Introduction

Sarcoidosis was first described by Besnier et al in 1889. It is a multi-systemic disease of unknown etiology characterized by the infiltration of various tissues by non-caseating granulomas. Even if sarcoidosis remains a disease of unknown etiology, the mechanisms underlying granuloma formation are well understood. Sarcoidosis can affect people from any ethnicity and occurs at any time of life although more often in young adults with onset occurring later in females than males. About 70% of cases involve 25- to 40-year-old patients at presentation and a second peak of incidence is observed in women over 50 years old. Its incidence is estimated between 2.3 and 11 per 100000 individuals/year. The estimated prevalence of sarcoidosis is a multi-system disease of unknown etiology characterized by the infiltration of various organs (especially lung and mediastinohilar lymph nodes). In more than half of patients, the disease resolves spontaneously. When indicated, it usually responds to corticosteroids, the first-line treatment, but some patients may not respond or tolerate them. An absence of treatment response is rare and urges for verifying the absence of a diagnosis error, the good adherence of the treatment, the presence of active lesions susceptible to respond since fibrotic lesions are irreversible. That is when second-line treatments, immunosuppressants (methotrexate, leflunomide, azathioprine, mycophenolate mofetil, hydroxychloroquine), should be considered. Methotrexate is the only first-line immunosuppressant validated by a randomized controlled trial. Refractory sarcoidosis is not yet a well-defined condition, but it remains a real challenge for the physicians. Herein, we considered refractory sarcoidosis as a disease in which second-line treatments are not sufficient to achieve satisfying disease control or satisfying corticosteroids tapering. Tumor necrosis alpha inhibitors, third-line treatments, have been validated through randomized controlled trials. There are currently no guidelines or recommendations regarding refractory sarcoidosis. Moreover, criteria defining non-response to treatment need to be clearly specified. The delay to achieve response to organ involvement and drugs also should be defined. In the past ten years, the efficacy of several immunosuppressants beforehand used in other autoimmune or inflammatory diseases was reported in refractory cases series. Among them, anti-CD20 antibodies (rituximab), repository corticotrophin injection, and anti-JAK therapy anti-interleukin-6 receptor monoclonal antibody (tocilizumab) were the main reported. Unfortunately, no clinical trial is available to validate their use in the case of sarcoidosis. Currently, other immunosuppressants such as JAK inhibitors are on trial to assess their efficacy in sarcoidosis. In this review, we propose to summarize the state of the art regarding the use of immunosuppressants and their management in the case of refractory or multidrug-resistant sarcoidosis.

Keywords: refractory sarcoidosis, JAK inhibitors, anti-TNF
varies from 2.17 to 160 cases per 100,000 individuals (this large variability could be explained by the diagnostic tools used to define sarcoidosis in older series, plus the ethnicity of each cohort). Sarcoidosis’ course can be divided into two distinct groups: a time-limited course (two-thirds of patients evolve through a self-remitting disease within 12 to 36 months), and a chronic course (10% to 30% of patients requiring prolonged treatment). Not all sarcoidosis patients require a systemic treatment, which is often reserved for life-threatening organ involvement (advanced pulmonary fibrosis and pulmonary hypertension, central nervous system (CNS), heart, renal sarcoidosis, etc.) or functional threat (severe or defacing skin disease, larynx involvement, and/or posterior uveitis). Functional symptoms and impaired quality of life also represent an indication for treatments. Ethnicity (especially African-American and Afro-Caribbean origins), age above 40 at presentation, lupus perniosis, chronic uveitis, sinonasal and osseous localizations, CNS involvement, cardiac involvement, severe hypercalcemia, nephrocalcinosis, and radiographic stages III and IV have been associated with a poorer prognosis.

Corticosteroids (CS) are the cornerstone of treatment for sarcoidosis but, in some patients, may not result in satisfactory clinical response or else lead to clinical response with unacceptable side effects. In such cases, additional treatments must be considered, either to achieve disease control or CS sparing.

**Pathophysiology of Sarcoidosis and Granuloma Formation**

Granuloma is a defense mechanism of the immune system to contain various antigens. Sarcoidosis is currently considered an exuberant immune response against unknown antigens. Many antigens may trigger granuloma formation (bacteria, fungi, viruses, or nanoparticles). Circulating monocytes recognize a specific antigen which interacts with monocytes pattern recognition receptors (Toll-like receptors (TLR) and especially TLR2 which is known to transduce signals mediated by bacterial lipoproteins) and then differentiate into specific antigen-presenting cells (macrophages or dendritic cells (DCs)). Macrophages then aggregate into epithelioid cells to form immature granuloma. The fusion of monocytes-macrophages generates multinucleated giant cells (MGC) then surrounded by T and B lymphocytes. Th1 lymphocytes (induced under cytokine secretion by MGC and macrophages) generate Th1-specific cytokines (interferon-gamma (IFN-γ), IL-2, tumor necrosis factor-α (TNF-α)), which promote inflammation at granuloma sites and help the granuloma to maintain its structure.

Secretion by DCs of interleukin (IL)-6, IL-23 and IL-12 promotes another type of polarized T cells, which are Th17 cells also promoting inflammation. Of note, a particular type of Th17 cells was found to be relevant in sarcoidosis, a subtype of IFN-γ producing Th17 cells called Th17.1 cells.

Autophagic process disruption could promote granuloma formation. Indeed, several polymorphisms in genes implicated in autophagy were also shown to be linked with sarcoidosis. The lack of clearance of certain antigens may represent one possible explanation for the granulomatous reaction linked to autophagy failure.

