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Evidence-Based Therapy for Cutaneous Sarcoidosis

Christy B. Doherty and *Ted Rosen*

Department of Dermatology, Baylor College of Medicine, Houston, Texas, USA

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Abstract

Although healthcare providers have arrived at a relatively comfortable zone of accepted clinical practice in the management of cutaneous sarcoidosis, virtually every treatment is based on minimal evidence-based data and relies almost exclusively on anecdotal information. Although it would be convenient to blame this state of affairs on the lack of certainty about disease aetiology, the unavoidable fact is that little has been executed, even in the realm of well designed comparative trials. Nonetheless, worldwide accepted standard therapies for sarcoidosis include the administration of corticosteroids, antimalarials and methotrexate.

A stepwise approach to patient care is appropriate, and potent topical corticosteroids (e.g. clobetasol) or repeated intralesional injections of triamcinolone (3–10 mg/mL) may be all that is needed in mild skin-limited disease. In patients requiring systemic therapy for recalcitrant or deforming skin lesions (or for widespread disease), corticosteroids (e.g. prednisone 40–80 mg/day, tapered accordingly) used alone or in combination with antimalarials or methotrexate may

be indicated. Antimalarials and methotrexate are considered second-line interventions and may be used as monotherapy for steroid-resistant sarcoidosis or in patients unable to tolerate steroids. Given the concern regarding ocular toxicity, the maximum dosages of chloroquine and hydroxychloroquine should not exceed 3.5 and 6.5 mg/kg/day, respectively. Methotrexate is given in weekly doses of 10–30 mg, with the caveat that haematological, gastrointestinal, pulmonary and hepatic toxicities are possible.

Despite universal acceptance as standard care, the aforementioned treatments often result in an incomplete clinical response or unacceptable adverse events. In such situations, more innovative treatment options may be used. Treatments that may well gain widespread future use include the tumour necrosis factor-α inhibitors infliximab and adalimumab. Experience is limited, but early reports are promising. Infliximab is administered via intravenous infusion at doses of 3–10 mg/kg at 0, 2 and 6 weeks and as indicated thereafter, whereas adalimumab is injected subcutaneously at doses of 40 mg either weekly or every 2 weeks. Because adalimumab is not approved for the management of sarcoidosis, the optimum dose administration interval is uncertain. However, it has been given in both weekly and every other week regimens. Isotretinoin, 0.5–2 mg/kg/day, has been used successfully in a handful of reported cases. However, the teratogenic potential of isotretinoin is often prohibitive considering that the primary demographic group likely to develop sarcoidosis is women of childbearing potential. Thalidomide at dosages of 50 to >400 mg/day has limited, albeit promising, supporting data. However, access is restricted in many countries because of a deserved pregnancy category X rating. Melatonin (20 mg/day) and allopurinol (100–300 mg/day) are not well studied in cutaneous sarcoidosis, and the clinical experience with tetracycline derivatives has been mixed. That said, there are compelling reports of therapeutic benefit with both doxycycline and minocycline. Because neither of these agents is associated with the severe toxicity of cytotoxic drugs, they may serve as effective therapy in some patients. Pentoxifylline (400 mg three times daily) has been of use in a small number of reported cases of pulmonary sarcoidosis, but there are no reports on its use in patients with primarily cutaneous disease. Both ciclosporin and chlorambucil have been largely abandoned given their associated toxicity and disappointingly unreliable efficacy. Finally, laser therapy is a newer modality that may provide patients with a quick and non-invasive treatment option for cutaneous sarcoidosis.

Sarcoidosis is a multisystem disorder characterized by non-caseating granulomata that primarily affect the lungs and lymphatic system, but may further (or solely) involve the skin, eyes, liver, spleen, nervous system, muscles, bones and other visceral organs.[1,2] The granulomas of sarcoidosis represent the accumulation of lymphocytes and mononuclear phagocytes, with secondary derangement of normal tissue or organ anatomy and function.[2] Although some sarcoidosis patients achieve full recovery within months to years, other individuals experience progressive disease with chronic disability.[3] Extrathoracic features, including cutaneous sarcoidosis, are more prominent in the latter group.[3]

Cutaneous manifestations appear in approximately 25% of sarcoidosis patients, with skin lesions often associated with pulmonary and osseous involvement.[4,5] However, not infrequently, cutaneous lesions occur in the absence of accompanying systemic abnormalities.[5] Common specific cutaneous lesions include brownish-purple infiltrated plaques that may be annular, polycyclic or serpiginous; yellowish-brown or purple maculopapular or papu-

lar lesions; firm, purple or brown nodules; diffuse, violaceous, soft doughy infiltrations of the face, termed lupus pernio; and deep subcutaneous nodules.[6] Uncommon manifestations of cutaneous sarcoidosis include verrucous plaques that resemble warts or severe psoriasis, macular hypopigmentation, aggregate tiny micropapules, scarring alopecia and skin ulcerations. Cutaneous biopsies classically demonstrate non-caseating granulomas histologically.[7] However, granulomas are not characteristic of erythema nodosum, which is a non-specific lesion considered the hallmark of acute sarcoidosis that is associated with a self-limiting course.[8,9]

1. Pathogenesis: the Basis for Possible Efficacy of Standard and Newer Therapies

A greater understanding of the assumed pathogenesis of sarcoidosis and the characteristic non-caseating granulomata has clarified key steps in the development and propagation of disease that is susceptible to targeted therapy. Generally speaking, granulomas are inflammatory responses composed of epithelioid macrophages and their derivatives. The inciting event in granuloma formation involves the deposition of persistent, poorly soluble antigenic material into tissues. The precise aetiological antigen in sarcoidosis is unknown, despite intensive efforts to identify it.[10,11]

After the antigenic material is phagocytosed or endocytosed by antigen-presenting cells (APCs) in the form of macrophages or dendritic cells,[12,13] it is processed within the phagolysosome or endolysosome and transported to the cell surface in the form of a class II major histocompatibility complex (MHC II) molecule-peptide complex, where it is recognized by CD4+ T cells bearing the corresponding antigen-specific T-cell receptor.[14] With CD4+ T cells now activated, cytokines and chemokines are secreted that aid in the organization of the granuloma.[15]

Sarcoidosis is characterized by a type 1 immune response, with elevated levels of interferon (IFN)-γ, interleukin (IL)-2 and the T helper (T_h)1 cell immunoregulatory monokine IL-12. The chemokine-associated recruitment of macrophages into the granulomatous lesion is intensified by tumour necrosis factor (TNF)-α,[16] which may contribute initially to antimicrobial action and clearance of granuloma-inducing mycobacterial or other infection.[17,18] However, if the granulomatous response does not successfully clear the inciting antigen(s), persistent inflammation, with sustained upregulation of the production of cytokines, such as TNF, results in tissue consolidation and functional impairment.[17] Surviving parenchymal cells trapped within areas of perpetual inflammation cannot re-establish normal tissue architecture.[19] Chronic disability may follow because the ultimate sequela is progressive fibrosis.[3,12]

Although it is generally accepted that sarcoidosis is mediated by excessive T_h1 cell activity, there is new evidence suggesting that an expansion of regulatory T cells may explain the sarcoidosis-associated 'immune paradox': the intense inflammatory activity of sarcoidosis, including granuloma formation and cytokine release, is accompanied by a relative state of anergy, as manifested by a poor response to antigens *in vitro* and *in vivo*.[20] Perhaps clarifying this situation is the amplification of a regulatory T-cell subset ($CD4+CD25^{bright}$), which has insufficient activity to control local inflammation but concurrently exerts an anergic effect peripherally via inhibition of both IL-2 production and T-cell proliferation.

Therapy of sarcoidosis is based on the presumed immunopathogenetic construct discussed previously. Future directions for sarcoidosis treatment may well target regulatory T cells because this is a growing area of interest. The mechanisms of action of the many agents used to treat sarcoidosis are summarized in table I.

