Journal of Pakistan Association of Dermatologists.2023;**33(3)**:1096-1105.

Review Article

Isotretinoin for cutaneous sarcoidosis: A potential therapy

Caroline Oktarina, Yudo Irawan, Sandra Widaty

Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia–Dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia.

Abstract Sarcoidosis is a chronic noncaseating granulomatous disorder with clinical manifestations involving various organs, including skin. The incidence of sarcoidosis reached 35.5 – 64 cases per 100,000 people in the United States while Dr. Cipto Mangunkusumo National Central General Hospital, Jakarta reported the incidence of cutaneous sarcoidosis of 0.07% in 2015-2019. Numerous treatment modalities have been developed for the treatment of sarcoidosis and steroid becomes the first-line treatment for sarcoidosis. However, cases of sarcoidosis recalcitrant towards steroid are often reported, leading to consideration of other medications with possible efficacy in sarcoidosis, one of which is isotretinoin. Isotretinoin plays a role in sarcoidosis through its effect on inhibiting Tumor Necrosis Factor (TNF) and enhancing the production of prostaglandin E_2 (PGE_2). Based on several studies reported, level of evidence (LoE) of isotretinoin for the management of cutaneous sarcoidosis is level IV. Therefore, albeit being quite potential for the management of cutaneous sarcoidosis, further studies are necessary to prove the effectiveness of isotretinoin.

Key words
Sarcoidosis; Isotretinoin; Management.

Introduction

Sarcoidosis is a chronic noncaseating granulomatous disease involving various organ systems.[1] The incidence of sarcoidosis reached 50–60 cases per 100,000 people in Scandinavia with the most cases identified in African-American ethnicity and females.[2] A report from the Department of Dermatology and Venereology, Dr. Cipto Mangunkusumo National Central General Hospital showed that there were 6 new cases of cutaneous sarcoidosis between 2015–2019 with incidence rate of 0.07%. To date, the definitive etiology of sarcoidosis has not yet been elucidated; however, the complex interactions between genetics, immune response, and antigen might play a role in the pathogenesis of sarcoidosis.[3]

Sarcoidosis can be diagnosed based on the results of clinical and diagnostic tests. It is managed based on the extent and severity of the disease. Fewer lesions can be managed with topical therapies while extensive or severe disease should receive systemic therapies.[4] The management of sarcoidosis can be classified into three levels with steroid as the first-line therapy. Nevertheless, various new drugs have been invented for sarcoidosis, especially for the ones recalcitrant against steroids.[5]

Isotretinoin is a vitamin A derivate which has been long known as the mainstay treatment for acne vulgaris. Apart from acne vulgaris, isotretinoin is also commonly used for other skin disorders, both skin inflammatory diseases, genodermatoses, and malignancies.[6] Although the use of isotretinoin for sarcoidosis has been reported since a long time, there has not been a

Address for correspondence
Dr. Caroline Oktarina
71 Diponegoro, Central Jakarta,
Jakarta, Indonesia, 10430.
Ph: +6281321338882
Email: caroline.oktarina17@gmail.com

clinical trial on the effectiveness of isotretinoin in cutaneous sarcoidosis. Previous reports had shown that isotretinoin could act as an anti-inflammatory agent and immunomodulator which can be a potential therapy for sarcoidosis.[7] Therefore, this review will discuss the use of isotretinoin for sarcoidosis and its potential pathway.

Sarcoidosis

Sarcoidosis is a chronic noncaseating granulomatous disease which involves multisystem. Skin is the second organ most commonly involved after lungs with the incidence of approximately 30% of all sarcoidosis cases.[1,4] A study by El-Khalawany *et al*. described sarcoidosis as one of the spectrum of paraneoplastic syndromes related to lymphoproliferative diseases.[2]

Epidemiology

The incidence of sarcoidosis is high in the Nordics and African-American ethnicity.[3,8] Scandinavia has the highest prevalence of sarcoidosis, which reaches 50-60 cases per 100,000 people. Sarcoidosis is predominantly found in females.[2] The age of onset of sarcoidosis is between 30-55 years old.[8] The Department of Dermatology and Venereology, Dr. Cipto Mangunkusumo National Central General Hospital reported six new cases of cutaneous sarcoidosis with the incidence rate of 0.07% between 2015-2021. Those cases consisted of four females and two males with age range of 46-54 years old.

