pulse therapy

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ABSTRACT

Objectives: The aim of the study was to examine the clinicoimmunologic pattern, therapeutic response, and long-term outcomes in connective tissue disease (CTD) patients who received steroid pulse therapy.

Material and Methods: Patients diagnosed with CTD (including diffuse cutaneous systemic sclerosis [dcSS], systemic lupus erythematosus [SLE], subacute cutaneous lupus erythematosus [SCLE], mixed CTD [MCTD], or overlap syndrome) who received steroid pulse therapy (period July 2017–June 2019) were identified in the hospital database and their relevant data were retrieved. Patients were followed up in June 2020 and response to treatment was evaluated by a self-devised patient-reported assessment scale.

Results: Among the CTDs (n = 22; M: F = 1:6.3. Mean age = 39.95 ± 11.2 years), dcSS (45.5%) was the most common CTD seen followed by SLE (31.8%), MCTD (9.1%), SCLE (9.1%), and overlap syndrome (4.5%). CTD patients most commonly presented with joint pains (77.2%) or Raynaud's phenomenon (77.2%). Antinuclear antibody (ANA) was positive in all patients. Fourteen patients received methylprednisolone; seven dexamethasone pulse, and one received dexamethasone-cyclophosphamide pulse. Only 10 patients could be followed up (mean duration of follow-up = 12.8 ± 6.4 months); two had complete remission, that is, clear; two had considerable benefit. Two did not tolerate pulse therapy and two died.

Conclusion: Pulsed steroids can be a well-tolerated therapeutic modality with some benefit in CTD patients presenting to a dermatologist.

Keywords: Connective tissue diseases, Methylprednisolone pulse, Dexamethasone pulse, Dexamethasone-cyclophosphamide pulse, Clinicoimmunologic pattern in connective tissue diseases.

INTRODUCTION

Pulse therapy is the administration of suprapharmacologic doses of drugs in an intermittent manner enhancing the therapeutic effects while minimizing side effects.[1] The first reported clinical use of steroid pulse is attributed to Kountz and Cohn who used it for the prevention of renal allograft rejection in 1973.[2] In India, the dermatological pioneers were Pasricha and Gupta who modified the methylprednisolone regimen and introduced dexamethasone-cyclophosphamide pulse (DCP) therapy for the pemphigus group of disorders in 1982. It has since then proven to be a life-saving intervention.[3]

Pulse therapy is particularly advantageous where rapid immunosuppression and anti-inflammatory effect is desired, such as in immune bullous disorders, connective tissue diseases (CTD), organ transplantation, steroid-resistant nephrotic syndrome, and crescentic glomerulonephritis.[3-7] In 1976, Lancet first used methylprednisolone pulse for lupus nephritis which has become the bench mark treatment of severe lupus nephritis since then.[8] High intracellular levels of glucocorticoids to inhibit pro-inflammatory NF-κβ action are achieved only by high intravenous/oral doses.[8] However, such therapy is not without risk; hence, high-dose steroid therapy should be used after careful patient selection and under specialist care.[9,10] The drug most widely used for this purpose is methylprednisolone. However, in view of its significantly lower cost, dexamethasone has been used more often, particularly in India, where DCP pulse was first used.[3]

Autoimmune diseases due to their multisystem involvement, non-remitting, and evolving disease course can be challenging to treat; in this regard, intravenous pulse therapy with steroids and/or immunosuppressive drugs has shown promising results.[3-6] The rationale behind high-dose methylprednisolone was that it would achieve a rapid reduction in circulating immune complexes and thereby lead to clinical improvement.[11] On literature review, there is a paucity of data on the use of steroid pulse therapy to achieve remission in CTDs where the predominant manifestations are cutaneous.[12] Despite its frequent use by rheumatologists and internists in various rheumatological diseases, low evidence has led to poor confidence among dermatologists to use it in severe CTDs with/without systemic involvement. The study aims to examine the clinicoimmunological pattern, therapeutic response, and long-term outcomes in CTD patients receiving steroid pulse therapy.