A better understanding of granuloma formation pathophysiology may help explain why various treatments, especially antimalarial drugs (which are known to modulate autophagy), targeted therapies such as TNF inhibitors (TNFi) and biodrugs targeting cytokines (tocilizumab (TCZ) against interleukin 6 receptor (IL-6R)) or their pathway (Janus kinase (JAK) inhibitors), can be effective in the course of sarcoidosis.

**What is Refractory Sarcoidosis?**

No consensual definition of refractory sarcoidosis is available in guidelines and medical literature; accordingly, the rate of refractory sarcoidosis patients is unknown.

In the STAT cohort (sarcoidosis treated with TNFi), refractory sarcoidosis was defined as a condition in which second-line immunosuppressants were not sufficient to achieve satisfactory control of the disease. In 2017, Korsten et al defined refractory pulmonary sarcoidosis as a condition in which CS cannot be tapered under the dose of 10 mg/day or was responsible for worrying side-effects. In a prospective trial, Sveiss et al defined refractory pulmonary sarcoidosis as patients with symptomatic sarcoidosis under CS over 10 mg/day or symptomatic sarcoidosis with a CS-sparing agent (CSA). We chose to define refractory sarcoidosis as a situation in which CS and second-line treatment(s) (methotrexate, azathioprine, leflunomide, antimalarials, or mycophenolate mofetil) are not sufficient to achieve clinical remission with a CS dosage under 10 mg/d.

**Is Sarcoidosis Refractory?**

The diagnosis of sarcoidosis is based on an evocative clinico-radiological presentation and evidence of non-caseating granulomas on biopsy specimens after exclusion.
of other granulomatous disorders. The sarcoidosis organ assessment instrument of the World Association of Sarcoidosis and Other Granulomatous Diseases is used to classify the diagnosis of sarcoidosis organ involvement is highly probable, probable, or possible while Bickett et al recently proposed a Sarcoidosis Diagnosis Score to help sarcoidosis diagnostic evaluation. Many diseases or pathological conditions may mimic sarcoidosis (Table 1). Atypical manifestations which may challenge the diagnosis of sarcoidosis are hemoptysis, crackles, digital clubbing, unilateral hilar lymphadenopathy or isolated mediastinal lymphadenopathy without hilar lymph node enlargement, compressive lymphadenopathy, non-lymphatic diffuse lung micronodules, cavitary mass on chest X-ray, and hypogammaglobulinemia. After the initial diagnosis, new organ involvement by sarcoidosis is rare and even more so once the disease remits. Accordingly, such unusual circumstances should question the assertion of sarcoidosis and lead the clinician to verify occupational and environmental exposures susceptible of inducing granulomatosis as well as links to infections (contact with tuberculosis, endemic risk for histoplasmosis or lepra). In such cases, clinicians are encouraged to repeat histologic samples and microbiologic analyses, including standard staining and cultures, as well as 16S-RNA and specific polymerase chain reaction analysis (PCR). Accurate pathological diagnosis is also crucial since neoplastic disorders and especially lymphoma can mimic sarcoidosis.

**Infectious Granulomatosis**

Tuberculosis remains the main differential diagnosis of sarcoidosis but some biological and histological elements can help to distinguish one from the other. Interferon-γ release assays (IGRA) have the same sensitivity as in the general population and are not affected by sarcoidosis activity as opposed to classic tuberculin skin testing (i.e., anergy). Mycobacterium-specific PCR despite its low sensitivity may be useful to differentiate tuberculosis and atypical mycobacterial infections from sarcoidosis. Caseating granuloma is atypical in sarcoidosis. It is evocative but not pathognomonic of tuberculosis. Atypical mycobacteria and histoplasmosis are also classical infectious differential diagnoses. Tropheryma whippelii infection is sometimes mistaken as sarcoidosis since granuloma formation within lymph nodes is not uncommon.

**Other Inflammatory Diseases**

Among inflammatory diseases with granulomatous manifestations, granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) may be differential diagnoses when the lung is involved. In inflammatory bowel diseases and more specifically Crohn’s disease, non-caseating granulomas are also possible features.

**Drug-Induced Granulomatosis**

Drug-induced sarcoid-like reactions (SLRs) are common with IFN therapy (especially interferon alpha), which was known to induce granulomatous reactions with lung involvement in up to 76% of patients with hepatitis C and granulomatosis. Cutaneous granulomas were also noticed in 60% of cases. Drug-induced SLRs have also been described with TNFi and especially with etanercept (ETN). Among new therapies, immune checkpoint inhibitors, such as anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibodies (ipilimumab) and anti-programmed cell death protein 1 (PD1) (nivolumab, pembrolizumab) or anti-PDL1 (ligand) antibodies (atezolizumab, durvalumab, avelumab) may trigger drug-induced SLRs. BRAF and

| Sarcoïdis Subtype | Possible Differential Diagnosis |
|------------------|-------------------------------|
| Mediastino pulmonary sarcoidosis | Tuberculosis and mycobacterial infections, Hodgkin disease and non-Hodgkin’s lymphoma, Histoplasmosis, coccidiodymycosis, aspergillosis, Pneumocionosis: chronic beryllium disease, titanium, aluminium, talc, Hypersensitivity pneumonitis, Drug reactions, Granulomatosis with polyangitis, eosinophilic granulomatosis with polyangiitis |
| Extra thoracic sarcoidosis | Tuberculosis and mycobacterial infections, Whipple disease, bartonellosis, Q fever, brucellosis, syphilis, toxoplasmosis, fungal infections, Hodgkin disease and non-Hodgkin’s lymphoma, Tumor associated sarcoid reaction, Crohn’s disease, primary biliary cirrhosis, Drug induced sarcoidosis (interferon α and β), intravesical BCG therapy, TNFα inhibitors, immune check point inhibitors, Common variable immunodeficiency |