2. Evidence-Based Grading of Cutaneous Sarcoidosis Treatments

There are no inviolate guidelines for initiating therapy in cutaneous sarcoidosis, but treatment is typically considered when widespread, progressive, disfiguring or function-impairing skin lesions develop.[22] Standard therapeutic interventions for cutaneous sarcoidosis have traditionally included topical, intralesional and systemic corticosteroids, antimalarial drugs, methotrexate, and combinations of these agents. Given the variable clinical response to these standard agents and the significant toxicity associated with them, there is growing interest in

Table I. Actions of agents used to treat sarcoidosis (reproduced from Badgwell and Rosen,[21] with permission from Elsevier)

Agent	Prevents antigen presentation	Inhibits cytokine synthesis	Inhibits cytokine activity	Suppresses granuloma formation	Suppresses T-cell response	Antibacterial effect	Debulks granuloma
Corticosteroids				X			
Antimalarials	X						
Methotrexate				X			
Pentoxifylline		X					
Tetracyclines				X	X	? Uncertain	
Isotretinoin	? Uncertain				X		
Leflunomide					X		
Thalidomide		X					
Infliximab			X				
Chlorambucil					X		
Melatonin		? Uncertain			? Uncertain		
Ciclosporin					? Likely		
Allopurinol				X			
Laser surgery							X
Adalimumab			X				

alternative and innovative treatment modalities. In the present review, available evidence regarding the use of each conventional and innovative treatment is judged on a four-point scale as level 1–4, with 1 connoting the strongest evidence.[23] A recommendation grade of A–D is given to each therapy discussed on the basis of the strength of supporting evidence.[23] Grade A is reserved for studies rated as 1 (randomized controlled trials, meta-analyses/systematic reviews of randomized controlled trials). Grade B is given to a body of evidence including studies rated as 2+ (high-quality case-control or cohort studies, systematic reviews of studies weaker than randomized controlled trials) or extrapolated evidence from studies rated as 1. Grade C refers to studies rated as 2 (well conducted case-control studies, open-label clinical trials or retrospective analyses) or extrapolated evidence from studies rated as 2+. Finally, grade D is given to a body of evidence consisting of studies rated as 3 (non-analytical studies such as case reports/series) and studies rated as 4 (anecdotal, expert opinion). It should be noted that despite the increasing use of innovative treatments for cutaneous sarcoidosis, therapy rated as grade D should be considered only after generally accepted standard therapy fails.

3. Standard Therapies

3.1 Corticosteroids

The worldwide accepted standard therapy for sarcoidosis is corticosteroids and it is theorized that the usefulness of corticosteroids lies in their ability to suppress inflammation and to thus halt ensuing granuloma formation. Corticosteroids increase gene transcription of IκB, the inhibitor of nuclear factor (NF)-κB. NFκB is the transcriptional activator of multiple genes involved in inflammatory responses[24] and inhibition of this activator prevents the transcription of proinflammatory signal molecules, such as TNFα, granulocyte-macrophage colony-stimulating factor, IL-1, IL-2, Il-3, IL-4, IL-5, IL-8, IL-11, IL-13, regulated upon activation, normal T expressed and secreted (RANTES), eotaxin, macrophage inflammatory protein 1α, monocyte chemoattractant protein (MCP)-1 and MCP-3.[25]

A stepwise approach in the treatment of patients with mild lesions limited to the skin may begin with ultrapotent topical corticosteroid therapy, which may prove to be all that is necessary.[8] Ulobetasol (halobetasol) and clobetasol have reportedly been used with success as topical treatments in cutaneous sarcoidosis.[26,27] Typical administration is twice daily application until lesions resolve. Topical corticosteroids have the advantage of minimal systemic

absorption, although possible effects include disturbance of the hypothalamic-pituitary-adrenal axis and localized skin atrophy. The risk of both these adverse effects increases with the duration and potency of treatment. As with any topical treatment, application may be both difficult and cost prohibitive if a large percentage of total body surface area is involved.

In an open-label clinical trial observing the benefit of clobetasol under a hydrocolloid occlusive dressing (Duoderm®)[1] in 141 patients with chronic skin conditions, the complete remission of cutaneous sarcoid lesions was noted in all three patients with skin disease after 3–5 weeks of treatment.[26] Because the treatment was only applied once a week, the need for frequent drug application and the amount of topical corticosteroid used was reduced by a factor of at least 20. Atrophy was much less likely given the decreased frequency of application and the amount of drug applied, and was not observed in any of the 141 subjects. In addition, lupus pernio has reportedly been treated successfully with 0.05% ulobetasol administered twice weekly.[27]

Intralesional corticosteroids are another localized treatment option for cutaneous sarcoidosis, with injections being most advantageous for small sarcoid plaques and papules. The concentration of the corticosteroid selected depends on the firmness and size of the lesion, but most lesions of sarcoidosis may be treated initially with intralesional triamcinolone at concentrations of 3–20 mg/mL repeated every 4 weeks until the lesions have flattened.[28] In typical therapeutic doses, intralesional corticosteroids should not give rise to systemic effects.[29] However, patients should be informed that numerous injections may be necessary before results are achieved and that recurrence of an apparently resolved lesion is possible.[29] Potential adverse effects include hypopigmentation and atrophy.[28]

Escalating therapy from topical or intralesional corticosteroids to oral, systemic corticosteroids is indicated for disfiguring or destructive lesions, widespread involvement, or lesions that have proven refractory to localized therapy.[2,28,30] The dosage of prednisone administered ranges from 40 to 80 mg/day and is tapered over weeks to months depending on the clinical response. For cutaneous-limited sarcoidosis, a dose of prednisone 30 mg on alternate days may be efficacious.[28,30] This dose may be tapered to 15 mg every other day, with recurrences treated by increasing the dose of prednisone to that administered initially. In order to find the minimal effective dose of corticosteroids needed in patients with both cutaneous and systemic disease, clinicians may use the response of cutaneous lesions as an external marker for overall dose response.[30]

Although corticosteroids are the accepted standard of care, it is interesting to note that there have been no adequately controlled trials performed to delineate the therapeutic effectiveness of such treatment. One of the most substantial reports of patients managed with systemic corticosteroids is a systematic review that presented 16 cases of ulcerative sarcoidosis treated with prednisone alone.[22] Of the 16 patients, 12 achieved cutaneous disease resolution and 4 experienced relapses during the prednisone taper. This systematic review only analysed reported success in patients with a rare sarcoid variant. It is difficult to extrapolate to other, more common types of skin sarcoidosis. That said, the recommendation for corticosteroids is classified as grade C on the basis of level 3 evidence from non-analytical studies (case reports, case series), level 2+ evidence extrapolated from a systematic review and level 2 evidence from a small number of patients treated in a nonrandomized, open-label, controlled trial.

One of the greatest challenges of treating patients with systemic corticosteroids is the lengthy list of possible adverse effects associated with this therapy. In the short term, patients may experience gastrointestinal irritation, increased appetite and various mood disturbances, such as insomnia or euphoria.[30] Special attention must be paid to the long-term complications of corticosteroid use, which include osteoporosis, peptic ulcers, hypertension, hyperglycaemia, acne, impaired wound healing, frank psychosis and Cushingoid features (buffalo hump, redistribution of body fat, purple striae, moon face, and weakening of the proximal upper and lower extremity muscles).[31,32]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

3.2 Antimalarial Agents

The effectiveness of chloroquine and hydroxychloroquine in sarcoidosis is thought to be related to the ability of these agents to inhibit antigen processing and presentation by APCs to CD4+ T cells. One of the initial steps in granuloma formation is antigen processing and presentation, and antimalarials may function to raise the pH within lysosomes, thus preventing assembly of MHC-peptide complexes and transport to the cell surface.[33] Without antigen processing and presentation via MHC-peptide complexes, T cells are not activated to propagate granuloma formation. Relapse following discontinuation of antimalarials is very common, which indicates that antimalarial agents are suppressive rather than curative.[34-36]

Originally developed for use as antimalarial agents, chloroquine and hydroxychloroquine were noted to have anti-inflammatory properties when used in the treatment of rheumatoid arthritis.[37] These agents have a relatively long history of use in the treatment of sarcoidosis and are considered standard therapy, typically in conjunction with corticosteroids or for patients in whom corticosteroids are neither desirable nor necessary for long-term treatment.[30,38] Based on reported clinical experience, the primary benefit of antimalarials appears to be their ability to suppress cutaneous lesions.[34]

In a 1961 open-label clinical trial on seven patients with cutaneous sarcoidosis who were treated with chloroquine for approximately 6 months, all patients exhibited significant improvement of lesions.[35] However, all four patients available for ample follow-up experienced relapse. In a subsequent open-label clinical trial in which 14 patients with cutaneous sarcoid lesions were given chloroquine for 4–17 months, all patients achieved improvement in skin lesions.[34] Relapse after discontinuation of therapy was again the rule, occurring in 9 of 13 patients available for follow-up assessment. Another open-label clinical trial investigating the use of hydroxychloroquine reported successful treatment of cutaneous lesions, because 12 of 17 treated patients experienced lesion regression within 4–12 weeks.[39] Intralesional chloroquine treatment consisting of six injections per lesion of chloroquine 50 mg/mL for 22 weeks has reportedly been efficacious, but there have been no clinical trials reported to date.[40]

As is true of corticosteroids, there are no placebo-controlled or paired comparison studies investigating the usefulness of antimalarials in cutaneous sarcoidosis. However, in 1991, a systematic review of chloroquine therapy in cutaneous sarcoidosis was undertaken and reached the conclusion that chloroquine should be considered a safe and effective alternative in the treatment of cutaneous sarcoidosis.[38] The recommendation for chloroquine treatment of cutaneous sarcoidosis is a classification of grade C based on level 2+ evidence from a systematic review, level 2 evidence from three small open-label clinical trials and level 3 evidence from non-analytical case reports.