Etiology and Pathogenesis

To date, the etiology of sarcoidosis has not yen been elucidated. The host's susceptibility towards sarcoidosis is due to the complex interaction between genetics, immune response, and antigen. The involved antigen might originate from the environment or infectious agents. As for the genetic susceptibility in sarcoidosis, it is associated with Human Leukocyte Antigen (HLA) system which plays a role in the antigen presentation, cytokine production, and granuloma formation. The granuloma formation begins with the antigen presentation and phagocytosis by the antigen presenting cells which is subsequently presented to the CD4 T cells.[3] T helper (Th)1 and Th17 will be activated. Afterwards, the cytokines are produced, which include tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-2, IL-6, IL-12, IL-15, IL-17, IL-18, and macrophage inflammatory protein 1. The immune responses will induce the production of granulomatous inflammation in the target organ.[3,9] TNF-α is one of the important proinflammatory cytokines in sarcoidosis because it plays a role in stimulation immune response, Th1 response, and granuloma formation. The high level of TNF-α is associated with the disease's progressivity.[10]

The immunopathogenesis of sarcoidosis can be explained through Kveim-Slitzbach reaction. This reaction shows that the granuloma is formed within 3-6 weeks after the intradermal injection of suspension containing human sarcoid tissue. This test showed that the influx of lymphocytes and monocytes at the beginning of granuloma formation is influenced by antigen presentation and collagen necrosis plays a role in the antigen immobilization which induces the granuloma formation.[10]

Factors related to works or environment which can induce sarcoidosis are exposure towards insecticides, yeasts, fungi, firewood, building material, firefighter, and industrial organic ashes.[3] The microorganisms which are reported to have close associations with sarcoidosis are Corynebacterium acnes and Mycobacterium

tuberculosis.[9] Other microorganisms, such as *Borrelia, Rickettsia helvetica, Chlamydia pneumoniae*, human herpesvirus-8, Epstein-Barr virus, and retrovirus, which was previously associated with sarcoidosis, turned out to have no association following thorough investigations.[3,9]

Clinical Manifestations

Cutaneous manifestations of sarcoidosis can be classified into specific and nonspecific lesions based on the presence of noncaseating granuloma in histopathological examination. Specific lesions which have caseating granuloma findings include: [1]

1. ***Macule or papule*** Macule or papule with various colors (red/purplish, skin-colored, brownish, and hypopigmented) can be found in the center of the face (eyelid and nasolabial fold), extremities, and trauma-prone areas. This lesion suggests good prognosis, resolving without scar.[1,3]

2. ***Plaque sarcoidosis*** The predilection is on the face, back, extensor side of the arm, and buttock. This manifestation denotes chronic disease course with high recurrence probability and leaving pigmentary disorder and scar. Annular sarcoidosis is a variant of plaque sarcoidosis with predilection on the forehead.[1,3]

3. ***Lupus pernio*** is characterized by erythematous or violaceous indurated plaque with scales on the center of the face, nose, and cheeks. This lesion is often identified in African-American female. Lupus pernio indicates sinus and oropharynx involvement, also often associated with intrathoracic, upper respiratory tract, reticuloendothelial, and ocular involvement. It also indicates chronic recalcitrant sarcoidosis.[1,3]

4. ***Subcutaneous sarcoidosis (Darier-Roussy)*** This type involves deep dermis and subcutaneous tissue with clinical manifestations of painless, firm, mobile, subcutaneous nodules, 0.5 – 2 cm in diameter. This lesion is often associated with less severe sarcoidosis but accompanied by systemic diseases, such as hilar lymphadenopathy and pulmonary fibrosis.[1,3]

5. ***Scar or tattoo sarcoidosis*** Scar is characterized by increased nodularity or color changes into erythematous or violaceous. The prognosis of this type varies, might be accompanied by rapid resolution or vice versa. A variant of scar sarcoidosis is sarcoidosis on tattoo or other injection sites.[1,3]