Abbreviations: BCG, Bacillus Calmette et Guérin; TNF, tumor necrosis factor.
MEK inhibitors (dabrafenib, vemurafenib, trametinib, cobimetinib) were also associated with SLRs in 37 patients in medical literature.\textsuperscript{34} SLRs occurring during cancer immunotherapy are generally characterized by paucisymptomatic lung, skin, and mediastinal hilar lymph nodes involvement. The onset of such manifestations varies between 1 and 22 months with a mean time of onset at 6 months after initiation of treatment.\textsuperscript{35,36}

Common Variable Immunodeficiency
Systemic granulomatosis can occur in the course of common variable immunodeficiency (CVID).\textsuperscript{37} Bouvry et al observed several differences in biological and clinical findings comparing CVID related granulomatous disease (CVID-RGD) and sarcoidosis. Patients with CVID-RGD were more likely to present with hepato- and splenomegaly compared to sarcoidosis patients. CVID-RGD patients had also more frequently history of recurrent infections and autoimmune diseases (especially autoimmune cytopenia). CD4/CD8 ratio in bronchoalveolar fluid was slightly more elevated in sarcoidosis than CVID-RGD. Chest computed tomography patterns were also different. Nodules and peribronchovascular micronodules were more frequent in sarcoidosis whereas nodules with halo signs were more frequently seen in CVID-RGD patients. For the clinician, the distinction between sarcoidosis and CVID can be made on the basis of the gammaglobulin levels on electrophoresis.

Neoplastic Disorders
Differentiating malignancies from sarcoidosis is of the utmost importance, since a wrong diagnosis, and the ensuing delay in properly treating the underlying malignancy, especially lymphomas, can be deleterious.\textsuperscript{38} Of note, sarcoidosis may precede, follow, or occur concurrently with a number of cancers, especially lymphomas, thus representing a diagnostic challenge.\textsuperscript{25,36,39} Both cancer and sarcoidosis are 18-fluorodeoxyglucose (18-FDG) avid; therefore 18-FDG positron emission tomography (PET) may be useful in selecting possible biopsy sites (in priority, sites with the greatest 18-FDG uptake), but not in distinguishing between the two entities.\textsuperscript{24} If uncertainty remains, multiple biopsies may be needed to determine whether all FDG-avid sites are involved with sarcoidosis or whether they harbor cancer cells as well.

Poor Treatment Adherence
Only very rare cases of sarcoidosis fail to respond to combined CS and second-line immunosuppressants, a situation which may suggest either poor treatment adherence or, as seen above, another granulomatous disease. Hydroxychloroquine (HCQ) levels as well as azathioprine (AZA) metabolites and mycophenolate mofetil (MMF) concentrations can be easily determined to assess patient adherence. However, currently there are no recommendations regarding therapeutic target values for these drugs in sarcoidosis.

Inherent Immunosuppression
Inherent immunosuppression is a consideration the physician must pay careful attention to when managing active sarcoidosis. Even if this condition is not well understood, several cases of opportunistic infections (cryptococcosis,\textsuperscript{40} progressive multifocal leukoencephalopathy)\textsuperscript{41} have been described in sarcoidosis even in patients with no immunosuppressants and with no human immunodeficiency virus (HIV) coinfection. Of note, several patients in those series had normal CD4 blood levels. Currently, inherent suppression in sarcoidosis is not a well-known condition but serious infectious risk should be considered when treating severe and refractory sarcoidosis to limit the side-effects of immunosuppressants, especially if the latter not strictly necessary.

What are Sarcoidosis First-Line Treatments?
There is no cure for chronic sarcoidosis, and treatment only changes the granulomatous process and its clinical consequences. The general indications for systemic therapy are shown in Table 2. In most cases, sarcoidosis is a self-remitting disease which does not require any treatment. Martusewicz-Boros et al reported only 16% of the patients requiring systemic treatment within a cohort of 1810 sarcoidosis.\textsuperscript{42}

CS remain the cornerstone of sarcoidosis treatment.\textsuperscript{6,7} Their efficacy has been shown in randomized controlled trials, particularly on pulmonary sarcoidosis.\textsuperscript{43} Overall, a response to CS is obtained in 80% to 90% of patients, from a few weeks (3 to 4 weeks in case of lung involvement,\textsuperscript{44} 4 weeks in case of renal involvement)\textsuperscript{15} to 3 months with a complete response often obtained at 6 weeks.\textsuperscript{46} Therefore, CS are the preferred first-line treatment since second-line immunosuppressants offer lower response rates and require more time, often 2 to 6 months for a clinical response. Due to multiple side effects (osteoporosis, weight gain, mood and behavioral changes, irritability, diabetes, infections, etc.), CS should be tapered to the lowest effective
dose as soon as possible since CS must be maintained for at least 1 year. Alternative or additional options to CS are discussed under various circumstances: involvement of specific organs, contraindication for CS, a need for an unacceptably high dose (CS-dependency) and CS-resistant disease. Among the CSA, AZA, methotrexate (MTX), MMF and antimalarial drugs are considered as second-line agents while other immunosuppressive drugs are third-line therapies. The main anti-inflammatory drugs used in sarcoidosis are shown in Table 3.

