Section: Dermatology

Original Research Article

A COMPARATIVE STUDY ON EFFICACY BETWEEN ORAL DOXYCYCLINE WITH TOPICAL TACROLIMUS AND ORAL DAFLON WITH TOPICAL TACROLIMUS IN STASIS DERMATITIS BY CLINICAL AND RADIOLOGICAL EVALUATION

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ABSTRACT

Background: Stasis dermatitis, a manifestation of chronic venous insufficiency (CVI), results from altered venous hemodynamics and affects 10–20% of the population, significantly impairing quality of life. Topical corticosteroids remain first-line therapy but are associated with various adverse effects. Diosmin + Hesperidin improve venous tone and reduce inflammation, while Doxycycline exhibits anti-collagenolytic and anti-inflammatory properties. Tacrolimus, a selective cytokine release inhibitor and anti-pruritic, avoids corticosteroid-related side effects. The aim and objective is to compare the combined efficacy and safety of oral Doxycycline with topical Tacrolimus versus oral Daflon (Diosmin + Hesperidin) with topical Tacrolimus in treating stasis dermatitis associated with primary CVI.

Materials and Methods: Thirty patients with CEAP-C4 and above, confirmed as primary CVI by venous Doppler, were randomly divided into two groups. One received oral Doxycycline with topical Tacrolimus; the other received oral Daflon with topical Tacrolimus. Clinical evaluation was performed using a predesigned proforma and the Venous Clinical Severity Score (VCSS), with clinical and radiological follow-up over two months.

Results: Most patients (40%) were aged 58–67, with 63% male. Both groups showed 100% resolution in pain, inflammation, and ulceration. Pigmentation improved more in the Doxycycline group (73% to 20%) than in the Daflon group (73% to 33%). Mean VCSS post-treatment: Daflon group – 6.7; Doxycycline group – 6.4 (p=0.3378). Compliance with compression therapy was poor.

Conclusion: Both combinations were equally effective and safe, offering steroid-sparing alternatives for managing stasis dermatitis.

Keywords: Chronic venous insufficiency, Stasis dermatitis, Venous clinical severity score, Venous segmental disease score.

INTRODUCTION

Stasis dermatitis is a common inflammatory skin disorder that arises as a complication of chronic venous insufficiency (CVI). CVI affects approximately 10–20% of the population and significantly impairs quality of life. It results from venous hypertension due to valvular incompetence, valvular destruction, or obstruction within the venous system. The underlying pathogenesis involves shear stress on venous walls caused by stagnation of blood flow, which triggers cytokine release and activates

matrix metalloproteinases (MMPs), particularly MMP-1, MMP-2, and MMP-13. These enzymes contribute to degradation of extracellular matrix proteins, including collagen and elastin, leading to tissue damage and inflammation.[1-4]

The primary pathological mechanisms include dysregulated apoptosis, inflammation of venous valves, and phenotypic changes in smooth muscle cells within the intimal layer of the vein. These processes promote structural and functional changes in the venous wall and surrounding tissues, contributing to the clinical manifestations of stasis dermatitis.[5,6]

Clinically, stasis dermatitis presents as eczematous, itchy patches on the lower legs and ankles. Other signs of chronic venous hypertension such as evening-predominant leg edema, hemosiderin pigmentation, lipodermatosclerosis, atrophic scarring, telangiectasias, and venous ulcers may develop over time. If venous ulcers become chronic and remain untreated, they carry the risk of malignant transformation into squamous cell carcinoma. Current standard treatment includes high-potency topical corticosteroids, compression therapy, and limb elevation. However, long-term steroid use is associated with adverse effects, prompting interest in safer alternatives.[7,8]

Several risk factors are associated with the development of stasis dermatitis. These include increasing age, female gender, obesity, trauma, pregnancy, prolonged immobility, and sedentary lifestyle. The condition typically emerges in middle-aged and elderly individuals, often presenting in the fifth decade of life. Although rare in young adults, early-onset cases may occur in the context of hereditary venous disorders. Women are disproportionately affected, likely due to pregnancy-related venous changes, with a reported female-to-male ratio of 3:1. Ethnic differences in prevalence are not well established.