Given the possible toxicities of antimalarials, lower doses are preferable to maximal administration and may prove to be as efficacious. The maximum oral chloroquine dosage is 3.5 mg/kg/day, whereas that of hydroxychloroquine is 6.5 mg/kg/day. In the short term, patients may experience nausea, anorexia, dizziness, headaches and blurred vision.[34,35] To help mitigate gastrointestinal discomfort, the medication should be taken with meals.[36,37] Bleaching of the hair rarely occurs with prolonged treatment, but hair grows darker after drug discontinuation.[36] Agranulocytosis is a rare but serious complication of therapy.[36] Potential ocular effects are the most serious adverse events associated with antimalarial treatment and include the development of corneal deposits or central retinopathy (maculopathy).[38] Corneal deposits occur secondary to drug deposition and lead to blurred vision.[30] These deposits disappear after therapy is discontinued. Conversely, chloroquine retinopathy may impair vision permanently. Typically, patients who demonstrate retinal changes or vision loss are aged >65 years, have been receiving chloroquine (or a derivative) for over 1 year (usually much longer), have been managed with a relatively high daily dose and have received a total dose >150 g.[36,41,42] It is thus recommended that patients be given a daily dose no greater than the maximums already cited (3.5 mg/kg/day for chloroquine and 6.5 mg/kg/day for hydroxychloroquine).[43,44]

Baseline screening for patients preparing to start antimalarial therapy includes laboratory tests to

evaluate renal and liver function, to ensure adequate drug metabolism, and an ophthalmological examination, with recording of near visual acuity and any visual field anomalies.[45] Ophthalmological examinations are recommended at least yearly and possibly every 4–6 months for patients with known risk factors.[8,43,45] Although it is felt that hydroxychloroquine has a much lower risk of ocular toxicity than chloroquine, maculopathy has been reported with the use of hydroxychloroquine and patients receiving it should be followed in the same fashion as those receiving chloroquine.[46,47] It has been proposed that patients be followed by an ophthalmologist during treatment and for several years after treatment because rare cases of delayed antimalarial retinopathy have been reported.[41] Hepatotoxicity is atypical and liver function may be monitored every 6–12 months.[48]

3.3 Methotrexate

Methotrexate is a folate analogue that inhibits dihydrofolate reductase and is antiproliferative at high doses.[49] At low doses, methotrexate is an anti-inflammatory agent and is thus thought to suppress granuloma formation. The mechanism of action of methotrexate is likely to be related to increased release of adenosine extracellulary, caused by methotrexate polyglutamate derivatives. Subsequently, adenosine inhibits monocyte and macrophage release of TNFα, IL-6 and IL-8; neutrophil release of reactive oxygen metabolites, leukotriene B_4 and TNFα; and lymphocyte proliferation. The clinically observed latent period between initiation of methotrexate therapy and the onset of anti-inflammatory action may be related to the intracellular accumulation of polyglutamated methotrexate derivatives.

Methotrexate is considered second-line standard therapy and is reserved for patients with steroid-resistant sarcoidosis or patients unable to tolerate the adverse effects of corticosteroids.[50] In 1986, the results of an open-label clinical trial investigating the use of methotrexate in 16 patients with cutaneous infiltrative sarcoidosis were reported.[30] At an initial weekly dose of methotrexate 25 mg tapered to a maintenance dosage of 5–15 mg weekly, 12 of 16 patients exhibited clearance of skin lesions. However, this study had only limited long-term follow-up. An open-label clinical trail published a few years later investigated the use of methotrexate 10 mg weekly for the first 6 months, followed by methotrexate 10 mg every 2 weeks thereafter (for 6–27 months), in 15 patients with cutaneous and widespread sarcoidosis.[50] In 9 of 11 patients receiving prednisone prior to methotrexate initiation, corticosteroids were discontinued or given at reduced doses. Of the four patients with skin as the major initial target organ, all showed improved with methotrexate. Two of these patients relapsed following decreased administration of methotrexate, but both achieved complete responses after retreatment with weekly methotrexate. In a case series of three patients treated with methotrexate 15–22.5 mg weekly for cutaneous sarcoidosis, all individuals experienced significant improvement in lesions over a 6–9 month period.[51] Facial granulomas and ulcerations responded most favourably. Following discontinuation of methotrexate, one patient was clear of lesions for 7 years without further treatment, one patient was lost to follow up after 6 months and one patient's condition was stable at the time the article was written (although no duration of time is specified).

The prolonged use of methotrexate was investigated in a nonrandomized interventional study following-up 50 patients who received at least 2 years therapy with methotrexate 10 mg weekly.[52] Of the 17 patients with cutaneous involvement, 16 improved with methotrexate. Methotrexate proved to be a steroid-sparing agent in 25 of 30 patients who were receiving prednisone at initiation of methotrexate therapy. Relapse was experienced by 35 of 40 patients who eventually discontinued methotrexate. Methotrexate was resumed in 27 patients, with 26 noting improvement of their symptoms. Methotrexate, similar to antimalarials, appears to have suppressive rather than curative capabilities.[8]

In 1999, a systematic review of reported methotrexate use in sarcoidosis was published, with the conclusion that methotrexate is an acceptable alternative to corticosteroids and should be considered in patients with chronic or refractory disease.[53] It should be noted that this review investigated the use of methotrexate in the treatment of various forms of sarcoidosis and only three of the studies included patients with cutaneous sarcoidosis. Thus, the evi-

dence from this systematic review must be extrapolated to patients with primarily cutaneous sarcoidosis. Furthermore, it is of note that the total number of methotrexate-treated sarcoidosis patients reported in the readily available peer-reviewed medical literature is well below 100 and that none of these patients participated in randomized, double-blind, placebo-controlled investigations. In summary, the evidence supporting methotrexate use consists of three nonrandomized open-label clinical trials judged as level 2, one case series judged as level 3 and a systematic review judged as level 2+. Because the information from the systematic review is not directly applicable to our population of interest, the overall recommendation can only amount to a classification of grade C.

Methotrexate is typically given in weekly doses of 10–30 mg. Patients must be prepared to wait as long as 6 months from the initiation of treatment to see objective evidence of a response.[53] Haematological, gastrointestinal, pulmonary and hepatic toxicities are associated with methotrexate use. Because of underlying organ involvement, the frequency of haematological and hepatic toxicity may be higher in sarcoidosis patients than in patients with other conditions.[53] Methotrexate is associated with dose-dependent mucositis, including mouth sores and nausea. By dividing the dose of methotrexate in half (so it is administered on 2 consecutive days each week) and giving oral folate (1 mg/day), these adverse effects can be eliminated.[52,54]

Because methotrexate is cleared by the kidney, renal function tests should be performed prior to and then routinely during therapy.[37] Monitoring of the white blood cell count on a regular basis, such as every 8 weeks, is usually sufficient to detect possible bone marrow suppression.[53] One problem that arises in treating sarcoidosis patients with methotrexate is differentiating methotrexate pulmonary hypersensitivity from a sarcoidal exacerbation.[51] The risk of methotrexate hypersensitivity pneumonitis is associated with the cumulative dose, usually occurring after many months to years of treatment.[53] A detailed evaluation is warranted in any patient who has received methotrexate and experiences worsening pulmonary symptoms.[53] Routine monitoring of liver enzymes (ALT and AST), alkaline phosphatase and serum albumin is recommended given the very realistic possibility of hepatotoxicity with the prolonged use of methotrexate.[55] Some conservative physicians monitor hepatic status via periodic liver biopsies performed after each 1.0–1.5 g of cumulative therapy (approximately every 2 years), because there are no liver function tests that have proven to be predictive of methotrexate toxicity.[53]

3.4 Combination Therapy

Both antimalarials and methotrexate are considered steroid-sparing medications in that they may either replace corticosteroids as primary treatment or may be used as adjuncts, allowing lower effective doses of corticosteroids. It has been proposed that the period of effective suppression may be prolonged with antimalarials and corticosteroids when the two treatments are used in sequence.[36] Such a regimen may reduce the complications of long-term use with either agent. It should be emphasized that none of the standard therapies or combinations thereof have been approved by the US FDA for the treatment of sarcoidosis.