Other rare specific lesions are psoriasiform, lichenoid, verrucous, ichthyosiform, lymphedematous, atrophic, ulcerative, hypopigmented, angiolupoid, erythrodermic, pigmented purpuric, photodistributed, scalp, nail, mucosal, and genital sarcoidosis. Nonspecific lesions include erythema nodosum, calcinosis cutis, digital clubbing, and neutrophilic dermatosis.[1] Erythema nodosum along with arthritis and bilateral hilar adenopathy is called Löfgren syndrome. Löfgren syndrome is acute and can be followed by mild fever and malaise with spontaneous resolution within 3–6 months.[11]

Apart from skin, sarcoidosis can involve several organs without symptoms or cause mild to life-threatening symptoms. The extracutaneous manifestations of sarcoidosis include pulmonary, ocular, cardiac, nervous system, spleen, liver, muscle, articular, lymph nodes, renal, and upper respiratory tract involvement.[12]

Diagnosis

The differential diagnoses of sarcoidosis are other granulomatous diseases, such as foreign reaction towards tattoo, siliconosis, granuloma annulare, necrobiosis lipoidica, cutaneous manifestations of Crohn's disease, necrobiotic xanthogranuloma, mycobacterium infection (leprosy, tuberculosis, atypical mycobacteria infections), coccidiomycosis, histoplasmosis, leishmaniasis, and syphilis.[1,12] The algorithm for establishing the diagnosis of sarcoidosis is based on Haimovic *et al*., shown in **Figure 1**.[12]

Diagnostic tests

Several diagnostic tests can be performed to support the diagnosis of cutaneous sarcoidosis, which are:

1. Diascopy examination on papules or plaques shows apple-jelly color or brownish-yellow color.[1]
2. Histopathology examination shows non-caseating granuloma consisting of epithelioid cells and giant cells, surrounded by mild infiltration of lymphocytes, also known as naked granuloma.[1]
3. Dermoscopy can be used to differentiate sarcoid granuloma and necrobiotic granuloma.[4]
4. Ultrasound on the subcutaneous sarcoid granuloma shows irregular hypoechoic findings heterogenous echogenicity, perilesional hyperechoic changes, and abnormal Doppler signal.[4]
5. Positron Emission Tomography-Computed Tomography (PET-CT) scanning can be used to identify cutaneous granulomatous inflammation and internal organ involvement.[4]

Sarcoidosis management

The management of cutaneous sarcoidosis depends on the extent and severity of the disease. Disease with few lesions can be managed with topical or intralesional steroid. Systemic therapy is indicated for severe sarcoidosis.[4] The therapy for cutaneous sarcoidosis is shown in **Table 1**.

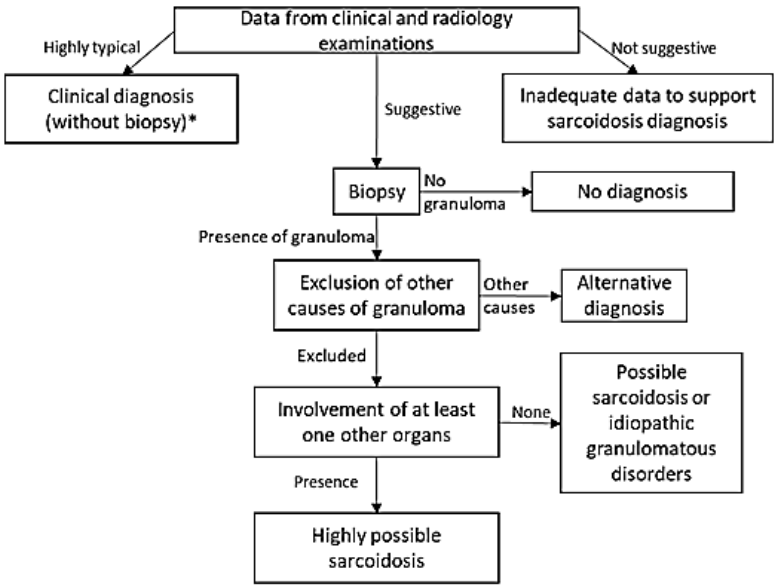

Figure 1 Algorithm for the diagnosis of systemic sarcoidosis by Haimovic *et al*. with modification[12].
*The diagnosis can be established directly if there are any characteristic findings, e.g., Löfgren syndrome, Heerfordt syndrome, and asymptomatic bilateral hilar adenopathy.