MATERIAL AND METHODS

The medical records of patients diagnosed with CTD (including diffuse cutaneous systemic sclerosis [dcSS], systemic lupus erythematosus [SLE], subacute cutaneous lupus erythematosus [SCLE], mixed CTD [MCTD], or overlap syndrome) who received steroid pulse therapy from July 2017 to June 2019 were retrieved from the hospital database.

Inclusion criteria

Patients clinically diagnosed with a CTD (dcSS, SLE, SCLE, MCTD, or overlap syndrome) who received intravenous steroid pulse therapy were included in the study.

A pre-designed pro forma was used to collect the baseline data (including patient demographics, presenting complaints, and relevant past and family history for autoimmune diseases). The mucocutaneous features, particularly the presence of malar/discoid rash, pigmentation, proximal scleroderma, sclerodactyly, heliotrope rash, shawl sign, Gottron's sign, decreased mouth opening, digital ulcers, digital pitted scars, swollen digits, and gangrene, were noted. Any systemic abnormality on physical examination was also noted.

The baseline investigations (i.e., complete blood count, erythrocyte sedimentation rate [ESR], renal function test, liver function test [LFT], C-reactive protein [CRP], rheumatoid factor [RF], electrolytes, blood sugar, urine routine analysis, anti-nuclear antibody [ANA/ANA profile], C3/C4, chest X-ray, and ECG) done for each patient along with special investigations (2-D echo, creatine phosphokinase, troponin, pulmonary function test, high-resolution computed tomography chest, electromyography, and skin biopsy) done as indicated were also retrieved from the hospital database.

As per our institutional protocol, after medical clearance and informed consent, patients receive pulse therapy for 3 consecutive days in a month for a period of 1 year. The type, number of pulses given, and final status of the patient (remission, relapse, pulse not tolerated, and demise) along with any complication/adverse effects were ascertained. Due to the COVID-19 pandemic, objective physical evaluation of the patients could not be done; their contact information was traced and patients were telephonically asked regarding improvement in clinical symptoms and relapse if any. Patients were followed up in June 2020 and response to treatment was evaluated by a self-devised patient-reported assessment scale [Table 1].

Statistical analysis

The data were entered into a spreadsheet and then described in terms of range; mean ± standard deviation (± SD), frequencies (number of cases), and relative frequencies (percentages) as appropriate. For comparing categorical data, Chi-square test was performed and the exact test was used when the expected frequency is <5. $P < 0.05$ was considered statistically significant. All statistical calculations were done using Statistical Package for the Social Sciences version 21.

RESULTS

Among the patients with CTDs (n = 22), there were 10 patients with dcSS, seven with SLE, two each with MCTD

Table 1: Assessment scale for response in patients.

Grade	Response after pulse therapy (%)
Clear	>90 Reduction in symptoms/complaints
Considerable benefit	>75 Reduction in symptoms/complaints
Some benefit	50–75 Reduction in symptoms/complaints
Persistent disease	<50 Reduction in symptoms/complaints

and SCLE, respectively, and one was diagnosed with overlap syndrome.

Demography

The M:F ratio of 1:6.3 with 19 (86.4%) females and only 3 (13.6%) males. The mean age overall was 39.95 ± 11.2 years (range 17–62 years); while disease-wise mean age was 42.5 ± 10.2 years for dcSS patients, 43.4 ± 9.7 years for SLE, 28.5 ± 16.32 years for MCTD patients, and 33.5 ± 13.4 years for SCLE patients. The mean duration of symptoms before presentation overall was 5.4 ± 4.9 years (range 2.5 months–20 years).

Symptomatology

The most common presenting complaints overall in CTD patients (n = 22) were joint pains (77.2%), Raynaud's phenomenon (77.2%) followed by hair loss (68.1%), binding down of skin (59%), and photosensitivity (59%) [Table 2, Figures 1a-d].

The disease associations seen were hypothyroidism (5/22; 22.7%), hypertension (3/22; 13.6%), and old treated pulmonary tuberculosis (2/22; 9%).

Mucocutaneous findings

The cutaneous examination findings among the disease groups were diverse. Among dcSS patients, proximal scleroderma was seen in all of them (10/10; 100%), followed by decreased mouth opening (9/10; 90%), digital pitted scar (8/10; 80%), salt and pepper pigmentation (6/10; 60%), mask-like facies (5/10; 50%), and radial furrowing (4/10; 40%). In patients with SLE, the most common finding was skin rash and hair loss (5/7; 71% each) followed by mucosal ulcers (3/7; 42.8%) [Figure 1]. Characteristic clinical findings were there in MCTD, SCLE, and patients with overlap syndrome [Table 3].