Efficacy of sarcoidosis treatments must be assessed with objective criteria. Such criteria vary according to the organ involved. In trials, improvement of forced vital capacity (FVC) is the most commonly used criterion to assess respiratory outcomes. A threshold of 10% is generally used to establish lung function improvement. For skin and eye improvement, clinical assessment is generally sufficient to judge treatment efficacy (visual acuity improvement, reduced skin lesions size, reduced steroid use, reduced flares). In cardiac sarcoidosis, left ventricular ejection fraction improvement and suppression or lowering of 18-fluorodeoxyglucose uptake in positron emission tomography help to assess treatment efficacy. In neurosarcoidosis trials, the ePOST or extrapulmonary physician organ severity tool is the most commonly used efficacy assessment tool even if clinical improvement, resolution of gadolinium uptake on magnetic resonance imaging, and improvement in cerebrospinal fluid inflammation are also used and may represent easier ways to ensure correct evaluation of treatment efficacy. In the case of renal sarcoidosis, improvement of serum creatinine levels, and the tapering of CS are the most commonly used criteria for assessing treatment efficacy.

## Corticosteroids

CS are indicated for most organ damage except Lofgren syndrome or asymptomatic lung involvement. Initial treatment for most cases is 20 to 40 mg a day of prednisone equivalent. After 4 weeks of treatment and obtention of a response, steroids must be tapered to 5–10 mg/d for 1–6 months representing the maintenance regimen. This maintenance regimen is continued 1–3 months then tapered off until treatment discontinuation. Judson et al proposed a 6-step scheme for managing of CS in sarcoidosis: 1) initial high dose to control inflammation, 2) maintenance dose to maintain inflammation control and lower toxic CS side effects, 3) continuing maintenance dosage until the decision taper off CS, 4) tapering off CS, 5) observation time to relapse, 6) initiate treatment again in case of relapse. Higher dosages (1 mg/kg/d equivalent prednisone) may be required in cases of CNS involvement due to more frequent relapses at lower CS doses.

In life-threatening situations like severe CNS and heart involvement, or optic neuritis, the use of methylprednisolone pulses are usually weighed but no evidence in the literature supports this effect. A current trend is to start an early treatment with a CSA in order to avoid the occurrence of CS side effects, particularly when the threshold dose for keeping the disease inactive is over 7–10 mg/d of prednisone. Other types of CS administrations were studied in the context of localized sarcoidosis. Local CS may be useful for limited cutaneous involvement as well as anterior uveitis. Subconjunctival injections of dexamethasone, triamcinolone acetate, or betamethasone may be used in case of persistence of uveitis despite topical CS therapy. Posterior sub-tenon and peribulbar injections of triamcinolone acetate permit direct administration of steroids.

### Table 2

| Indications                                                                 | Treatment                                      |
|-----------------------------------------------------------------------------|------------------------------------------------|
| Cardiac, neurologic, kidney sarcoidosis                                      | General corticosteroid therapy                 |
| Ocular sarcoidosis, not responding to topical therapy or bilateral posterior |                                                  |
| uveitis                                                                      |                                                  |
| Severe pulmonary sarcoidosis (intractable cough, dyspnea on exertion)       |                                                  |
| Laryngeal or nasosinusal sarcoidosis                                        |                                                  |
| Severe liver sarcoidosis                                                    |                                                  |
| Incapacitating general symptoms                                             |                                                  |
| Malignant hypercalcemia                                                     |                                                  |
| Progressive deterioration of pulmonary function                             |                                                  |
| Contraindication to corticosteroids                                         | Immunosuppressive drugs (methotrexate > azathioprine) |
| Refractory sarcoidosis (corticosterolna)                                    |                                                  |
| When cortisone-sparing effect is required (prednisone >10 mg/day)           |                                                  |
| Severe cardiac or neurologic sarcoidosis, refractory to corticosteroids     |                                                  |
| Severe sarcoidosis, refractory to other treatments                          | Anti-TNF-α (infliximab or adalimumab)          |

Abbreviation: TNF-α, tumor necrosis factor-α.
### Table 3 Main Anti-Inflammatory Drugs in Sarcoidosis

| Drugs            | Line n° | Efficacy Evidence | Usual Dose                  | Main Contra Indications or Limitations                                                                 | Main Adverse Effects                                                                 | Comments                                                                                         |
|------------------|---------|-------------------|-----------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Corticosteroids  | 1       | Very high         | Up to 40 mg/d initially and 5 to 10 mg/d in maintenance therapy    | Unstable psychiatric disorders, infection, unstable cardiomyopathy, unstable diabetes, severe osteoporosis | Weight gain, osteoporosis, diabetes, infections, hypertension                            | Rapid onset of efficacy but multiple adverse events if prolonged treatment                         |
| Methotrexate     | 2       | High              | 10 to 25 mg weekly (subcutaneous injections or oral intake)         | Chronic kidney failure, hepatic failure, infection, pregnancy, important alterations in lung function tests (especially FVC) due to risk of MTX induced pneumopathy | Leucopenia, anemia, thrombopenia, digestive disorders, infections, renal impairment, abnormal liver tests, drug induced pneumonia | Preferred 2nd line treatment, contraception needed                                                 |
| Leflunomide      | 2       | Low/few data      | 20 mg/d                     | Planned pregnancy, hypertension, liver and renal failure                                                | Digestive disorders, skin carcinoma, liver and blood cell toxicity                      | Well tolerated, contraception needed                                                              |
| Azathioprine     | 2       | High              | 2-3 mg/kg/d                 | Use of allopurinol, TPMT polymorphism                                                                  | Digestive disorders, skin carcinoma, liver and blood cell toxicity                      | Available during pregnancy, measurement of drug metabolites in blood available                   |
| Mycophenolate mofetil | 2       | Very low/few data | 2–3 g/d                     | Planned pregnancy, infections                                                                         | Digestive disorders, neoplasia/lymphoma, skin carcinoma                                | Contraception needed, few available data                                                          |
| Cyclophosphamide | 2       | Low/few data      | 750 mg/m2 IV pulse (oral form must be abandoned because of high rates of hematological malignancies) | Planned pregnancy, cytopenia, infections                                                                | Cytopenia, severe infections (pneumocystosis), hemorrhagic cystitis, bladder neoplasia    | Contraception needed, infertility risk (gametocytes preservation)                                |
| Aminoquinolines  | 2       | Low               | 200–400 mg/d                | Macula impairment, QT interval elongation                                                              | Digestive disturbance, retinal impairment, cardiac impairment (rare but severe)         | When urgent response is not needed. Possible for arthritis and skin involvement. Useful in hypercalcemia |
| Thalidomide      | 2       | Very low          | 50–200 mg/d + thromboprophylaxis                                     | Planned pregnancy                                                                                        | Teratogenicity, peripheral neuropathy, deep vein thrombosis                               | Dubious efficacy, severe complications, not recommended                                           |