Table 1 Therapy for cutaneous sarcoidosis. [1,3]

	Drugs	Dosage	Level of Evidence
Topical therapy	Clobetasol	Twice a day (can be alternate with tacrolimus)	IIB
	Betamethasone dipropionate	Twice a day	IIB
	Halobetasol	Twice a day	IIB
	Tacrolimus	Twice a day (can be alternate with topical steroid)	IV
	Tretinoin, tazarotene	Once a day	IV
Intralesional	Triamcinolone acetonide (10 – 40 mg/kg)	Every 4 – 8 weeks as necessary	IIB
Physical therapy	Phototherapy (Ultraviolet A)	Thrice a week	IV
	Photodynamic therapy	-	
	Laser	Pulsed dye, CO_2, ruby, potassium titanyl phosphate	IV
	Surgery	-	IV
Immunomodulator	Hydroxychloroquine	200 – 400 mg/day	IIB
	Chloroquine	250 – 500 mg/day	IIB
	Minocycline (or doxycycline or tetracycline)	2x100 mg per day	IIB
	Pentoxifylline	3x400 mg per day	IV
	Apremilast	2x20 mg per day	IIB
	Isotretinoin	20 – 60 mg/day	IV
	Acitretin	25 mg/day	-
	Thalidomide	50 – 200 mg every night	IIB
Immunosuppressive agent	Prednisone	10 – 60 mg per day	IIB
	Methotrexate	7,5 – 25 mg per week	IIB
	Azathioprine	50 – 200 mg per day	IIB
	Mycophenolate mofetil	500 – 1500 mg, twice a day	IIB
TNF-inhibitor	Adalimumab	40 mg/week (or every alternate week)	IIB
	Infliximab	3 – 5 mg IV at week 0, 2, 6 then every 4 – 8 weeks	III

* Modified from Wanat *et al*.

The algorithm for cutaneous sarcoidosis management is shown in **Figure 2**.

Although steroid is well-known as the first-line therapy for sarcoidosis, several conditions might need considerations for switching with other agents, such as contraindications against steroid, side effects due to long-term steroid use, and cases recalcitrant to steroids.[5] Therefore, alternative therapy should be considered apart from steroids. Isotretinoin is an alternative therapy for cutaneous sarcoidosis which has been reported quite effective in several case reports. However, due to its low level of evidence, the use of isotretinoin has not been recommended but it can be a therapy of choice by considering the available alternatives and patient's preferences.

Isotretinoin

Isotretinoin or 13-cis-retinoic acid is a vitamin A derivate which is water-soluble and can be found in a small amount within the human's blood and tissues. Isotretinoin is a prodrug that will be transformed into five types of active metabolites in the cells, binding to retinoic acid receptor. This will form heterodimers to regulate the genes responsible for cells' proliferation, differentiation, survival, and death. Isotretinoin is absorbed at maximum if administered with fatty foods. The half-time of isotretinoin is 10–20 hours; hence, the ideal administration is twice a day. Isotretinoin is metabolized in the liver by the cytochrome p450 (CYP450) enzyme. The peak level of isotretinoin in the plasma is reached in 1–4 hours. Isotretinoin is bound 99.9% at albumin in the plasma. The metabolites will be excreted through feces (53–74%) and urine. The retinoid level in blood returns as before within 1 month after the drug is discontinued.[6]

Retinoid has been used for various skin disorders, from psoriasis to malignancy. Apart from acne therapy, isotretinoin is also used off-label for psoriasis, rosacea, Gram-negative folliculitis, sarcoidosis, granuloma annulare,