In a few of the aforementioned open-label clinical trials evaluating the use of standard therapies for sarcoidosis, corticosteroids are used in conjunction with steroid-sparing medications at reduced doses or during the time of transition from corticosteroids to methotrexate or antimalarials.[39,50,52] In addition, there is a cross-sectional retrospective analysis of 30 patients with cutaneous sarcoidosis, six of whom were judged to have recalcitrant sarcoidosis (i.e. it was unresponsive to oral prednisone alone) that necessitated the use of sequential treatment.[56] All patients were initially treated with between two and five courses of oral prednisone, tapered over 6 weeks to a maintenance dose, and topical betamethasone dipropionate. For the six patients with recalcitrant sarcoidosis, chloroquine 200 mg twice daily was initiated and resulted in complete remission in two patients. The remaining four patients then underwent 6 months of treatment with methotrexate, with two patients achieving remission. The remaining two patients were treated with sequential trials of more experimental treatment that included allopurinol, azathioprine and isotretinoin. The lesions of both patients eventually responded to treatment.

The use of combination therapy is supported by level 2 evidence (open-label clinical trials and retrospective analysis), giving a recommendation of grade C.

4. Innovative Therapy

4.1 Pentoxifylline

Pentoxifylline, a methylxanthine non-selective phosphodiesterase inhibitor that is FDA approved for claudication, has been demonstrated to suppress lipopolysaccharide (LPS)-stimulated TNFα production by human peripheral blood monocytes and alveolar macrophages.[57-59] As mentioned, TNFα is necessary for the persistence of granulomas.[60] *In vitro*, pentoxifylline at therapeutic doses has produced near complete inhibition of spontaneous TNFα release from alveolar macrophages from patients with pulmonary sarcoidosis.[58]

In addition, pentoxifylline may assist in shifting from a type 1 towards a type 2 cytokine response via inhibition of IL-12.[61] Under less regulated conditions, IL-12 stimulates IFNγ production, the result of which is enhanced type 1 responses and downregulated type 2 responses. However, other investigations of patients with active pulmonary sarcoidosis have demonstrated that the only cytokines inhibited by pentoxifylline are TNFα and IL-10.[59] The mechanism by which pentoxifylline suppresses cytokines is not fully understood, but a postulated explanation is that pentoxifylline inhibits phosphodiesterase.[59]

To the best of our knowledge, there are no reported experiences with pentoxifylline in patients with primarily cutaneous sarcoidosis. In an open-label trial of pentoxifylline in 23 previously untreated patients with pulmonary sarcoidosis, improvement was demonstrated in 11 of 18 patients who received the drug in a dosage of 2 mg/kg/day for 6 months.[62] Three patients with corticosteroid-refractory pulmonary sarcoidosis were treated with combination therapy of pentoxifylline and corticosteroids. All three patients achieved complete remission, even after corticosteroid discontinuation or tapering of prednisone to 7.5 mg/day, indicating synergistic benefits of pentoxifylline-corticosteroid combination treatment. Two of the three patients required continuing treatment with prednisone, indicating that pentoxifylline monotherapy was not sufficient in these patients. These results suggest that pentoxifylline may best serve as a steroid-sparing agent.

The use of pentoxifylline in sarcoidosis is based on limited clinical experience and there is no evidence-based proof of its efficacy or safety. The single trial looking at pentoxifylline as a treatment for sarcoidosis does not address the use of this medication for patients with cutaneous sarcoidosis other than to mention that 6 of the 23 patients in the trial presented with skin lesions in addition to pulmonary sarcoidosis.[62] For this reason, the recommendation for the use of pentoxifylline in cutaneous sarcoidosis is a classification of grade D. Before the benefit of pentoxifylline in cutaneous sarcoidosis can be assessed, larger studies that specifically investigate the use of pentoxifylline in this patient population must be available. The authors' own experience has not been favourable when pentoxifylline monotherapy is used.

The oral dosage of pentoxifylline is 400 mg three times daily. The drug has a relatively benign adverse effect profile. Of the 23 patients in the aforementioned trial, three discontinued the drug because of reversible gastrointestinal symptoms and restlessness.[62] Mild bleeding diathesis is a possible adverse event, as is an increased susceptibility to mycosis given suppression of the type 1 response by pentoxifylline.[63]

4.2 Tetracyclines

The reported efficacy of the antimicrobial tetracycline in some cases of sarcoidosis has fuelled speculation that *Propionibacterium acnes* or cell wall-deficient bacteria may be causative antigens in this condition.[12,64] Jarisch-Herxheimer shock has been observed in sarcoidosis patients after treatment with antibacterials, and has been presented as 'proof' that sarcoidosis is a bacterial process and that the bacteria are killed by antibacterial therapy.[65] Tetracyclines are bacteriostatic by binding the 30S subunit of bacterial ribosomes and blocking protein synthesis, but some argue that the usefulness of tetracyclines in sarcoidosis lies not in their antibacterial action but, instead, in their well known anti-inflammatory properties. *In vitro*, tetracyclines suppress granuloma formation by inhibiting protein

kinase C phosphorylation of histone.[66] *In vivo*, tetracyclines downregulate IL-2 and chemokine secretion, thus preventing accumulation of T cells.[67] Furthermore, tetracycline derivatives interfere with matrix metalloproteinases that mediate tissue damage.[68] Minocycline has been shown to downregulate the expression of intercellular adhesion molecule (ICAM)-1 and to reduce leukocyte chemotaxis *ex vivo* and *in vitro*.[68] Doxycycline has been shown to inhibit T-cell proliferation *in vitro*[69] and macrophage chemotaxis *in vivo*.[70]

In a nonrandomized open-label clinical trial of 12 patients with cutaneous sarcoidosis, minocycline 200 mg/day was given for a median duration of 12 months with a 2 year follow-up period.[71] A complete response was observed in eight patients, with a partial response in another two. Skin lesions progressed in one patient and remained unchanged in another. Minocycline was discontinued in seven of the patients who exhibited a complete response, with three of these patients developing a relapse of cutaneous lesions. Reportedly, all three minocycline relapses achieved complete remission with doxycycline 200 mg/day.

Fifty patients with a mix of cutaneous, pulmonary and nervous system disease were treated with minocycline 25–200 mg every 48 hours in an observational cohort study.[65] All but three patients reported improvement induced by minocycline alone or in combination with olmesartan medoxomil (an angiotensin II receptor antagonist). This study is difficult to evaluate critically because the degree of improvement was not measured in a quantitative manner and the subjects were not stratified either by minocycline dose or by who received monotherapy versus dual drug therapy. Nonetheless, the overall results reported are impressive enough to warrant further investigation and give further empirical support to those who feel that cell wall-deficient bacteria may be aetiological.

In contrast with the favourable data noted previously, the efficacy of tetracyclines in sarcoidosis has been called into question, with some clinicians going so far as to claim that these antimicrobials can aid in differentiating cutaneous sarcoidosis from lesions that may be clinically and histologically identical. These authors claim that tetracyclines induce remission of the sarcoid-like lesions of granulomatous rosacea or granulomatous papular dermatosis, but have little or no effect on true sarcoid lesions.[72,73] A case series reported the successful clearing of granulomatous rosacea lesions in ten patients, whereas there was no change in the lesions of three patients with multisystem sarcoidosis treated with the same protocol.[72]

The evidence supporting the use of tetracyclines consists of a nonrandomized open trial regarded as level 2 and a cohort study (with a risk of bias) of level 3. In addition, there is a case series with opposing evidence of level 3. In summary, the total number of all patients reported in the available tetracycline derivative studies is quite small, nonrandomized placebo-controlled studies exist and any recommendation for this type of therapy is based on scant and contradictory evidence. Therefore, the recommendation is a classification of grade D.