(Continued)
Alternatively, intravitreal injections of steroids can be suggested to treat unilateral macular edema or when it resists systemic therapy and periocular injections. Inhaled CS are not effective on lung disease but may help in reducing or stopping cough when there is no indication for a general treatment.
Second-Line Treatment (i.e., CS-Sparing Agents)

Corticosteroid resistance in sarcoidosis is unusual (except for neurosarcoidosis). CS-dependency is more common and a Delphi consensus study concluded that a maintenance dose regimen of over 10 mg of prednisone equivalent a day is unacceptable. If the clinician fears CS side effects or if the maintenance dose of CS is unacceptable, CSA must be discussed.

Methotrexate

Among CSA options, MTX is the only one to have been assessed in a randomized controlled trial. This randomized controlled trial is the only one concerning the use of MTX in the case of pulmonary sarcoidosis. MTX remains the preferred second-line CSA in sarcoidosis. In 1995, Lower et al showed a benefit with MTX therapy both in symptomatic pulmonary and extra-pulmonary sarcoidosis: 66% of the treated patients (33/50) experienced disease improvement. In 17 remaining patients, total elimination of CS was possible, and among them, 6 individuals had no relapse. However, particular attention should be paid to the risk of hepatotoxicity, especially in patients with initially abnormal liver tests. The most frequently used weekly dose is 10–15 mg (or 0.3 mg/kg/week). In the case of oral administration failure or intolerance in rheumatoid arthritis patients, a switch to subcutaneous administration may lead to better tolerance and efficacy outcomes, especially in extreme-range body mass index patients. Of note, concomitant folic acid administration may prevent gastrointestinal and hepatic side effects.

Antimalarial Drugs

Hydroxychloroquine and chloroquine (CQ) may be useful in non-life-threatening organ involvement (symptomatic persistent pulmonary sarcoidosis) such as mild hypercalcemia, moderate cutaneous sarcoidosis, and mild cranial neuropathies.)

Sarcoidosis-related joint involvement may also improve under treatment. The advantage of antimalarial drug use is based on its excellent safety profile (especially for HCQ). Nevertheless, some rare but severe complications may occur such as anti-malarial myopathy or cardiomyopathy and antimalarial maculopathy. Among the two available anti-malarial drugs, HCQ is the one with the lowest retinal toxicity.

Azathioprine

AZA is a prodrug converted in vivo into its active metabolite, 6-mercaptopurine. Its immunosuppressive effects are linked to cytotoxicity against T lymphocytes. There is currently no prospective clinical trial on the effectiveness of AZA in the case of sarcoidosis. In a large nonrandomized retrospective comparative study evaluating AZA and MTX in thoracic sarcoidosis, a similar corticosteroid-sparing benefit was observed with a similar gain in vital capacity, 1 second forced expiratory volume, and carbon monoxide diffusing capacity (DLCO). Adverse events may also be very similar except for infections which might be more frequent with AZA. In cases of refractory sarcoidosis treated with AZA, dosage of metabolite blood level dosages can be performed in order to rule out lack of adherence. However, no data regarding target ranges of blood metabolites are available in the literature for sarcoidosis.

Leflunomide

Leflunomide is an immunomodulating agent active via its metabolite (A771726) for selective dihydroorotate dehydrogenase inhibition. Only a limited number of patients with sarcoidosis have been investigated in two open studies and reported cases. In a retrospective study, potential beneficial effects on skin, eyes, and lung sarcoidosis were observed when given at 20 mg/day, but with a mild response as to lung involvement. Leflunomide has been shown to be effective in refractory sarcoid uveitis, either alone or in combination with MTX.

Mycophenolate Mofetil

MMF is a prodrug of mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase (IMDH). Scant data regarding the efficacy of MMF in sarcoidosis are available in the medical literature. Reported experiences mainly concern extrapulmonary sarcoidosis (e.g., neurologic, cutaneous, and ophthalmologic involvement). Data obtained in neurologic sarcoidosis with CNS involvement do not suggest any advantage of MMF over MTX. Benefits of MMF therapy rely on rapid onset of action and limited toxicity in hematological and infectious complications. The usual dose range varies from 2 to 3 g a day in maintenance therapy (Table 3).