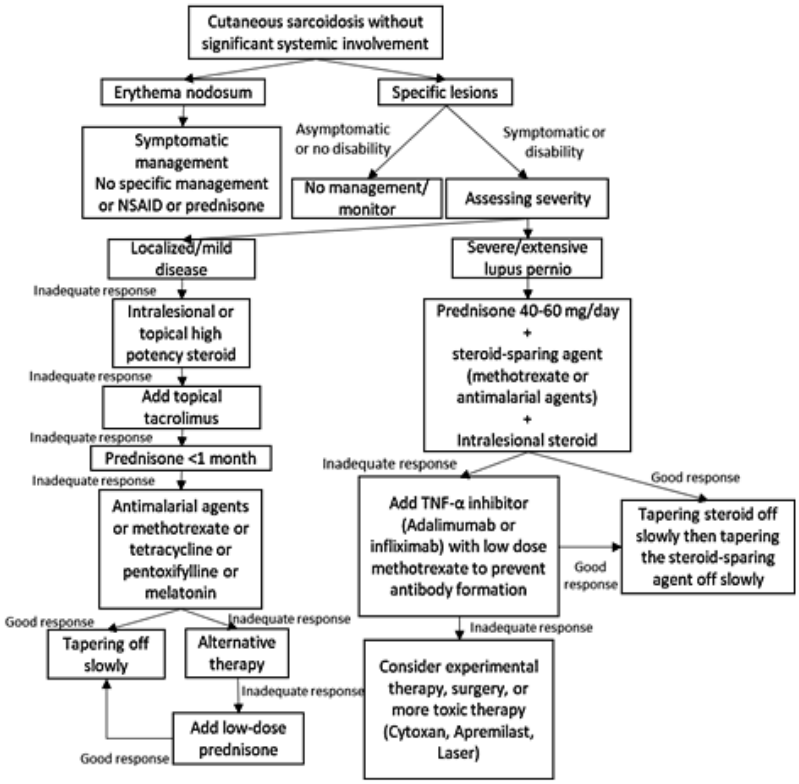

Figure 2 Algorithm for cutaneous sarcoidosis management from Marchell.[13]

pilaris, lupus erythematosus, Darier's disease, keratoderma, and ichthyosis. In addition, isotretinoin is also used as chemoprevention for skin malignancy and various genodermatoses (epidermodysplasia verruciformis and xeroderma pigmentosum).[6,14] Contraindications of isotretinoin administration include hypersensitivity towards isotretinoin or its components (soy, paraben, or other retinoids), excessive alcohol consumption, pregnancy, and breastfeeding. Patients who received isotretinoin are not allowed to become blood donor because it can expose pregnant women with high isotretinoin levels if they receive the blood. Several cases should be considered when administering isotretinoin, which include psychiatric disorders, suicidal thoughts, hyperlipidemia, diabetes mellitus, anorexia nervosa, bone disorders, seizures, inflammatory bowel diseases, and pancreatitis. The most common side effects of isotretinoin are mucocutaneous side effects (cheilitis, pruritus, dry nasal mucosa, dry mouth, dry eyes, acral desquamation, eczema, facial erythema, paronychia, bruise easily, pyogenic granuloma, eruptive xanthoma, photosensitivity, alopecia, and brittle nails), lipid level alterations, inflammatory bowel disease, neuropsychiatric disorders, bone disorders, and teratogenic.[6]

Tetracycline should not be administered with isotretinoin because it can increase the risk of pseudotumor cerebri. Vitamin A supplement should not be administered because it can increase the risk of toxic effects of isotretinoin. Considering that isotretinoin is metabolized by CYP450, the interactions of other drugs which are metabolized by the same enzymes should be paid attention, such as carbamazepine and ketoconazole. Related to isotretinoin's bond with albumin, salicylic acid and indomethacin which have high affinity towards albumin can replace isotretinoin, leading to increase its fraction in the blood and its activity.[6] In addition, the efficacy of hormonal contraceptives, such as ethinyl estradiol,

norethindrone, and micro-dose progesterone has been reported to decrease when administered with isotretinoin.[14]

Use of isotretinoin in the management of sarcoidosis

One of off-label indications for isotretinoin is sarcoidosis.[6] To date, there has been no clinical study on the use of isotretinoin for sarcoidosis. Previous studies were only in the forms of case reports with various outcomes. **Table 2** shows the summary of case reports on the use of isotretinoin for cutaneous sarcoidosis.