Laboratory findings

Among the SLE patients, 4 patients (57%) had pancytopenia. Two (28%) had significant proteinuria and 1 (14%) had hematuria. ESR was raised in four patients while CRP was raised in two patients; RF was positive in two patients. The CRP for the overlap patient was extremely elevated (3550 mg/dl). The rest of the baseline investigations were within normal limits.

The ANA test was positive in all patients; however, 14 (63.6%) patients had rapid screening ELISA while ANA by immunofluorescence was done in 8 (36.4%) patients where the highest titer (1:1280) was seen in a patient with MCTD followed by an SCLE patient (1:160). This was followed by an ANA profile in 17 (77.2%) patients.

Chest X-ray changes were seen in 4 patients (18%); these included (a) dcSS patient: Changes suggestive of early interstitial lung disease, (b) dcSS: Bronchiectasis in the left lower lung), (c) SCLE: Fibrocystic changes in the bilateral upper zones, and (d) SLE: Thin-walled cyst in the right upper lobe.

ECG changes were noted in 3 (13%) which included in the study. SLE patient: Increased heart rate and slow R wave; 2-D echo findings were tricuspid regurgitation, systolic pulmonary artery

Table 2: Clinical features seen in study patients.

Symptoms	Diagnosis (number [percentage])					Total
	dcSS	SLE	MCTD	SCLE	Overlap (SS+PMS)	
Joint pains	6 [60]	6 [85]	2 [100]	2 [100]	1 [100]	17 [77.2]
Photosensitivity	4 [40]	6 [85]	1 [50]	2 [100]	-	13 [59]
Rash	1 [10]	5 [71]	1 [50]	2 [100]	-	9 [40.9]
Raynaud's	9 [90]	4 [57]	2 [100]	1 [50]	1 [100]	17 [77.2]
Fever	2 [20]	3 [42]	1 [50]	2 [100]	-	8 [36.3]
Oral/nasal ulcers	2 [20]	3 [42]	1 [50]	1 [50]	-	7 [31.8]
Digital ulcers	3 [30]	1 [14.2]	1 [50]	-	-	5 [22.7]
Binding down of skin	10 [100]	1 [14.2]	1 [50]	-	1 [100]	13 [59]
Proximal muscle weakness	2 [20]	1 [14.2]	1 [50]	-	1 [100]	5 [22.7]
Dryness of eyes/mouth	-	1 [14.2]	-	-	-	1 [4.5]
Hair loss	8 [80]	5 [71]	-	1 [50]	1 [100]	15 [68.1]
Dyspnea	4 [40]	1 [14.2]	1 [50]	1 [50]	1 [100]	8 [36.3]
PIH	-	1 [14.2]	1 [50]	-	-	2 [9]
GERD/dysphagia/altered bowel movements	5 [50]	1 [14.2]	1 [50]	1 [50]	1 [100]	9 [40.9]
Weight loss/appetite loss	2 [20]	1 [14.2]	-	-	-	3 [13.6]
Decreased mouth opening	9 [90]	-	1 [50]	-	1 [100]	11 [50]

dcSS: Diffuse cutaneous systemic sclerosis, SLE: Systemic lupus erythematosus, SCLE: Subacute cutaneous lupus erythematosus, MCTD: Mixed connective tissue disease, PMS: Polymyositis, GERD: Gastroesophageal reflux disease, PIH: Post-inflammatory hyperpigmentation