Third-Line Treatments

If disease activity is not controlled through CS at an acceptable dose and CSA, a third-line treatment should be considered.
The induction protocol often includes and other disabling sarcoidosis-related in a multicentric retrospective series. However, treatment in another controlled trial, among have been proposed as a third-line option. Where one randomized clinical trial on ETN reported no improvement in refractory ocular sarcoidosis, several studies on infliximab (IFX) showed efficacy in refractory sarcoidosis. In a randomized trial on IFX in pulmonary sarcoidosis, Baughman et al reported a modest but significant improvement of pulmonary vital capacity at 24 weeks. Nevertheless, the pulmonary function test improvement canceled out during the subsequent 24-week washout. Furthermore, in the post-hoc analysis of this trial, IFX was also effective in extrapulmonary sarcoidosis. Judson et al observed the same results in a trial dedicated to extrapulmonary sarcoidosis assessing its activity via the ePOST scoring system, a scoring system assessing 17 organs and the severity of their involvement on a scale from 0 (not affected) to 6 (severely affected). In another controlled trial, among chronic active pulmonary sarcoidosis patients, Rossman et al found no significant difference between the IFX group and the placebo group although the study was underpowered and failed to reach its target number of enrolled patients. The improvement in FVC in the IFX group of this study was higher than in any other study on IFX.

The STAT study, reporting on 132 sarcoidosis patients treated with TNFi (IFX in 91% of cases) in a large French nationwide multicentric retrospective study, found that TNF antagonists were efficient in about two-thirds of the patients and permitted a substantial reduction in prednisone dosages (from 23 to 11 mg/day). The efficacy of adalimumab (ADA) has been reported in a randomized controlled clinical trial of 16 patients with skin sarcoidosis (ADA, n=10 vs placebo, n=6) and in a prospective case series of 26 patients with refractory sarcoid uveitis, and other disabling sarcoidosis-related symptoms such as dyspnea.

Finally, in a recent systematic review of the efficacy and safety of TNFi in sarcoidosis from inception to November 2017, Adler et al looked at non-randomized studies of cutaneous, ocular, neurologic, and multisystemic sarcoidosis and reported an improvement in 89%, 69%, 77%, and 71% of cases, respectively. Schimmelpennink et al recently reported in a retrospective study of 29 patients that the IFX biosimilar (i.e., Inflectra®) appears to be effective in the treatment of refractory sarcoidosis with a profile comparable to the reference.

In contrast to randomized controlled trials versus placebo, in retrospective and open-labeled studies TNFi had more overall and serious adverse events and more severe infections. These adverse events seemed to be more frequent during sarcoidosis treatment than during other inflammatory diseases.

The use of high-dose TNFi has been reported to adversely affect the clinical condition of patients with moderate-to-severe chronic heart failure. In a multicentric retrospective series of 20 patients with definite cardiac sarcoidosis refractory to CS plus immunosuppressive therapy, TNFi showed a complete/partial response in 75% of patients, with a significant CS-sparing effect. Harper et al described another retrospective series of 36 patients with cardiac sarcoidosis refractory to conventional CS therapy. Twenty-four patients out of 36 (67%) were categorized as responders, meaning they had at least an improvement on CS dose, ejection fraction, or dysrhythmia burden. Steroid dose, dysrhythmia control, and ejection fraction were improved, respectively, in 20, 12, and 8 patients among responders.

Overall, current data suggest the efficacy of IFX in pulmonary, cutaneous, ocular, and multisystemic sarcoidosis and of ADA in cutaneous and ocular sarcoidosis. To date, no available data support the use of other TNFi, such as golimumab in sarcoidosis.

The recommended IFX dosage is usually 5 mg/kg intravenously but 3 mg/kg may be enough to treat lung involvement. The induction protocol often includes intravenous administration at weeks 0, 2, and 6. Then, a four-week maintenance interval may be recommended in sarcoidosis in view of establishing better responses and fewer flares. For ADA, a weekly administration using low doses is preferred, with a loading dosage of 80 to 120 mg.
at week 0, and at least 40 mg at weeks 1 and 2. Then, maintenance therapy is based on 40 mg every other week.

Some studies evidenced frequent relapses when treatment lasted only 4 to 8 months. Thus, before considering withdrawal, the duration of TNFi treatment should be 6 to 12 months after obtention of the clinical response. Before discontinuing IFX or ADA, the treatment should be gradually spaced apart. In 2014, Vorselaars et al showed that patients who experienced high levels of soluble IL-2 receptor (≥4000 pg/mL) and high mediastinal standardized uptake value (SUV) (≥6.0) on initial FDG-PET-CT before initiation of IFX therapy had a higher risk of disease relapse after IFX discontinuation.

Primary and secondary non-responders to TNFi should be distinguished. Primary TNFi failure may necessitate a change in therapeutic class. Secondary failure occurring in the course of TNFi therapy should raise an alert about patient treatment adherence or immunization against TNFi. Recommendations incite the clinician to prescribe a TNFi in combination with another anti-inflammatory drug (either MTX, AZA, or CS).

As shown in patients with rheumatoid arthritis (RA) and inflammatory bowel diseases, serum assays with bio drug titers and TNFi antibodies can be performed before concluding to failure in patients receiving TNFi. The use of low-dose MTX might increase TNFi efficacy with re-increased IFX or ADA serum levels linked to antidrug antibody elimination. Moreover, one TNFi can be changed to another in cases of lack of response and immunization, if TNFi blood levels are in the normal range. In non-immunized patients with low drug concentrations, reducing the intervals between two injections should be considered.