Various acquired and genetic factors contribute to CVI. Mechanical trauma, leg fractures, and surgeries that cause prolonged immobility can damage venous valves and disrupt normal venous drainage. Genetic predisposition is also suggested, with mutations in genes like FOXC2 and NOTCH3 implicated in venous wall abnormalities. Congenital absence of venous valves and inherited conditions such as Klippel-Trenaunay syndrome, Ehlers-Danlos syndrome, and CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) may lead to early-onset varicose veins and chronic venous disease.

Hypercoagulable states further increase the risk of CVI and stasis dermatitis. Factor V Leiden mutation is one such condition that promotes thrombosis and venous hypertension. A history of deep vein thrombosis (DVT) can damage the deep venous system, while superficial thrombophlebitis affects superficial veins—both contributing to ambulatory venous hypertension. Other thrombophilic disorders, such as prothrombin gene mutations, protein C and S deficiencies, antithrombin deficiency, antiphospholipid syndrome, and elevated homocysteine levels, have also been linked to CVI.

Lifestyle and occupational factors play a critical role. Prolonged standing or sitting, low physical activity, western dietary habits, and straining during defecation may increase venous pressure. In pregnancy, hormonal changes, especially elevated progesterone levels, cause venous dilation and valvular insufficiency, predisposing to varicosities.

Disruption in microcirculation and endothelial dysfunction are central to the progression of chronic venous disease (CVD). The vascular endothelium maintains vascular tone and regulates hemostasis. Factors such as infection, trauma, autoimmune disorders, smoking, diabetes mellitus, and environmental exposures can damage endothelial integrity, compromising the microcirculatory network and contributing to chronic venous inflammation.

The CEAP classification (Clinical, Etiologic, Anatomic, and Pathophysiologic) serves as a standardized system for staging chronic venous disorders, including stasis dermatitis. It aids in diagnosis, treatment planning, and monitoring disease progression in clinical and research settings. [Table 1]

Table 1: CEAP classification.

CEAP Classification system and reporting standard Revision 2020	
C (Clinical Manifestations), E (Etiology), A (Anatomic Distribution), P (Pathophysiology)	
Co	No visible or palpable signs of venous disease
C1	Telangiectasia or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C4c	Corona phlebectatica
C5	Healed
C6	Active venous uler
C6r	Recurrent active venous ulcer

An Ad hoc Committee of the American Venous Forum on Venous Outcome Assessment proposed venous clinical severity score (VCSS) and venous disability score (VDS), in March 2000.[9] VCSS is a

dynamic scoring system, which avoids static elements of CEAP classication, with ability to reect changes after treatment over a short period (months). This scoring system was reliable with acceptable inter-and intra observer variability. [Table 2]

Table 2: venous clinical severity score

Attributes	Absent=0	Mild=1	Moderate=2	Severe=3
Pain	None	Occasional, not restricting activities or requiring analgesics	Daily, moderate activities limitation, occasional analgesics	Daily, Severe activities limitation or requiring regular use of analgesics
Varicose veins	None	Few, scattered: Branched varicose veins	Multiple: GS* varicose vein continued to calf or thigh	Extensive: Thigh and calf or GS* and LS* distribution
Venous edema	None	Evening ankle edema only	Afternoon edema, above ankle	Morning edema above ankle and requiring activities changes, elevation
Skin pigmentation	None or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower ½) or recent pigmentation (purple)	Wider distribution (above lower ½) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involvers most of gaiter area (lower ½)	Severe cellulitis (lower ½ and above) or significant venous eczema
Induration	None	Focal circummalleolar (<4cm)	Media or lateral, less than lower third of leg	Entire lower third of let or more
No of active ulcer	0	1	2	>2
Active ulcer duration	None	<3 months	>3 months, <1 year	Not healed >1 year
Active ulcer size	None	<2 cm diameter	2 to 6 cm diameter	>6cm diameter
Compressive therapy	Not used or not compliant	Intermittent use of stocking	Wear elastic stockings most days	Full compliance: Stockings+elevation

Venous doppler is considered to be the gold standard investigation for assessing the venous system. The advent of this technique has revolutionized the diagnostic modality in identifying venous disorders. All the venous systems namely the superficial, deep and the perforator system of veins can be assessed separately for obstruction and reflux. Obstruction is defined as the absence of flow while a retrograde flow that lasts more than 0.5 s is considered as the sign of reflux 0.5 s is the time required for valve closure. Venous Doppler is highly recommended when the venous ulcer has set in.[10]