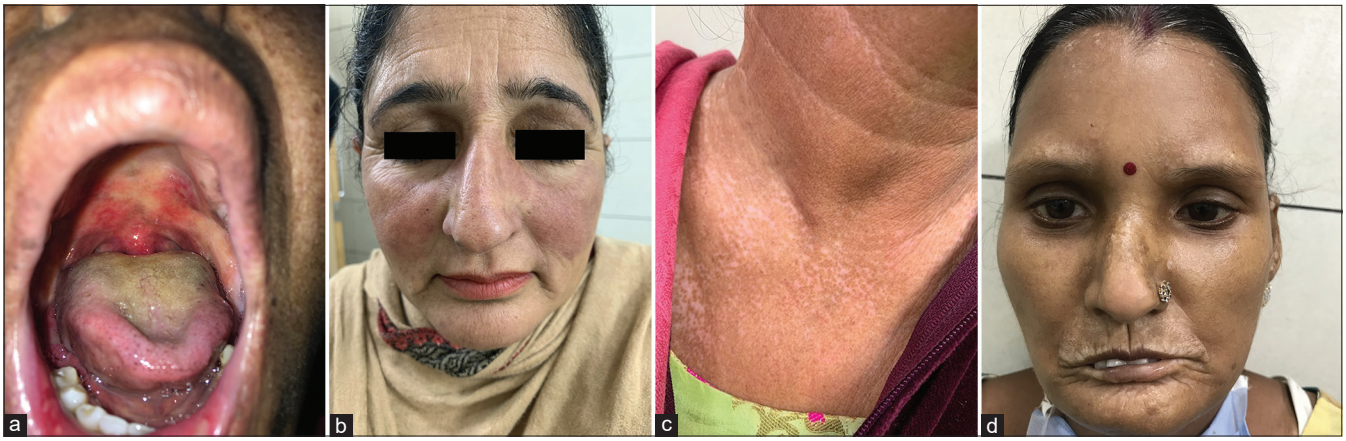

Figure 1: (a) Oral ulcers are seen on the soft palate in a patient with systemic lupus erythematosus (SLE). (b) Malar rash sparing nasolabial fold in an SLE patient. (c) Salt and pepper pigmentation seen over the neck and upper chest of a diffuse cutaneous systemic sclerosis (dcSS) patient. (d) Radial furrowing over face with salt and pepper pigmentation over forehead and perioral area of a dcSS patient.

pressure = 40 mmHg, (b) MCTD: Left ventricular hypertrophy; 2-D echo showed mild TR, and (c) SLE patient: ST elevation, Q wave changes; patient refused consent for 2-D echo.

Electromyography was done in one patient with overlap syndrome which showed spontaneous activity in the form of fibrillation and positive sharp waves in the right transverse abdominis, right vastus lateralis, and bilateral biceps. The motor unit action potential was small in size, short, and polyphasic suggestive of inflammatory muscle disease.

Skin biopsy was done for diagnosing one case which demonstrated changes suggestive of SCLE.

Pulse type and duration

Fourteen patients were put on methylprednisolone while seven were given dexamethasone pulse and one who had dcSS was given DCP therapy as she had interstitial lung disease and pulmonary artery hypertension [Figure 2]. Mean number of pulses received by patients was 10.3 ± 2.8 (range 3–12) (dcSS = 11.0 ± 1.7, SLE = 10.3 ± 3.4, MCTD =8.0 ± 5.6, and SCLE = 9.0 ± 4.2). Fifteen (61.2%) patients completed the pulse therapy for 12 months.

Adverse effects

Among the patients included (n = 22), seven did not complete the standard regimen of 12 pulses. Out of these, 3 (42.8%) patients were in the midway of their pulse therapy, 2 (28.5%) did not tolerate the therapy (1 [14.2%] had weight and appetite loss with altered LFT [received nine pulses]; 1 [14.2%] had bradycardia [received seven pulses]) while 2 (28.5%) patients left the treatment on their own and could not be traced. Two (28%) patients died, one where pulse therapy was stopped due to liver dysfunction was a case of dcSS; the other was a young male who had SCLE

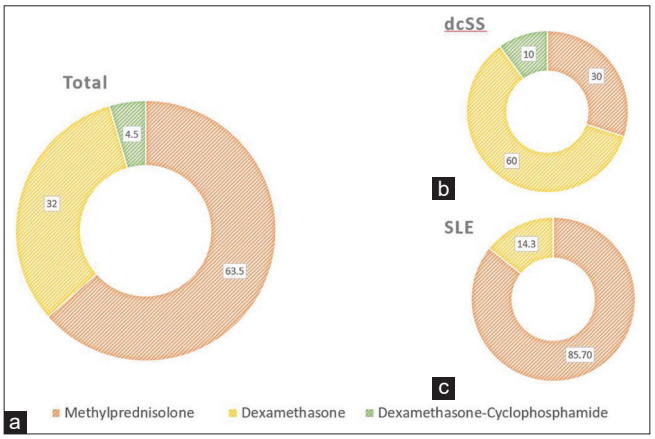

Figure 2: Various types of pulse therapy used for patients (a) Total; (b) diffuse cutaneous systemic sclerosis; and (c) systemic lupus erythematosus.