Based those case reports, four patients reported total resolution while two patients reported partial resolution. In patients experiencing total resolution, the isotretinoin dose was 0.25–1 mg/kg/day with duration of 4-8 months.[7,18-20] This dose is in line with usual recommended dose for the use of isotretinoin, which ranges from 0.5-2 mg/kg/day. Isotretinoin is recommended to be administered at low dose first (0.5 mg/kg/day) and the dose is increased gradually if well-tolerated. The use of isotretinoin is not advised for long-term use because various side effects. Hence use of 4-8 months is considered safe as long as it was observed closely.[6] From all case reports above, only one case showed no changes. In that report, the therapy was discontinued early due to exfoliative dermatitis following the administration of etretinate for 7 weeks.[16] Etretinate is a second generation monoaromatic retinoid which is very lipophilic. Etretinate has life-time of 80–160 days and can be detected in circulation up to 2.9 years following discontinuation. Etretinate has higher bioavailability compared to isotretinoin (44% vs. 25%) and it achieves the peak plasma level in 4 hours. Its metabolism and excretion are similar to isotretinoin. Etretinate has been withdrawn from the market because it is accumulated in the adipose tissues and causes high risk of teratogenicity.[21] Five of six patients with resolution had been given steroid previously but there were no significant changes or there was relapse.

Although steroid is the first-line therapy for sarcoidosis, recalcitrant case has been reported increasingly. Not only steroid, a patient in the study by Mosam *et al*. did not show a good response towards chloroquine, methotrexate, doxycycline, allopurinol, and azathioprine.[18]

Table 2 Summary of case reports on the use of isotretinoin for cutaneous sarcoidosis

Study	*Patient's Characteristics*	*Extracutaneous Manifestations*	*Dosage*	*Duration of therapy*	*Outcome*
Waldinger et al. (1983)[15]	Female, 39 years old	Cervical, preauricular, postauricular, and inguinal lymphadenopathy	0,67 – 1,34 mg/kg/day	30 weeks	Improvement of nodule and plaques along with 75% regression of peripheral lymphadenopathy
Spiteri et al. (1985)[16]	Female, 33 years old	Hilar lymphadenopathy, peripheral bone cysts, upper respiratory tract involvement	Etretinate 2x25 mg	7 weeks	Therapy was discontinued due to exfoliative dermatitis Sarcoid nodule had not been resolved
Valliant et al. (1986)[17]	Female	None	0,4 – 1 mg/kg/day	6 months	Total resolution of one lesion and reduced size of another lesion
Georgiou et al. (1998)[7]	Female, 31 years old	None	1 mg/kg/day	8 months	Total resolution
Mosam et al. (2004)[18]	Female, 41 years old	Hilar lymphadenopathy, hepatosplenomegaly, dactylitis with terminal phalanges resorption and pseudocysts	0,25 mg/kg/day	6 months	Total resolution
Chong et al. (2005)[19]	Male, 22 years old	None	Not described	Not described	Partial resolution
Choi et al. (2009)[20]	Male, 31 years old	None	20 mg/day	4 months	Total resolution

With the administration of isotretinoin, sarcoidosis patients who were recalcitrant towards steroid finally experienced resolution. These patients were also reported to free of lesions until 7 months following the discontinuation of isotretinoin.[7]

The mechanism of action of isotretinoin in sarcoidosis has not yet been elucidated but it is thought to be its immunomodulating and anti-inflammatory properties.[15] Macrophage and cytokines produced by macrophages play important roles in the formation of granuloma.[22] Granuloma is a tissue inflammatory response characterized by infiltration of mononuclear cells. In macrophage granuloma, various active substances were produced, including reactive oxygen intermediates, enzymes, and cytokines, e.g., TNF-α and IL-1.[23] Sarcoidosis, a chronic granulomatous disease, had a characteristic finding of chronic inflammatory process with accumulation of T-cell and macrophage in the involved organs. Both TNF-α and IL-1 are thoughts to play important roles in the pathogenesis of sarcoidosis. In addition, a study by Nakayama *et al*. reported that the plasma level of TNF receptor can become a parameter for assessing the progression and activity of sarcoidosis.[24] Retinoic acid is reported to reduce TNF receptor and its antiproliferative effects, leading to modulation of cytokine response. The mechanism is thought by replacing or degrading TNF receptor. A study also stated that retinoic acid can inhibit the activation of nuclear factor-κB (NF-κB), a transcription factor which plays a role in macrophage activation; thus, the production of TNF by macrophages is also inhibited. The inhibition effects of retinoic acid towards TNF depend on the duration and dose of retinoid acid exposure towards the macrophage.[25-27] Considering the importance of TNF role in the pathogenesis of sarcoidosis, isotretinoin might be a potential therapy for sarcoidosis.