The concept behind the VSDS was to combine pathophysiologic designation of reflux and obstruction with venous segments of anatomic classification. In addition to an objective score that could complement clinical score, a major motivation for pursuing this approach was the opportunity to gather necessary information for scoring by duplex scanning. [Table 3]

Table 3: venous segmental disease score

	REFLUX		Obstruction
½	LESSER SAPHENOUS		*
1	GREATER SAPHENOUS	1	Greater saphenous (only if thrombosed from groin to below knee)
½	PERFORATORS, THING		*
1	PERFORATORS, CALF		*
2	CALF VEINS, MULTIPLE (PT alone = 1)	1	Calf veins, multiple
2	POPLITEAL VEIN	2	Popliteal vein
1	SUPERFICIAL FEMORAL VEIN	1	Superficial femoral vein
1	PROFUNDA FEMORIS	1	Profunda femoris
1	COMMON FEMORAL VEIN AND ABOVE	2	Common femoral
		1	ILISC VEIN
		1	IVC
10	MAXIMUM REFLUX SCORE	10	Maximum Obstruction Score

Doxycycline, a broad-spectrum antibiotic belonging to the tetracycline group, possesses additional pharmacologic actions such as matrix metalloproteinase (MMP) inhibition, anti-collagenolytic, and anti-inflammatory effects. These properties extend its therapeutic utility beyond antimicrobial action, particularly in managing chronic venous leg ulcers.

Daflon is a micronized purified flavonoid fraction (MPFF), primarily composed of 90% micronized diosmin and 10% flavonoids (including hesperidin, diosmetin, linarin, and isorhoifolin). This venoactive agent enhances venous tone, reduces capillary permeability, improves lymphatic drainage, and exhibits anti-inflammatory activity. It also inhibits inflammatory mediator release, such as oxygen free radicals, prostaglandins, and thromboxanes, especially noted in ischemia-reperfusion models.

Tacrolimus, a macrolide immunosuppressant, acts by binding to macrophilin-12 and inhibiting calcineurin, thereby preventing inflammatory cytokine release. In dermatology, its topical form is particularly useful

due to its anti-inflammatory and anti-pruritic properties, without the adverse effects associated with corticosteroids.

Aim of the Study

To compare the combined efficacy and safety of oral Doxycycline with topical Tacrolimus versus oral Daflon (Diosmin + Hesperidin) with topical Tacrolimus in treating stasis dermatitis associated with primary chronic venous insufficiency (CVI).

MATERIALS AND METHODS

This randomized controlled trial was conducted on 30 patients attending the Dermatology Outpatient Department at a tertiary care hospital between September 2019 and August 2021. The study was approved by the Institutional Ethics Committee, and informed consent was obtained from all participants.

Inclusion Criteria

a) Age >18 years
b) Patients With The Following Skin Changes Of Lower Extremities (CEAP CLASSIFICATION-C4 TO C6):
    1. Pigmentation Or Eczema (C4a)
    2. Lipodermatosclerosis (C4b)
    3. Atrophie Blanche (C4b)
    4. Healed Venous Ulcer With Eczematous Changes Of Surrounding skin(C5)
    5. Active venous ulcer (C6)
c) Patients confirmed of having primary chronic venous insufficiency by Venous Doppler.

Exclusion Criteria

1. Any patient presenting with ulcers and dermatitis due to secondary CVI and causes other than CVI.
2. Patients who had been subjected to any oral or topical steroids or growth factors used in treatment of venous ulcers 1 month prior to enrolment.
3. Patients allergic to doxycycline, tacrolimus and daflon.
4. Pregnant and lactating mothers.
5. Patients with hepatic and renal derangements.
6. Patients on oral contraceptives.