left treatment due to poor response and flare of the disease. The other adverse effects seen in the patients were decreased visual acuity, steroid striae, moon facies, viral warts, and post-pulse fever.

Follow-up

The mean duration of follow-up was 12.7 ± 6.4 months (range 6–26 months); however, only 10 patients (10/22; 45%) were successfully contacted after tracing. Among the 12 patients, which could not be contacted; three were undertreatment, two received incomplete pulses, and the other seven completed 12 pulses. Two patients had complete remission, that is, clear (20%); one patient each with SLE and SCLE, respectively. Two (20%) patients; one each with dcSS and SLE had >75% improvement, that is, considerable benefit. One (10%) patient of dcSS reported >50% improvement, that is, some benefit.

Table 3: Cutaneous signs seen in patients with other CTDs.

Symptoms	MCTD (*n*=2)	SCLE (*n*=2)	SS+PMS overlap
Malar rash	-	1	-
Discoid rash	-	1	-
Annular rash	1	2	-
Oral/nasal ulcers	1	1	-
Non-cicatricial alopecia	-	2	-
Salt and pepper pigmentation	-	-	1
Atrophy/scarring/depigmentation	-	1	-
Diffuse hyperpigmentation	1	-	1
Proximal scleroderma	1	-	1
Swollen digits	1	-	-
Digital pitted scars	1	-	-
Digital ulcers	1	-	-
Mask-like facies	1	-	-
Beak-like nose	1	-	-
Mat-like telangiectasias	1	-	-
Decreased mouth opening	1	-	1

SS: Systemic sclerosis, SCLE: Subacute cutaneous lupus erythematosus, MCTD: Mixed connective tissue disease, PMS: Polymyositis

Relapse

One patient with overlap syndrome developed relapse after completing therapy (after 18 months of completion), although she had shown considerable benefit (>75% improvement) initially.

Statistical associations

There was a statistically significant association of binding down of skin, decreased mouth opening, proximal scleroderma, sclerodactyly, salt and pepper pigmentation, and digital pitted scars with dcSS compared to other disease groups. The presence of skin rash had a significant association with SLE.

On correlating various clinical features with ANA profile; anti-SSA/Ro antibody had a statistically significant correlation with the presence of photosensitivity and discoid rash in SLE patients. Furthermore, in the dcSS group, anti-SSA/Ro had a statistically significant association with skin tightening, decreased mouth opening, salt and pepper pigmentation, sclerodactyly, proximal scleroderma, digital pitted scarring, and radial furrowing ($P < 0.05$, Chi-square).

The duration of disease had no statistically significant association with remission ($P = 0.6$, Chi-square) or relapse ($P = 0.5$, Chi-square) following pulse.

DISCUSSION

Methylprednisolone followed by dexamethasone is the most frequently used pulses in autoimmune diseases, usually, in combination with an immunosuppressive agent.[13] Various authors have reported benefits of intravenous methylprednisolone pulse in rheumatoid arthritis management; however, even among rheumatologists, pulse therapy is largely overlooked despite extensive evidence.[14,15]

Methylprednisolone is generally preferred however in dcSS patients; DCP has additional benefits in interstitial lung disease as well as skin tightening. A recent study demonstrated improvement in skin changes in dcSS patients (particularly in early stage) with cyclophosphamide pulse; with benefits seen in 43% of patients.[16]

The patients included had a mean age of 39.95 ± 11.2 years (range 17–62 years) which concurs with findings by various authors who have reported CTDs to be most common from the 2nd–5th decade.[17-22]

In the present study, the mean duration of disease presentation was 5.4 ± 4.9 years. Therefore, it can be inferred that patients will not seek specific therapy till the disease is well established. Since pulse therapy is a time and labor-intensive therapy regimen, only motivated patients with considerable disease burden consent to it. Viswanath *et al.* have reported a lower mean duration of disease at presentation in dcSS patients (2 years).[18] This can be attributed to the fact that only dcSS patients were included in their study; changes in appearance seen therein are more alarming for patients whereas our cases were more heterogeneous CTD*s*.