Most clinicians are quite familiar with the use of and associated adverse events related to tetracyclines. Typical dosages are 1000 mg/day for tetracycline and 200 mg/day for minocycline and doxycycline. The toxicity of these agents is minimal in patients other than pregnant or breast-feeding women and children aged <8 years. Possible adverse effects include gastric discomfort, flare of reflux disease, phototoxicity, mild dizziness that improves with decreased dose and blue-grey cutaneous hyperpigmentation (predominantly in areas of previous sarcoid lesions). Vulvovaginal candidiasis may be precipitated by tetracycline therapy. A more serious complication of minocycline therapy is the development of a drug hypersensitivity syndrome occurring several weeks after the initiation of treatment that is characterized by general malaise with fever, generalized pruritic rash, superficial lymphadenopathy and an interstitial pneumopathy or hepatitis.[31,71] Tetracyclines are contraindicated in pregnant women and young children because of deposition in the bone and primary dentition.[31]

4.3 Isotretinoin

Isotretinoin is a synthetic retinoid with various off-label uses and FDA approval for recalcitrant nodulocystic acne. Although retinoids are thought to work by binding to retinoic acid receptors and retinoid X receptor, with subsequent modulation of DNA transcription, isotretinoin has no clearly iden-

tified affinity for any retinoid receptor.[74] Although the specific immunomodulatory effects of isotretinoin are not well characterized, it has been demonstrated that synthetic retinoids suppress T-cell responses (activation and proliferation) to an antigenic stimulus,[75] possibly by acting directly on the antigen-presenting properties of epidermal cells.[76] Retinoids may inhibit T-cell-mediated immunity enough to suppress the ongoing immune response necessary to maintain granuloma organization, as evidenced by the decreased release of IL-2 seen with these agents.[75]

The evidence in support of the use of isotretinoin in sarcoidosis is limited and consists only of case reports. Four case reports document an improvement in cutaneous sarcoid lesions with isotretinoin therapy, with three specifying the treatment duration as ≥6 months at dosages of 0.4–1.3 mg/kg/day.[77-80] One report documented complete remission of cutaneous lesions without recurrence at 15 month follow-up.[79] Lesions responding the earliest and most completely were described as nodular and plaque like.[77]

Obviously, controlled data supporting the use of isotretinoin in sarcoidosis are lacking. The evidence supporting the use of isotretinoin is level 3, giving isotretinoin a recommended classification of grade D.

Isotretinoin is administered at a dosage of 0.5–2 mg/kg/day for the treatment of cutaneous sarcoidosis, with the majority of adverse events being dose related. Cheilitis, dryness of the nasal mucosa, xerosis and myalgia are commonly reported.[79,81] Isotretinoin has the potential to cause liver function abnormalities and to elevate triglyceride and cholesterol levels, so routine laboratory monitoring is recommended.[81] Given the public concern over the teratogenic effects of isotretinoin, physicians and patients must enrol in the iPLEDGE™ programme, which requires registration of all wholesalers distributing isotretinoin, healthcare professionals prescribing isotretinoin, pharmacies dispensing isotretinoin, and male and female patients prescribed isotretinoin.[82] This US government-sponsored programme, initiated at the request of the FDA, aims to prevent any female patients from becoming pregnant while taking isotretinoin or starting the medication while pregnant. We are unaware of similar programmes in other countries.

4.4 Leflunomide

Leflunomide has been found to be useful in the treatment of rheumatoid arthritis secondary to its anti-inflammatory and antimetabolite properties. Leflunomide inhibits pyrimidine synthesis, thereby preventing T cells from accumulating sufficient pyrimidines to support DNA synthesis and subsequent proliferation.[83] In addition, leflunomide-induced tyrosine kinase inhibition results in the suppression of TNFα and reduction of cell-cell contact activation, thus halting monocyte activation by proliferating T cells.

Improvement of otherwise refractory cutaneous and respiratory sarcoidosis has been documented with leflunomide 20 mg/day therapy in a 2003 case report.[84] In a retrospective review of 32 patients with sarcoidosis involving the eye, lung and/or skin, complete or partial responses were seen in 12 of 17 patients treated with leflunomide alone and in 13 of 15 patients treated with both leflunomide and methotrexate.[85]

The experience with leflunomide is limited to a single case report of evidence level 3 and a retrospective review of evidence level 2, giving leflunomide a recommendation of a grade D classification. It should be noted that FDA approval for leflunomide is granted only for the treatment of rheumatoid arthritis.

Leflunomide is 80% orally bioavailable and is given with a loading dosage of 100 mg/day for 3 days, followed by 20 mg/day thereafter.[84] The effect of leflunomide is selective for proliferating lymphocytes and is reversible. Therefore, leflunomide has an improved toxicity profile that does not typically include anaemia, leukopenia, thrombocytopenia or increased risk of opportunistic infections.[83,84] The most commonly reported adverse events associated with leflunomide treatment include gastrointestinal disturbances, such as diarrhoea, elevated liver function tests, abdominal pain, and nausea and/or vomiting.[83] Potentially significant hepatic damage is possible at high dosages.[86] Hypersensitivity skin reactions, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson

syndrome and toxic epidermal necrolysis, are also of paramount concern.[87,88]

4.5 Thalidomide

Thalidomide (α-N-pthalimidoglutarimide) has been used for various conditions given its immunomodulatory and anti-inflammatory properties, although it was originally prescribed as a sedative in the late 1950s.[89,90] Because of its teratogenic effects and the development of peripheral neuropathy in some patients, thalidomide was ultimately withdrawn as a sedative. Thalidomide is now FDA approved for use in erythema nodosum leprosum and, more recently, for use in multiple myeloma.[91,92] Although its exact mechanism of action is not understood, thalidomide has been found to inhibit TNFα production by human monocytes[93] and alveolar macrophages,[94] possibly via accelerated degradation of TNFα messenger RNA.[95] Under different experimental conditions, thalidomide has been shown to have both suppressive and stimulating effects on cell-mediated immunity.[89,96,97] In one study, thalidomide induced and enhanced the production of IL-4 and IL-5 (T_h2-associated cytokines) but inhibited IFNγ production (T_h1-associated cytokine).[89] Thus, thalidomide may assist in the therapeutic switching from a predominantly T_h1 response, such as that seen in sarcoidosis, to a T_h2 response. The effect of thalidomide on the IFNγ stimulator IL-12 is complex, because IL-12 production has been inhibited when monocytes were stimulated with LPS or staphylococcal organisms, but enhanced when cells were stimulated by cross linking the T-cell receptor of activated T cells.[96,98]

Case reports, with one to four patients each, note the efficacy of thalidomide in treating skin and pulmonary sarcoidosis at dosages of 50–400 mg/day,[99-103] with some patients continuing on long-term therapy at dosages ranging from 50 mg every 15 days to 100 mg on alternate days.[100,101]

In an open-label clinical trial, 15 patients with lupus pernio were treated with thalidomide for 4 months. All experienced some subjective improvement, with 10 of the 12 evaluable patients showing objective improvement based on photographic evaluation.[104] Another open-label clinical trial published the same year presented eight patients with cutaneous sarcoidosis, two of whom were treated with thalidomide monotherapy and six who were treated with a combination of thalidomide and prednisone.[97] One of the two patients treated with thalidomide monotherapy exhibited an improvement of skin lesions. Of the six patients receiving combination therapy, four reportedly improved and one patient experienced increased elevation and nodularity of lesions with central necrosis and ulceration. Skin biopsies performed on all eight patients after treatment showed decreased granuloma size and a reduction in epidermal thickness.

A retrospective study investigating the course of 12 patients with cutaneous sarcoidosis treated with thalidomide reported that partial or complete lesion regression occurred in ten patients.[105] Critical evaluation of this study is complicated by the fact that two of the responsive patients received concomitant oral corticosteroids, one used potent topical corticosteroids and one received methotrexate for 5 months during the course of thalidomide treatment.

The reported use of thalidomide in cutaneous sarcoidosis is limited. One open-label clinical trial of evidence level 2 showing thalidomide to be of use in patients with lupus pernio had only 12 evaluable patients; the other open-label clinical trial of evidence level 2 studied only two patients receiving thalidomide monotherapy and only one of these patients showed improvement. The retrospective study of evidence level 2 is confounded by the use of concomitant therapies (methotrexate and corticosteroids). Finally, the evidence of case reports supporting thalidomide use is of level 3. Therefore, the recommended classification for thalidomide must be grade D.