Methodology

After obtaining approval from institutional ethics committee, informed consent was taken from patients and history was taken as per preformed questionnaire. Patients above 18 years of age who came with clinical features suggestive of stasis dermatitis, pertaining to C4 and above of CEAP classification were subjected to clinical examination. Venous Clinical Severity Score was ascertained to each patient. Later they were subjected to venous Doppler of lower limb to evaluate for Venous Segmental Disease Score. After confirming the presence of primary CVI, they were recruited for the study and divided into two equal groups of fifteen each and started on drug trial with combination of Doxycycline 100mg once daily with tacrolimus 0.1% ointment twice daily for one group and Daflon 500mg once daily with tacrolimus 0.1% ointment twice daily for another group, both for a period of two months each with monthly follow-ups in between for evaluation by clinical examination and photographs. Using R programming software, the statistical difference between the efficacies of combined regimens was assessed and also the correlation between Venous Clinical Severity Score and Venous Segmental Disease Score was analysed.

RESULTS

40% of age 58-67. Overall male preponderance (63%); in Diosmin +Hesperidin group-pain, inflammation, ulcer, edema subsided in 100%, moderate pigmentation seen in 73% at baseline dropping to 33% after trial, induration reduced in 33%. Doxycycline group-pain, inflammation, ulcer subsided in 100%, edema-93%, moderate pigmentation seen in 73% at baseline dropping to 20% after trial, induration reduced in 26%. No change in varicose veins; compliance to compressive therapy poor in both groups. Mean VCSS after trial-Diosmin +Hesperidin group=6.7; Doxycycline=6.4. No significant difference between therapeutic efficacies of both drug combinations with p value=0.3378. No change in VSDD was noted after drug trial in both groups. A minute positive correlation between Venous Clinical Severity Score and Venous Segmental Disease Score was found with r value = 0.25. [Figure 1-3]

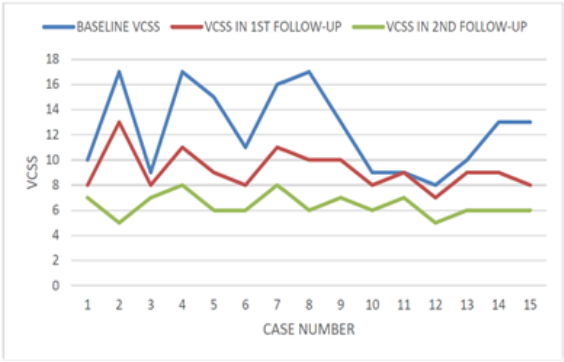

Figure 1: Venous clinical severity scores in group a (doxycycline+tacrolimus)

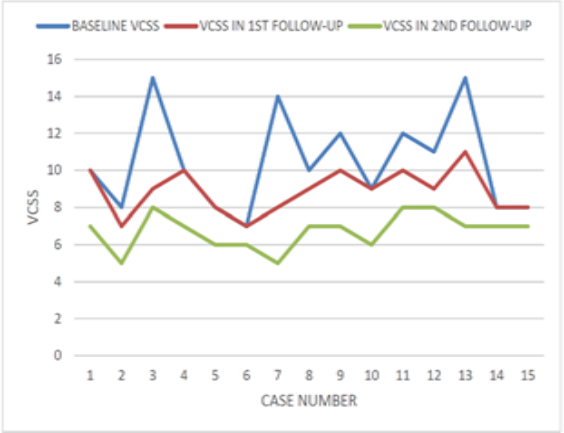

Figure 2: Venous clinical severity scores in group (Daflon+Tacrolimus)

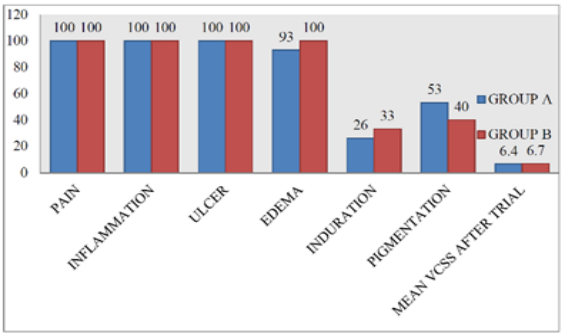

Figure 3: Percentage of cases that showed improvement post drug trial in both groups