Retinoic acid is also reported to stimulate cellular lipid deacetylation and increase the production of prostaglandin.[28] Prostaglandin E2 (PGE_2) is the main prostanoid produced by the lung's fibroblasts and plays a role in the inhibition of fibroblast proliferation, differentiation into myofibroblast, and collagen synthesis. In sarcoidosis, there is an increase of TNF-α dan IL-1 which induces inflammatory process and profibrotic mediator. However, in this condition, the fibroblast cannot increase the production of PGE_2, leading to continuing fibrosis process.[29] Retinoic acid is reported to play a role in inducing Prostaglandin-E Synthase (PTGES) enzyme in macrophages. This enzyme will mediate the changes of prostaglandin H_2 (PGH_2) into PGE_2, leading to increase production of PGE_2 and inhibition of fibrosis process in sarcoidosis.[30] Reviewing the safety profile of isotretinoin and its effects on sarcoidosis patients from previous reports, isotretinoin might be a safe and effective therapy for cutaneous sarcoidosis.[7,18]

Conclusion

Sarcoidosis is a chronic granulomatous disease with clinical manifestations in various organs which can decrease the patient's quality of life. Various therapeutic modalities have been developed for its management but recalcitrant cases area often reported. Isotretinoin, a vitamin A derivate with anti-inflammatory and immunomodulatory properties, has a potency to be used for cutaneous sarcoidosis. Nevertheless, use of isotretinoin in sarcoidosis needs further studies to prove its effectiveness and safety.

References

1. Wanat KA, Rosenbach M. Cutaneous sarcoidosis. *Clin Chest Med*. 2015;**36**:685-702.
2. El-Khalawany M, Mosbeh A, Aboeldahab S, Ali S. Cutaneous sarcoidosis: A new subset