The dosage of thalidomide used ranges from 50 to >400 mg/day, although access is restricted in the US. Somnolence, dizziness, constipation and nausea are commonly reported adverse effects.[104] Peripheral neuropathy occurs quite frequently following the prolonged administration of thalidomide. In a retrospective study of 135 patients treated with thalidomide for dermatological conditions, clinical and electromyelographic evidence of thalidomide-induced neuropathy was found in 25–56% of patients.[106] A detailed history and physical examination may be sufficient to monitor for thalidomide-induced neuropathy; the necessity of electrophysiological or quantitative sensory tests has yet to be

determined.[103] Neutropenia is a rare adverse effect, occurring in <1% of patients, but it is recommended that patients be monitored with a baseline and periodic complete blood cell count. Thalidomide therapy should not be not initiated if the absolute neutrophil count is <750/mm^3.[91] The notorious teratogenic effects of thalidomide are of primary concern, with the agent carrying a pregnancy category X designation.

4.6 Infliximab

The chimeric monoclonal antibody infliximab binds to and inactivates TNFα, a proinflammatory cytokine necessary for the formation and maintenance of granulomas.[60,107] Infliximab is currently an FDA-approved treatment for ankylosing spondylitits, Crohn's disease, ulcerative colitis, both rheumatoid and psoriatic arthritis, and severe plaque psoriasis.[92]

A handful of case reports documenting the efficacy of infliximab in treating cutaneous sarcoidosis began to be published in 2001.[108-113] Success has also been reported in stabilizing or improving pulmonary sarcoidosis,[60,108] neurosarcoidosis[114] and multiorgan disease.[110,115-118]

In a small, open-label clinical study, three patients (two of whom had lupus pernio as the index lesions) were treated with infliximab 5 mg/kg per treatment.[119] The lupus pernio lesions improved significantly during treatment. In a later retrospective study, of the ten patients who received infliximab for refractory sarcoidosis, all demonstrated objective evidence of improvement over treatment periods ranging from 6 weeks to 2.5 years.[120] Six patients were receiving corticosteroids prior to infliximab treatment and the dose was reduced in all but one of the patients after treatment. All five patients with lupus pernio experienced significant improvement of their lesions.

A retrospective chart review that evaluated the use of infliximab between January 2001 and October 2004 in nine patients with refractory sarcoidosis found infliximab to be both well tolerated and effective in such patients.[121] Two patients experienced partial clearance of skin lesions, one patient had complete resolution of skin lesions and one patient with deep and painful bilateral lower extremity ulcerations achieved complete healing of the ulcers.

In a nonrandomized open study, 12 patients with chronic multisystem sarcoidosis refractory to corticosteroids or alternative therapy were treated with infliximab 3 mg/kg at weeks 0, 2, 4, 6, 10 and 14,[122] and all patients experienced significant improvement in disease activity. In three patients, the indication for commencing infliximab was skin involvement. Although all three patients achieved improvement, lesions reappeared in two of the patients and required resumption of treatment for a total of 15 months in one patient and 13 injections in the other. Of note, in two additional patients treated with infliximab for other organ involvement, cutaneous lesions were noted to improve or subside.

The first randomized, double-blind, placebo-controlled clinical study evaluating patients with chronic pulmonary sarcoidosis was published in 2006.[123] In this study, 138 patients (19 with lupus pernio) were randomized in a 1 : 1 : 1 ratio to receive intravenous infusions of placebo, infliximab 3 mg/kg or infliximab 5 mg/kg at 0, 2, 6, 12, 18 and 24 weeks, with follow-up through to 52 weeks. Treatment with infliximab resulted in a statistically significant improvement in the percentage predicted forced vital capacity at week 24, but there were no significant differences between the treatment groups in regard to facial skin involvement. The skin lesions of one patient improved in the placebo group, there was no noted improvement in the infliximab 3 mg/kg group and four patients in the infliximab 5 mg/kg group experienced improvement. *Post hoc* exploratory analyses suggested that patients with more severe disease tended to benefit more from infliximab therapy.

Case reports of evidence level 3, two open clinical trials of level 2 and retrospective reviews of level 2 support the use of infliximab in the treatment of cutaneous sarcoidosis. A randomized placebo-controlled clinical trial of evidence level 1 reported an improvement in four patients with cutaneous sarcoidosis who were given infliximab 5 mg/kg, but this outcome did not prove to be statistically significant. Therefore, the recommended classification for infliximab remains, at best, grade C.

Infliximab is administered via slow intravenous infusion at dosages of 3–10 mg/kg at 0, 2 and

6 weeks, and as indicated thereafter. Ongoing infusions are typically performed at 8- to 12-week intervals. Infliximab is an expensive, inconvenient and off-label treatment modality. There is the possibility of the formation of blocking antibodies to infliximab during treatment, prompting some clinicians to use concomitant low-dose methotrexate.[108,109,119] Infliximab is an immunosuppressive agent and there is substantial concern that patients receiving it may be at an increased risk of developing lymphoma and infections such as tuberculosis (TB), histoplasmosis, coccidiomycosis, cryptococcal infection and blastomycosis.[124-127] Infliximab has been associated with an increased reactivation rate of TB,[124] so all possible candidates for infliximab therapy must have a purified protein derivative (PPD) test prior to the initiation of therapy. For patients with a positive PPD and radiographic or microbiological evidence of active TB, standard anti-TB therapy under the guidance of a specialist should be commenced. Patients with a positive PPD and no detectable active TB are considered to have latent TB infection and should be treated with isoniazid for 9 months. Whether the 9-month course should be completed prior to or during infliximab therapy has yet to be determined definitively. In addition, one must avoid misdiagnosing TB as sarcoidosis, or mislabelling the signs and symptoms of active TB as worsening sarcoidosis.[60] Infliximab and other TNF inhibitors have been reported to reactivate or worsen hepatitis B, motivating many clinicians to check serology (hepatitis B viral surface antigen) before initiating therapy.[128]

Reports have surfaced documenting the development of neurosarcoidosis in a rheumatoid arthritis patient treated with infliximab and methotrexate, and the occurrence of pulmonary sarcoidosis in a patient with ankylosing spondylitis treated with infliximab.[129,130] Sweiss and Baughman[131] have postulated that the appearance of sarcoidosis in the setting of anti-TNF therapy may be the result of a 'break through' of disease activity, changes in cytokine balance (including increased IFNα levels or rebound TNF secretion), exposure to an infectious agent prompting a granulomatous reaction or a combination of these factors. Sarcoidosis arising in the setting of TNF inhibitor treatment appears to be self-limiting.

Although infliximab appears to be a promising treatment for sarcoidosis, its use for this indication is currently experimental. Given the costs and risks of immunosuppression, infliximab may be most beneficial in patients with progressive, inexorable cutaneous sarcoidosis that fails to respond to traditional mono- and combination therapy.

4.7 Chlorambucil

Chlorambucil is an alkylating agent that interrupts DNA and RNA synthesis, resulting in cell death and decreased numbers of B and T lymphocytes.[132] As outlined previously, T lymphocytes are essential for the orchestration and maintenance of granuloma formation.

In an open-label clinical study published in 1980, ten patients with sarcoidosis were treated with chlorambucil alone or in combination with corticosteroids.[133] Eight of the ten patients improved with therapy, and two of three patients with cutaneous sarcoidosis experienced a lasting improvement of lesions. A few years later, a report was published detailing the successful use of chlorambucil in a patient with sarcoidosis who presented with biliary cirrhosis.[134]

In a clinical study from the early 1990s, chlorambucil therapy was given to 31 patients with severe sarcoidosis who were unresponsive to, or intolerant of, corticosteroids.[135] In 28 of 31 patients, marked or moderate improvement was achieved. However, a 6-month course of chlorambucil was often followed by relapse and prolonged therapy with reduced doses was required in most patients.

Typical administration for chlorambucil is 4–12 mg/day with weekly monitoring of complete blood count for surveillance of possible bone marrow suppression.[133,134] Patients receiving chlorambucil are at an increased risk of developing a malignancy, particularly one that is haematological in nature, and patients may be at an increased risk of infection.[132,133,136] Both herpes zoster and fatal herpes simplex infection during chlorambucil therapy for sarcoidosis have been reported.[133,136] The evidence supporting the use of chlorambucil is scant and most physicians have abandoned using this relatively toxic agent given that the effects are not markedly better than those achieved with other

drugs. Therefore, the recommended classification for chlorambucil is grade D.