In the present study, among the various clinical features, the most common presenting complaints were joint pains (77.2%) and Raynaud's phenomenon (77.2%), followed by hair loss (68.1%), decreased opening in the mouth (50%), binding down of skin (59%), photosensitivity (59%), skin rash (40.9%), dysphagia (40.9%), digital pitted scar (40.9%), oral/nasal ulcers (31.8%); salt and pepper pigmentation (31.8%), and sclerodactyly (27.3%), whereas Kadiru *et al.* reported skin tightness (36%) as the most common feature followed by photosensitivity, salt and pepper pigmentation (30%), Raynaud's phenomenon (28%), malar rash (28%), sclerodactyly, pitted scars (22%), and oral ulcers (20%) in CTD patients.[23]

We found photosensitivity (85%) and joint pain (85%) as the most common complaints in SLE patients followed by skin rash (71%) and hair loss (71%). This is similar to the findings of Dhabhai *et al.* who reported photosensitivity (92.8%) as the most common clinical feature among their 14 SLE patients, followed by a malar rash (85.7%), hair loss (71.4%), and discoid rash (50%).[17]

In our dcSS patients, binding down of skin was seen in all cases (100%), followed by Raynaud's phenomenon (90%), decreased mouth opening (90%), digital pitted scars (80%), hair loss (80%), sclerodactyly (60%), salt and pepper

pigmentation (60%), and joint pain (60%). Similarly, Viswanath *et al.* reported Raynaud's phenomenon (100%) and skin tightening (100%) in all of their SS patients, followed by sclerodactyly (35.7%), joint involvement (28.6%), and hyperpigmentation (28.6%).[18] In contrast, Sameem *et al.*, who studied patients of both diffuse and limited systemic sclerosis, reported acrosclerosis as the most common clinical feature, severe sclerosis and contractures were seen only in two patients of dcSS.[21]

In this study, three pulses, that is, methylprednisolone, DCP, and DP, were used based on clinical judgment; Shah and Mehta similarly used different pulses whereas most other authors used only one type of pulse [Figure 3a-c].[18-22,24] We gave a fixed regimen of monthly pulse therapy for 12 consecutive months; most other authors also used a fixed regimen (Viswanath *et al.* [12 pulses]; Das *et al.* [6–9 pulses], and Sharada *et al.* [6 pulses]) while Sameem *et al.* varied their pulse regimen as per clinical response.[18,19,21,22]

All the other similar studies were prospective, while this is a retrospective analysis. However, none of the other studies reported any long-term follow-up post-treatment. Out of the 22 patients, we were able to successfully contact 10 patients to determine their long-term outcomes. However, a drawback of the assessment method used is that we were unable to do an objective clinical evaluation due to the ongoing COVID-19 pandemic; therefore, a less reliable patient-reported assessment scale was used. No major or long-term side effect was observed in our patients. This was similar to the mild side effects observed by other authors.[17-20,22,24] However, Sameem *et al.* reported three deaths due to chronic renal failure and miliary tuberculosis while the cause of the third death was unexplained and one other patient developed malignant hypertension.[21] Dhabhai *et al.* reported cardiac arrest in one of their patients.[17] In our study, two patients when followed up had unfortunately passed away though the deaths did not occur during or immediately after therapy. The death in one of those patients may be attributed to the disease process itself due to other poor prognostic factors (SCLE patient: Young, male, and early disease onset). The other was a female whose family members reported hepatitis as the cause of death, it could not be verified what the exact nature of the hepatitis was; we can only speculate that an infectious etiology could also have been at play.

We noted relapse in one patient after a duration of 18 months of completion of pulse therapy. Dhabhai *et al.* also reported relapse in two of their patients, where pulse therapy was reinitiated and clinical cure was achieved.[17] The disease duration had no bearing on the outcome of relapse/remission following pulse therapy. However, it is the authors' experience that patients treated with early, aggressive therapy (pulse steroids) fare better than their counterparts.