Fourth-Line Agents
We proposed defining refractory sarcoidosis here as a situation in which CS and second-line treatment are not sufficient to achieve clinical remission with a CS dosage under 10 mg/day. Among the 132 patients from the Sarcoidosis Treated with Anti TNF (STAT) registry, we recently reported on nine who were considered to be TNFi non-responders. Among them, seven experienced a clinical response (complete or partial) with additional immunosuppressive therapy which had previously been used in all but one case. The disease only progressed in 2 patients CS treated with no adjunctive immunosuppressants.

Recently, new therapeutic approaches have been proposed in refractory sarcoidosis with targeted synthetic drugs, such as JAK inhibitors, or biologics, such as rituximab (RTX) and tocilizumab (TCZ), and additional trials are currently underway (Table 4). Other immunosuppressive agents targeting the NFκb pathway have been assessed in sarcoi disease including ciclosporin and mammalian target of rapamycin (mTOR) inhibitors.

Rituximab
B-cells were suspected of participating in the pathophysiology of sarcoidosis since hypergammaglobulinemia and B cell accumulation in granuloma are frequently observed. In 2012, Saussine et al found that patients with an active chronic form of sarcoidosis had significantly fewer circulating memory B cells, more transitional B cells, and increased number of IL-10 producing B-cells. Thus, B-cell targeting therapies could theoretically be efficient in sarcoidosis. RTX is a monoclonal chimeric antibody targeting CD20, which is preferentially expressed on B cells.

In 2014, Sweiss et al conducted a Phase I/II open-label clinical trial to assess the safety and tolerance of RTX in 10 patients with pulmonary sarcoidosis. Unfortunately, the efficacy of RTX was inconstant on objective criteria regarding pulmonary involvement. About half the patient improved their forced vital capacity while only 3 patients out of 10 improved their 6-minute walk test. The two major adverse events which occurred during the study were deaths linked to sarcoidosis progression.

Apart from this study, medical literature evidence on the use of RTX in sarcoidosis concerns case reports establishing response for some patients with refractory pulmonary, CNS, eye, or heart manifestations. Severe infections may represent a limit to the use of rituximab although no large series are available on sarcoidosis, so this risk is presupposed on the basis of rheumatoid arthritis trials.

Tocilizumab
As previously described, sarcoidosis is a granulomatous disease with a Th1, Th17 and Th17.1 cytokine signature associated with high levels of interleukin-6 (IL-6) in active sarcoidosis.

Few cases in the medical literature report the use of antiIL-6 or IL-6R agents in sarcoidosis. In 2012, Awano et al reported a case of Castleman’s disease occurring in the case of chronic sarcoidosis which dramatically improved upon TCZ, a recombinant, humanized, anti-human IL-6 receptor monoclonal antibody. In 2017, Semiz et al described an association of adult-onset Still’s disease and sarcoidosis and both diseases dramatically improved under TCZ.
| Indication                                      | Molecule on Trial                                                                 | Measured Outcomes                                                                 | Phase | NCT                  | Control          | Advancement         |
|------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------|----------------------|------------------|---------------------|
| Cardiac sarcoidosis (CHASM-CS-RCT)            | Methotrexate + prednisone: Methotrexate 15–20 mg orally, SC, or IM once a week for 6 months + prednisone 20 mg daily for one month then 10 mg po daily for one month then 5 mg daily for one month and then stop. Also, Folic Acid 2 mg daily for 6 months. | Summed perfusion rest score (SPRS) on FDG-PET scan, mortality, cardiovascular hospitalization | 3     | NCT03593759          | Prednisone        | Recruiting          |
| Cardiac sarcoidosis                           | Anakinra (100 mg subcutaneous each day for 4 weeks) (MAGIC ART)                    | Change in c-reactive protein in participant plasma samples, change in cardiac PET, change on cardiac MRI, number of serious cardiac events | 2     | NCT04017936          | Placebo          | Not yet recruiting  |
| Chronic pulmonary sarcoidosis                 | Tranilast (0.1 g each time, three times a day, 12 months)                         | Changes in the size of the pulmonary nodule by ultrasound, changes of the forced vital capacity (FVC) | 1     | NCT03528070          | ND               | Not yet recruiting  |
| Chronic pulmonary sarcoidosis with fibrosis   | Roliumilast                                                                       | Reduction in number of episodes of acute exacerbation, change in FVC, change in quality of life | 4     | NCT01830959          | Placebo          | Unknown status      |
| Pulmonary sarcoidosis                          | Azithromycin (250 mg/d 3 months)                                                  | 24h cough monitoring with ambulatory cough monitor will be performed at baseline and at 1mth and 3 months post treatment | 2     | NCT04020380          | ND               | Not yet recruiting  |
| Progressive fibrotic pulmonary sarcoidosis    | Pirfenidone 267 mg 3/d                                                           | Change in FVC and Time until clinical worsening                                  | 4     | NCT03260556          | Placebo          | Recruiting          |
| Pulmonary sarcoidosis                          | Canakinumab (300 mg subcutaneous each month for 6 months)                         | Change between baseline and week 24 in pulmonary function as measured by spirometry | 2     | NCT02888080          | Placebo          | Completed/not available |
| Corticosteroid pulmonary sarcoidosis          | Tofacitinib 5 mg twice a day                                                      | 50% reduction in corticosteroid requirement in at least 60% of subjects          | 1     | NCT03793439          | ND               | Recruiting          |
| Pulmonary sarcoidosis (HySSAS)                | Hydroxychloroquine + prednisone (Hydroxychloroquine per os 200 mg/die (or adjusted for body weight if less than 61 kg), twice/day + prednisone 0.15 mg/ kg per os daily, once/day for 3 months, than for further 6 months between responders). | The primary efficacy measure is the per-subject overall success rate at the 3-month visit | 3     | NCT02200146          | Prednisone        | completed without results posted |
| Chronic pulmonary sarcoidosis (ACPS)          | Acthar Gel (ACTH) 80 or 40 units ACTHAR gel will be given twice a week for 22 weeks after initial loading | Cumulative toxicity between two arms of study over 24 weeks of study This will be assessed using a steroid toxicity questionnaire | 4     | NCT02188017          | ND               | Unknown status      |
| Chronic pulmonary sarcoidosis                 | Acthar Gel (ACTH) 80 units weekly                                                | Assessment of sarcoidosis treatment score                                         | 4     | NCT03320070          | Placebo          | Recruiting          |