in the spectrum of paraneoplastic dermatoses. *Clin Exp Dermatol*. 2018;**43**:683-91.
3. Haimovic A, Sanchez M, Judson MA, Prystowsky S. Sarcoidosis: A comprehensive review and update for the dermatologist: Part I. Cutaneous disease. *J Am Acad Dermatol*. 2012;**66**:699e1-18;quiz 717-8.
4. Noe MH, Rosenbach M. Cutaneous sarcoidosis. *Curr Opin Pulm Med*. 2017;**23**:482-6.
5. El Jammal T, Jamilloux Y, Gerfaud-Valentin M, Valeyre D, Seve P. Refractory sarcoidosis: A review. *Ther Clin Risk Manag*. 2020;**16**:323-45.
6. On SC, Zeichner J. Isotretinoin updates. *Dermatol Ther*. 2013;**26**:377-89.
7. Georgiou S, Monastirli A, Pasmatzi E, Tsambaos D. Cutaneous sarcoidosis: Complete remission after oral isotretinoin therapy. *Acta Derm Venereol*. 1998;**78**:457-9.
8. Arkema EV, Cozier YC. Epidemiology of sarcoidosis: Current findings and future directions. *Ther Adv Chronic Dis*. 2018;**9**:227-40.
9. Inaoka PT, Shono M, Kamada M, Espinoza JL. Host-microbe interactions in the pathogenesis and clinical course of sarcoidosis. *J Biomed Sci*. 2019;**26**:45.
10. Bordignon M, Rottoli P, Agostini C, Alaibac M. Adaptive immune responses in primary cutaneous sarcoidosis. *Clin Dev Immunol*. 2011;**2011**:235142.
11. Ungprasert P, Ryu JH, Matteson EL. Clinical manifestations, diagnosis, and treatment of sarcoidosis. *Mayo Clin Proc Innov Qual Outcomes*. 2019;**3**:358-75.
12. Haimovic A, Sanchez M, Judson MA, Prystowsky S. Sarcoidosis: A comprehensive review and update for the dermatologist: Part II. Extracutaneous disease. *J Am Acad Dermatol*. 2012;**66**:719 e1-10; quiz 29-30.
13. Marchell R. Sarcoidosis. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, *et al*., editors. Fitzpatrick's dermatology. 9th ed. USA: McGraw-Hill Education; 2019. p. 572-84.
14. Lowenstein EB, Lowenstein EJ. Isotretinoin systemic therapy and the shadow cast upon dermatology's downtrodden hero. *Clin Dermatol*. 2011;**29**:652-61.
15. Waldinger TP, Ellis CN, Quint K, Voorhees JJ. Treatment of cutaneous sarcoidosis with isotretinoin. *Arch Dermatol*. 1983;**119**:1003-5.
16. Spiteri MA, Taylor SJ. Retinoids in the treatment of cutaneous sarcoidosis. *Arch Dermatol*. 1985;**121**:1486.
17. Vaillant L, le Marchand D, Bertrand S, Grangeponte MC, Lorette G. annular cutaneous sarcoidosis of the forehead: Treatment with isotretinoin. *Ann Dermatol Venereol*. 1986;**113**:1089-92.
18. Mosam A, Morar N. Recalcitrant cutaneous sarcoidosis: An evidence-based sequential approach. *J Dermatolog Treat*. 2004;**15**:353-9.
19. Chong WS, Tan HH, Tan SH. Cutaneous sarcoidosis in asians: A report of 25 patients from Singapore. *Clin Exp Dermatol*. 2005;**30**:120-4.
20. Choi KH, Kim SY, Kim GM. A case of cutaneous sarcoidosis treated with isotretinoin. *Korean J Dermatol*. 2009;**47**:629-31.
21. Hossein M, Nessa A, Maryam G, Vahideh L. A review of three systemic retinoids in dermatology: Acitretin, isotretinoin and bexarotene. *Iran J Dermatol*. 2013;**16**:144-58.
22. Wolter NJ, Kunkel SL, Lynch JP, 3rd, Ward PA. Production of cyclooxygenase products by alveolar macrophages in pulmonary sarcoidosis. *Chest*. 1983;**83**:79s-81s.
23. Kasama T, Kobayashi K, Yamagata N, Iwabuchi H, Matsuda T, Nakatani K, *et al*. Augmentation of pulmonary foreign body granulomatous inflammation in mice by lipopolysaccharide: Involvement of macrophage activation and tumor necrosis factor-alpha. *Int Arch Allergy Immunol*. 1992;**97**:130-8.
24. Nakayama T, Hashimoto S, Amemiya E, Horie T. Elevation of plasma-soluble tumour necrosis factor receptors (TNF-r) in sarcoidosis. *Clin Exp Immunol*. 1996;**104**:318-24.
25. Totpal K, Chaturvedi MM, LaPushin R, Aggarwal BB. Retinoids downregulate both p60 and p80 forms of tumor necrosis factor receptors in human histiocytic lymphoma u-937 cells. *Blood*. 1995;**85**:3547-55.
26. Mehta K, McQueen T, Tucker S, Pandita R, Aggarwal BB. Inhibition by all-trans-retinoic acid of tumor necrosis factor and nitric oxide production by peritoneal macrophages. *J Leukoc Biol*. 1994;**55**:336-42.

27. Hong K, Zhang Y, Guo Y, Xie J, Wang J, He X, *et al*. All-trans retinoic acid attenuates experimental colitis through inhibition of nf-kappab signaling. *Immunol Lett*. 2014;**162**:34-40.
28. Levine L, Ohuchi K. Retinoids as well as tumour promoters enhance deacylation of cellular lipids and prostaglandin production in mdck cells. *Nature*. 1978;**276**:274-5.
29. Hill MR, Papafili A, Booth H, Lawson P, Hubner M, Beynon H, *et al*. Functional prostaglandin-endoperoxide synthase 2 polymorphism predicts poor outcome in sarcoidosis. *Am J Respir Crit Care Med*. 2006;**174**:915-22.
30. Mamidi S, Hofer TP, Hoffmann R, Ziegler-Heitbrock L, Frankenberger M. All-trans retinoic acid up-regulates prostaglandin-e synthase expression in human macrophages. *Immunobiology*. 2012;**217**:593-600.