4.8 Melatonin

The principal hormone of the pineal gland, melatonin has been shown to have anti-inflammatory and immunoregulatory properties that are not yet understood.[137] Depending on the investigational setting, melatonin has been shown to either inhibit or enhance immune responses. Melatonin has been found to inhibit the release of IFNγ and TNFα from mononuclear cells in culture,[138] whereas later murine studies have shown that melatonin upregulates the gene expression of these cytokines.[139] *In vitro*, melatonin has been observed to increase IL-2 and IFNγ production by T cells, and IL-6 production by monocytes.[140] Melatonin has been shown to enhance thymocyte proliferation in rats with induced states of chronic immunoinflammation,[137] but has also been shown to inhibit lymphoproliferation in response to phytohaemagglutinin, pokeweed mitogen and *Staphylococcus aureus* protein A.[141] Given the varying hypotheses as to the abilities of melatonin, the possible mechanism of action for this agent in sarcoidosis is not clear.

A small case series involving one patient with pulmonary sarcoidosis and one patient with both pulmonary and cutaneous sarcoidosis documents the successful use of melatonin 20 mg/day over a period of 8 months to >1 year.[142] In the patient with cutaneous sarcoidosis alone, almost complete resolution of skin lesions was noted after 5 months of therapy, but lesions reappeared 6 months after discontinuation of therapy. Another course of melatonin for 3 months cleared the skin lesions.

In 2006, results were published from a 24-month open-label pilot trial that investigated the use of melatonin in 18 patients with chronic sarcoidosis that was unresponsive to corticosteroids.[143] Cutaneous lesions consistent with lupus pernio were present in three patients and reportedly disappeared by month 24 of therapy.

The evidence supporting the use of melatonin in cutaneous sarcoidosis is limited to a case report of level 3 and an open-label clinical trial of level 2 involving only three patients. Given the scant evidence available, the recommended classification for melatonin is grade D.

Although no adverse effects were noted for melatonin among the patients involved in the previously mentioned reports, clinical investigations of melatonin and melatonin agonists have been hindered by adverse effects, such as hypothermia, hypotension and bradycardia.[144] Somnolence is a common effect of melatonin administration; a controlled trial of the melatonin agonist β-methyl-6-chloromelatonin demonstrated that the agent had soporific effects, but none of the other adverse effects reported for melatonin.[144]

4.9 Ciclosporin

Ciclosporin (cyclosporine A) inhibits calcineurin, an essential element of the T-cell activation pathway following stimulation of cell surface receptor.[145] Given that sarcoidosis is a disorder of T_h cells, ciclosporin is an agent with potential use in sarcoidosis based on its inhibitory effect on T-cell activation and cytokine production.[146] However, the clinical application of ciclosporin has proven to be of less benefit in the treatment of sarcoidosis than would be suggested by its mechanism of action. *In vitro*, adding ciclosporin to T cells recovered from the lungs of sarcoidosis patients suppressed the release of IL-2 and monocyte chemotactic factor and inhibited exaggerated T-cell replication.[146] However, oral administration of ciclosporin to seven patients with pulmonary sarcoidosis for over 6 months was not accompanied by measurable suppression of T-cell activation, a decrease in the spontaneous release of IL-2 or monocyte chemotactic factor, or a reduction in lymphocyte proliferation.[146] As may be expected, clinical improvements in pulmonary function were not observed.

One clinical investigation demonstrated that a low dose of ciclosporin decreased LPS-stimulated secretion of IL-1β, TNFα, IL-6 and IL-8, whereas intermediate and high doses decreased basal and LPS-stimulated secretion of TNFα and IL-8.[147] Therefore, ciclosporin may potentially act via suppression of inflammatory cytokine production.

There are two case reports documenting the efficacy of ciclosporin alone or in combination with corticosteroids in pulmonary sarcoidosis,[148,149] as

well as reports of ciclosporin treatment resulting in no objective improvement of pulmonary sarcoidosis,[150] or precipitation and exacerbation of subcutaneous sarcoidosis.[151] A report from 1990[152] documents the successful use of combination therapy with ciclosporin and corticosteroids in the treatment of pulmonary sarcoidosis in a patient with systemic lupus erythematosus.

A randomized controlled trial investigating the effect of ciclosporin combined with prednisone versus prednisone monotherapy for the treatment of pulmonary sarcoidosis did not support the use of ciclosporin.[153] Not only was the therapeutic response from baseline not significantly different between the prednisone and ciclosporin plus prednisone combination groups, but the prednisone-ciclosporin combination group also experienced more adverse effects, including a doubling of the number of infections and an elevation of mean serum creatinine concentrations at 3 and 9 months.

Ciclosporin is administered at doses adequate to maintain serum levels of 100–660 ng/mL.[148,150] Renal function tests should be performed on a regular basis; drug-induced nephrotoxicity is the diagnosis if the baseline glomerular filtration rate falls by >25%. This degree of impairment may not be entirely reversible after ciclosporin therapy is discontinued.[154] Hepatotoxicity, glucose intolerance and hypertension are also possible following the use of ciclosporin.[154]

The use of ciclosporin is controversial because of the conflicting clinical experience and possible adverse events, including the most common adverse effect of nephrotoxicity.[31] The evidence in support of ciclosporin use is limited to a few case reports of level 3, whereas there is more substantial evidence against the use of this agent. Consequently, the recommended classification for ciclosporin cannot be greater than grade D and the authors discourage the use of this agent in the treatment of skin sarcoidosis.

4.10 Allopurinol

Allopurinol is a xanthine oxidase inhibitor classically used to treat hyperuricaemia by preventing purine nucleotide degradation into uric acid. The proposed mechanism of action of allopurinol in granulomatous disorders is inhibition of multinucleate giant cell (MGC) formation, possibly via downregulation of monocyte receptor P2X7 and ICAM-1.[155] The P2X7 receptors are presumably involved in the process of cell fusion that leads to MCG formation during granulomatous inflammation, whereas adhesion molecules (e.g. ICAM-1) play a role in the formation of MGC.[156] It has been demonstrated that P2X7 receptor expression is significantly higher on monocytes from patients with sarcoidosis compared with monocytes from healthy controls.[156] MGCs and epithelioid cells, both derivatives of mononuclear cells, are the basic components of granulomas.[157]

Case reports document the efficacy of allopurinol in the treatment of 11 patients with cutaneous sarcoidosis,[158-162] including cutaneous sarcoidosis in a 13-year-old boy.[163] One report noted the recurrence of skin granulomas after discontinuation of allopurinol therapy, with remission upon reintroduction of the agent.[158] An open-label treatment trial involving six patients with cutaneous sarcoidosis demonstrated improvement in four patients at initial publication, with no serious adverse effects reported.[164] Conversely, failure of allopurinol in the treatment of subcutaneous sarcoidosis has also been reported.[165]

Larger and longer-term studies are needed to fully ascertain the usefulness and safety of allopurinol in the setting of cutaneous sarcoidosis, with the evidence that currently supports it consisting of case reports of level 3 and a small clinical trial of level 2. Given this limited evidence, the recommended classification for allopurinol is grade D.

Allopurinol is given in dosages of 100–300 mg/day.[159] The most common adverse reaction is the development of a pruritic maculopapular rash, although other reported adverse effects include gastrointestinal upset, reversible clinical hepatotoxicity and an increased incidence of acute gouty attacks.[159] To minimize the risk of the latter, it has been recommended that the dosage of allopurinol be slowly escalated from 100 mg/day for 1 week to 200 mg/day for 1 week, eventually reaching 300 mg/day.[159] Allopurinol is not without possible risks and data supporting its use are largely anecdotal. Because it does not appear to have the associated toxicity of cytotoxic agents, allopurinol may serve

as an effective therapy for patients in whom immunosuppression is not an acceptable risk.

4.11 Laser Therapy

Laser therapy is a newer modality that may provide patients with a quick and non-invasive treatment option for cutaneous sarcoidosis. Compared with conventional surgical interventions, laser treatment provides relatively precise resculpting and a bloodless field.[166] It is theorized that the usefulness of lasers in sarcoidosis lies in their ability to debulk granulomatous lesions,[167] possibly via activation of immunological processes.[168]

Reports of laser-treated sarcoidosis began to be published in the mid-1980s, although the specific use of lasers in the treatment of cutaneous sarcoidosis was not reported until some years later. Two case reports of lupus pernio treated successfully with flashlamp pulsed dye laser were published in the 1990s, although erythema and telangiectasias reportedly recurred after 6 months in one patient.[169,170] Lupus pernio has also been treated with CO_2 laser with reported disease-free periods of 2 years and 32 months, as well as an instance of partial disease recurrence within 7 years.[171,172] In three lupus pernio patients treated with CO_2 laser more recently, one patient required post-laser intralesional triamcinolone for residual lesional tissue and one required intralesional triamcinolone in addition to prednisone 5 mg/day for systemic sarcoidosis.[166] The patient treated with a combination of laser, intralesional triamcinolone and systemic corticosteroids remained free of cutaneous lesions for 6 years, and the patient treated with laser alone was reportedly disease free for 14 months. The remaining patient, who received both laser and intralesional triamcinolone, developed partial recurrence of nasal swelling 9 months after laser therapy.