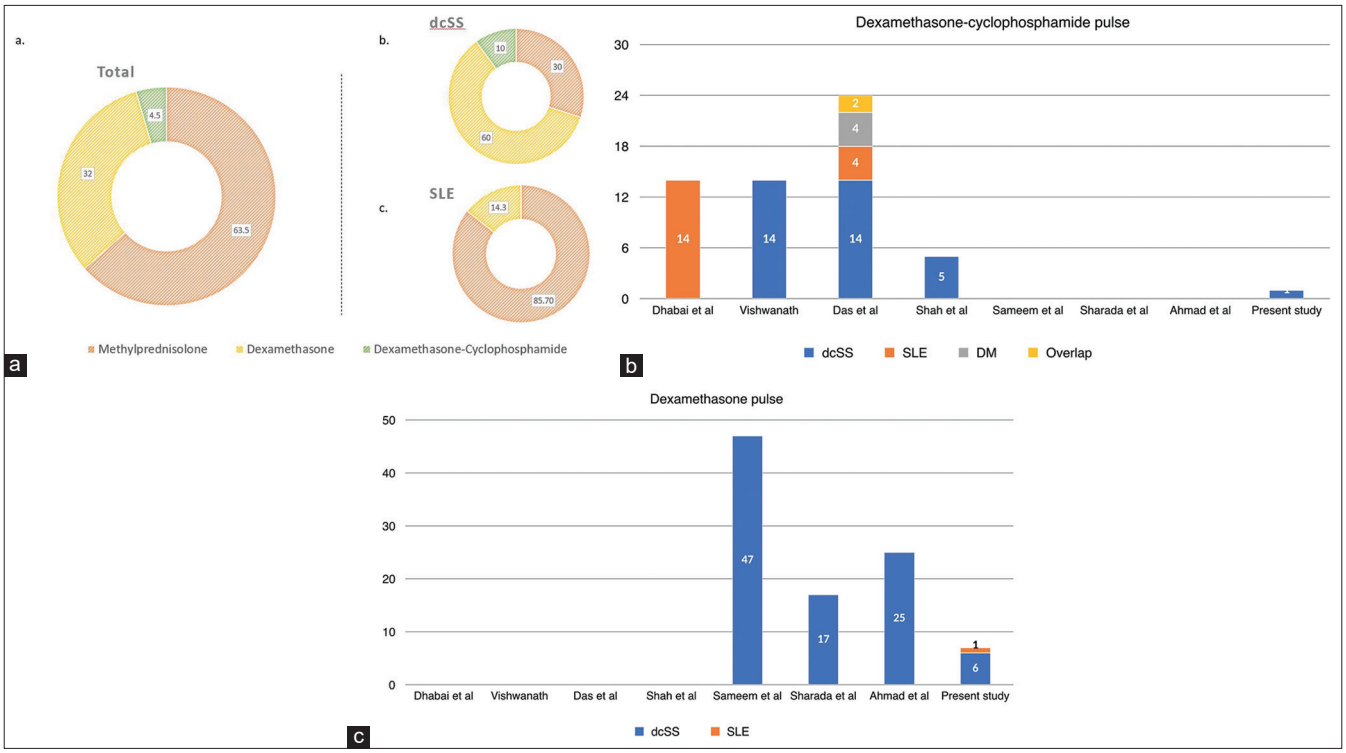

Figure 3: Steroid pulses used by various authors. (a) Methylprednisolone pulse, (b) dexamethasone-cyclophosphamide pulse, and (c) dexamethasone pulse.

CONCLUSION

The most common presenting features in CTDs in our study were joint pain, hair loss, Raynaud's phenomenon, and photosensitivity with considerable overlap among disease groups. Therefore, a high index of suspicion, thorough pertinent investigations and early institution of specific therapy, can considerably lessen the disease burden. In such patients, steroid pulse therapy is a viable, well-tolerated, and efficacious therapeutic modality for patients with CTDs. In the era of biologics, all that is old may not be forgotten in the name of progress. To quote an adage, never be first to try something new or the last to leave something old.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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