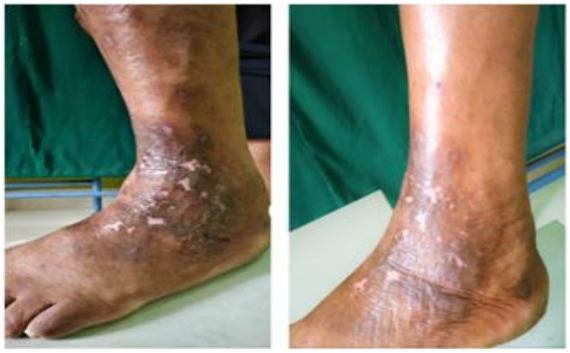

Image 1: Diffuse, ill-defined pigmentation with interspersed areas of atrophie blanche over dorsum of left foot, anterior aspect of ankle extending onto proximal 1/3 of leg (image on left). Post-treatment with Doxycycline+Tacrolimus (image on right)

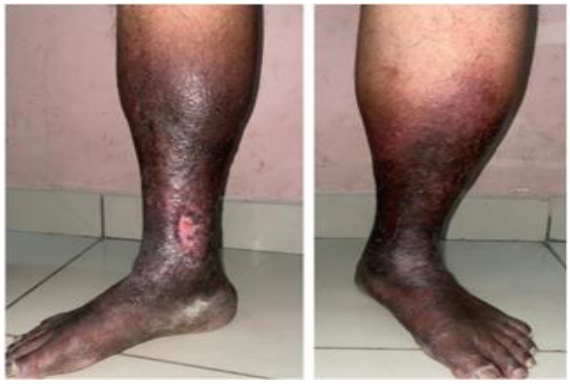

Image 2: Inverted champagne bottle appearance of both legs with healing ulcer over right lower 1/3rd of leg on medial aspect and pigmentation over lower 2/3rd of both legs.

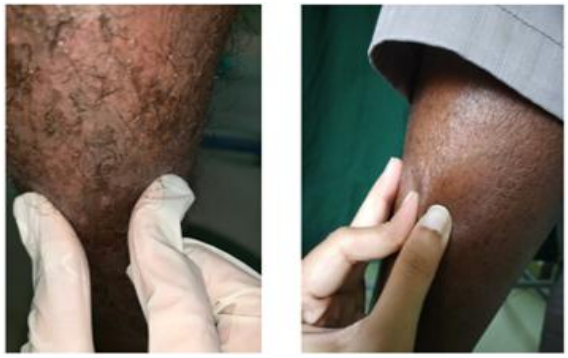

Image 3: Skin induration over affected areas (image on left) Reduction in induration post-treatment with Daflon+Tacrolimus (image on right)

DISCUSSION

The incidence of chronic venous insufficiency is common after fifth decade of life, as already stated, with increase in prevalence as the age advances. In a cross sectional study conducted in the French population to assess the risk factors, prevalence and clinical patterns of chronic venous insufficiency, the prevalence was found to increase with the advancing age, with the highest prevalence reported in patients above 80 years of age.[11,12] In this study more than 80 percent of the patients were above 50 years of age which shows age plays a significant role in progression and development of the disease. 56% of these patients were in the age group of fifty to sixty-five years who are still a part of the working population in the Indian community which adds to the socio-economic burden of the family and the society as a whole. None of the patients in the study group had signs and symptoms suggestive of superficial venous thrombophlebitis and cellulitis, that can damage the superficial venous compartment of lower limbs, thereby leading to venous valvular damage resulting in venous incompetence. Also, none of the cases from the entire study population had thromboembolic features. About 13% of the study group had a family history of chronic venous insufficiency, and all of them were first degree relatives with no hereditary disease running in the family. This may not be a significant finding considering the high prevalence of stasis dermatitis in the general population, although family history of the disease in the first degree relatives is a strong risk factor reported in the previous studies.[12] All the patients had blood pressures and random glucose levels monitored at the time of presentation and also during every follow up until the set period of drug trial was completed, with all of them having values falling within normal ranges. 46.6% of cases from group A belonged to C4b of CEAP CLASSIFICATION. 66.6% of cases from group B belonged to C4b of CEAP CLASSIFICATION. A study by Mackelfresh J et al,[13] showed complete re-epithelialization of recalcitrant venous ulcer when treated with combination of Doxycycline & Tacrolimus at 2 months which was similar to the results in the current study. A study by Dissemond J et al,[3] showed complete remission of dermatitis area managed with topical Tacrolimus monotherapy in about 5 days compared to the current study that showed complete remission in an average of 10.8 days. A study by Zuzana et al,[14] showed significant (p=0.001) drop in VCSS at 2 months post drug trial with Diosmin-Hesperidin 500mg OD monotherapy which was similar to the result in the current study. Complete healing was demonstrated through a case study in which an 81-year-old patient of acute stasis dermatitis was treated with topical 0.1% tacrolimus ointment twice daily for 5 days.[5] Another study was conducted on a 71-year-old female with chronic venous ulcer who was not responsive to local wound