Scar sarcoidosis has been treated with Q-switched ruby laser after initial treatment with pulsed dye laser three times proved ineffective; following Q-switched ruby laser treatment, the patient was relapse free after 3 years.[168] In addition, sarcoidosis of the larynx has reportedly been treated with a combination of CO_2 laser and mitomycin with a disease-free interval of at least 2.5 years after treatment.[167] In this case, it was postulated that laser surgery debulked the granuloma, whereas mitomycin inhibited the reformation of granulomas via direct inhibitory effects on fibroblast proliferation and aggregation.

The type of laser used, laser settings, the number of pulses administered and spot size treated will vary depending on the degree of skin involvement, the pigmentation of the patient's skin, the availability of certain lasers and the clinician's level of comfort with laser therapy. Numerous laser treatments may be necessary before results are seen, and patients should be aware of this possibility. Laser resurfacing may cause secondary pigmentary changes or punctate bleeding and crusting at sites of laser treatment. Laser treatment use should be performed with caution in sarcoidosis patients because there are reports of the development of ulcerating sarcoidosis within existing lesions[173] and the development of new sarcoidal lesions at sites of laser resurfacing.[174] Although promising, the data supporting the use of laser therapy are not analytical and are entirely anecdotal in nature. The recommended classification for laser therapy is grade D, and it must be emphasized that laser surgery should only be considered after more conservative therapeutic interventions have proven to be ineffective or undesirable.

4.12 Adalimumab

One of the most recently investigated treatments for use in sarcoidosis is the TNFα inhibitor adalimumab. This human monoclonal IgG1 TNFα antibody has potential usefulness based on its ability to bind and inactivate TNFα, which has an active role in the formation and persistence of granulomatous inflammation.[92] Adalimumab is currently FDA approved for use in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis and Crohn's disease.[175]

Over the past few years, isolated case reports have emerged documenting the successful use of adalimumab in sarcoidosis, including a patient with ulcerative cutaneous and systemic sarcoidosis who had not improved with hydroxychloroquine or methotrexate, but who responded to adalimumab 40 mg/week for 9 weeks in addition to a baseline dosage of oral prednisone 0.6 mg/kg/day.[176] After treatment, the patient was able to tolerate a reduction

in corticosteroid dose without experiencing a flare of systemic or cutaneous disease. An additional case report documented the improvement of cutaneous sarcoidosis in a patient treated with adalimumab who had been unable to tolerate minocycline and had not responded to corticosteroids (oral, intralesional and potent topical), hydroxychloroquine and pentoxyfylline.[177] Adalimumab was given at a dosage of 40 mg/week for 10 weeks and was given in combination with hydroxychloroquine and pentoxyfylline. Multiorgan sarcoidosis that is resistant to therapy with methotrexate, cyclophosphamide and corticosteroids has also reportedly improved with adalimumab therapy at a dosage of 40 mg every 2 weeks.[178]

Evidence supporting the use of adalimumab in sarcoidosis appears promising, but remains very limited at this time, consisting of only a few isolated case reports. Therefore, the recommended classification for adalimumab is grade D. More data are likely to become available regarding this agent; a randomized placebo-controlled study is underway to investigate the effect of adalimumab in cutaneous sarcoidosis.[179]

Adalimumab may be a more convenient alternative for patients who require treatment with an anti-TNF biological agent because it is injected subcutaneously once weekly or every 2 weeks by the patient at home. Doses vary depending on the condition being treated and there are no set guidelines for sarcoidosis, given the off-label use of adalimumab. Reported experience with adalimumab is currently with dosages of 40 mg/week and 40 mg every 2 weeks. The most commonly reported adverse events include reactions at the injection site and increased susceptibility to infection, although drug-induced lupus has also been reported with use.[180]

As with the other TNFα inhibitors, there are potential risks of the development of lymphoma and serious infections, including reactivation of TB or hepatitis B.[128,175] Patients should have a PPD test prior to initiation of treatment and screening for hepatitis B should be strongly considered. Adalimumab is pregnancy category B.[92]

Table II. Safety of agents in pregnancy and breast feeding (reproduced from Badgwell and Rosen,[21] with permission from Elsevier)

Agent	Pregnancy category	Safety in breast feeding
Topical corticosteroids	C	Unknown
Intralesional corticosteroids	C	Unknown
Systemic corticosteroids	C	Safe
Chloroquine, hydroxychloroquine	C	Safe
Methotrexate	X	Not safe
Pentoxifylline	C	Unknown
Tetracyclines	D	Not safe
Isotretinoin	X	Not safe
Leflunomide	X	Not safe
Thalidomide	X	Not safe
Infliximab	B	Unknown
Chlorambucil	D	Not safe
Melatonin	Unknown	Unknown
Ciclosporin	C	Not safe
Allopurinol	C	Safe
Laser surgery	Unknown[a]	Unknown[a]
Adalimumab	B	Unknown

a Although there is no formal pregnancy categorization for laser therapy, it is thought to be safe in pregnancy because lasers only penetrate a few millimetres of skin.[182]

B = animal studies show no risk or adverse fetal effects, but controlled human first-trimester studies are not available or do not confirm the observations in animals, there is no evidence of second- or third-trimester risk, and fetal harm is possible but unlikely; **C** = animal studies show adverse fetal effect(s) but no controlled human studies, or no animal or human studies are available (weigh possible fetal risk against maternal benefit); **D** = positive evidence of human fetal risk (maternal benefit may outweigh fetal risks in serious or life-threatening situations); **X** = contraindicated because of positive evidence of serious fetal abnormalities in animals, humans or both (fetal risks clearly outweigh maternal benefit).[181]

Table III. Recommendation grade of therapies for cutaneous sarcoidosis

Therapy	Recommendation grade
Corticosteroids	C
Chloroquine, hydroxychloroquine	C
Methotrexate	C
Pentoxifylline	D
Tetracyclines	D
Isotretinoin	D
Leflunomide	D
Thalidomide	D
Infliximab	C
Chlorambucil	D
Melatonin	D
Ciclosporin	D
Allopurinol	D
Laser surgery	D
Adalimumab	D

C = evidence from well conducted case-control studies, open-label clinical trials or retrospective analyses or extrapolated evidence from studies rated as 2+ (see section 2 for details); **D** = evidence from non-analytical studies, such as case reports/series, anecdotal evidence and expert opinion.

5. Pregnancy

The primary demographic group likely to develop sarcoidosis is women of childbearing potential (aged 20–40 years), making the safety of sarcoid treatments in pregnant and breast-feeding women particularly pertinent. This information is summarized in table II.

6. Conclusion

The use of standard therapy in cutaneous sarcoidosis is potentially complicated by a variable clinical response and assorted associated toxicities. Although it is appropriate to begin therapy with one of the generally accepted treatments for sarcoidosis, it may become necessary to attempt therapy with a more innovative, less well accepted modality. Making an evidence-based decision whether to initiate treatment with these latter agents is difficult because adequate controlled trials are lacking. Neither the potential benefits nor the complications of protracted use of these modalities for cutaneous sarcoidosis are fully known. At this point, any recommendation for these novel therapies is based primarily on anecdotal data and small numbers of total patients treated. Nonetheless, the reported success of newer treatments for cutaneous sarcoidosis in selected patients is promising. It should be noted that even the well established treatments for cutaneous sarcoidosis are associated with less than ideal levels of evidence supporting their use in this condition. Table III provides a summary of recommendation grades given to each intervention discussed in this article. Sufficiently powered, randomized, double-blind controlled trials with longitudinal follow-up are sorely needed to help provide solid evidence-based justification for currently accepted clinical standards of care.

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Correspondence: Dr *Ted Rosen*, Department of Dermatology, Baylor College of Medicine, 2815 Plumb Street, Houston, TX 77005, USA.
E-mail: vampireted@aol.com