care, limb elevation and also non tolerant to compression stockings. The active ulcers demonstrated marked healing on treatment with 0.1% topical tacrolimus and 100 mg of doxycycline hyclate twice daily for two weeks, and got completely re-epithelialized after two months.[13] Similar results pertaining to ulcer healing was noted in this study with this drug combination that showed complete healing by one month of follow-up. This proved their efficacy concerning treatment of even recalcitrant cases of stasis dermatitis. Of the 15 patients present in the group treated with Diosmin + Hesperidin and topical Tacrolimus combination, pain was reduced in 100% of the patients by one month of follow-up period, degree of severity of varicose veins could not be altered as their modification requires surgical intervention to halt the progression of the disease and thereby their pathophysiological consequences, edema also subsided in 100% of the patients by one month of follow-up period, pigmentation status came down to mild degree in 10 patients and was moderate in 5 of them, inflammation was reduced in 100% of the patients similar to edema and pain, induration dropped to zero in 6 patients, was mild in 8 and moderate in 1, ulcer number, duration and size were zero in all 15 patients after completion of the drug trial. Based on the analysis done by Lenkovic M et al., symptoms like sensations of heaviness, pain, nocturnal cramps, and edema disappeared in 60.2%, 62.5%, and 73% of patients, respectively, after 6 months of therapy with Diosmin + Hesperidin 500 mg.[11,14] A double-blind study using Diosmin + Hesperidin 500 mg in combination with compression showed accelerated ulcer healing.[15] This was confirmed in 2005 by a meta-analysis of 5 trials with adjunctive MPFF in 723 patients with venous ulcers.[16] Since the study by Lenkovic M et al. focused on difficult-to-heal venous ulcers, it was deemed satisfactory to have achieved a 13% rate of healing.[11] The results of the study were encouraging and larger randomized controlled trials need to be performed to better specify which CEAP clinical class would benefit the most from such a treatment.[11] and would give further strength to the current recommendation of Diosmin + Hesperidin 500 mg as an adjuvant to standard treatment in PCVD to relieve clinical symptoms like pigmentation, edema and active venous ulcers.[17] No treatment-related side effects were reported and the acceptability was considered excellent by most patients,[14] which was similar to this study wherein none of the 30 patients complained of any burning or tingling sensations with use of topical Tacrolimus ointment. The limitations of this study include smaller size of the sample, lack of inclusion of control group, lack of evaluation of disease progression after the completion of drug trial and also lack of comparison of differences in the efficacies of these drug combinations on post-surgical cases. These combinations are surely novel options for short-term treatment of stasis dermatitis, but a randomized controlled trial with larger sample sizes are needed to validate and establish the efficacy and safety of these combinations.

CONCLUSION

Stasis dermatitis, despite its high prevalence and potential for significant morbidity, remains under-recognized in clinical practice. Timely diagnosis and appropriate intervention are critical to prevent disease progression and improve patient outcomes. Radiological assessment with venous Doppler is essential, as underlying venous pathology may silently advance, resulting in severe cutaneous manifestations.

In this randomized comparative trial, both treatment groups—Doxycycline with topical Tacrolimus and Daflon (Diosmin + Hesperidin) with topical Tacrolimus—exhibited comparable efficacy. Both combinations led to notable improvements in pain, edema, inflammation, pigmentation, and ulcer healing. The absence of adverse effects and the overall safety profile of both regimens suggest that they are promising steroid-sparing alternatives in the management of stasis dermatitis.

These novel therapeutic approaches integrating Tetracyclines, Flavonoids, and Calcineurin inhibitors may represent a significant advancement in the non-surgical management of primary CVI-associated dermatitis. Their utility may be particularly beneficial in patients with recalcitrant disease or contraindications to corticosteroids.

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