(Continued)
| Indication                                      | Molecule on Trial                                                                 | Measured Outcomes                                                                 | Phase | NCT                     | Control | Advancement      |
|------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------|-------------------------|---------|------------------|
| Cutaneous sarcoidosis                          | Tofacitinib 5 mg twice a day                                                       | Change in Cutaneous Sarcoidosis Activity and Morphology Instrument                | ND    | NCT03910543            | ND      | Recruiting       |
| Cutaneous sarcoidosis                          | Acthar Gel (ACTH) 40 or 80 units twice weekly (phase 2/phase 3)                    | The change in SASI induration & erythema score                                    | 3     | NCT02348905            | ND      | Unknown status   |
| Central nervous system sarcoidosis             | Acthar Gel (ACTH) Injection, 80 U daily for 10 days, then 80 U twice weekly for up to a total of 48 weeks on therapy | Proportion of patients with clinically significant improvement - successful glucocorticoid tapering | 4     | NCT02920710            | ND      | Recruiting       |
| Central nervous system sarcoidosis             | Acthar Gel (ACTH) 80 IU subcutaneously daily for 10 days then followed by 80 IU subcutaneously three times per week through Month 12 | On MRI: change in total number of lesions and in the number and size of enhancing lesions 1, 3, 6 months and 12 months relative to baseline | 4     | NCT02298491            | ND      | Completed        |
| Sarcoidosis and uveitis (any active uveitis)   | Acthar Gel (ACTH) 80 U daily for 10 days, then 80 U twice weekly for up to a total of 24 weeks on therapy | Proportion of patients with clinically significant improvement in visual acuity   | ND    | NCT02725177            | ND      | Recruiting       |
| Sarcoidosis and uveitis                        | Acthar Gel (ACTH) 40 units twice weekly injections in patients who have sarcoid uveitis | Degree of aqueous and vitreous inflammatory cells - change is being assessed by SUN score (Standardization of uveitis nomenclature) | ND    | NCT03473964            | ND      | Recruiting       |
| Sarcoidosis hypercalcemia                      | Acthar Gel (ACTH) 80 units twice a week for 12 week                               | Reduction of 24-hour urine calcium                                                | 3     | NCT02155803            | ND      | Unknown status   |
| Corticosteroid dependent sarcoidosis          | Sarilumab (200 mg subcutaneous every two weeks)                                   | flare-free survival of sarilumab-treated patients compared to placebo-treated controls | 2     | NCT04008069            | Placebo | Not yet recruiting |
| Severe extrathoracic sarcoidosis (induction protocol with infliximab) EFRITES trial | Infliximab (Experimental: INFLIXIMAB 5 mg/kg D1-D15, then infliximab every 4 weeks W6-W10-W14/Placebo: placebo injection D1-D15 then infliximab 5 mg/kg W6-W8-W12-W16-W20) | Percentage of patients [Time Frame: week 6] who have a severity assessment score (ePOST score) inferior to 1 in all organs and absence of hypercalcemia at W6, whatever the corticosteroid dosage received | 3     | NCT03704610            | Placebo | Not yet recruiting |
| Efficacy of remission-induction regimen (cyclophosphamide versus infliximab) for severe extrathoracic sarcoidosis | Infliximab 5 mg/kg D1-D15 and every 6 weeks, in association with low dose methotrexate (10 mg/week) Corticosteroids tapering regimen until 0.1 mg/kg/day | evaluate the efficacy of infliximab and cyclophosphamide to induce remission in sarcoidosis with extrathoracic localization and serious organ involvement or relapse with at least one first-line immunosuppressive drug | ND    | Eudra CT 2015-002442-31 | IV CYC  | Recruiting      |

**Abbreviations:** ACTH, adrenocorticotrophin hormone; D, day; ePOST, extrapulmonary physician organ severity tool; FDG PET scan, fluoro-deoxy-glucose positron emission tomography; FVC, forced vital capacity; IV CYC, intravenous cyclophosphamide; MRI, magnetic resonance imaging; ND, no data; W, week.
| Organ Involvement | When to Treat | First-Line Treatment | When to Use Second-Line Treatment | Second-Line Treatment | Third Line | Fourth Line | References |
|------------------|---------------|----------------------|-----------------------------------|-----------------------|------------|-------------|------------|
| Lung sarcoidosis | Stage II or III with worsening respiratory symptoms, worsening of functional impairment (FVC < 65%, DLCO < 60%), progression of parenchymal abnormalities on CT (honeycombing, excavations, . . .), endobronchial stenosis, active stage IV | Corticosteroids 20–40 mg/d for at least 4 weeks then tapering to 5–10 mg/d (maintenance regimen) on 1–6 months. Maintain 5–10 mg/d for 1–3 months then slow tapering depending on clinical benefit | Increasing symptoms despite CS, or issues with CS tapering (if CS cannot be lowered under 10 mg/d). The clinician needs to be sure that parenchymal lesions are due to active disease (using PET-CT) | MTX 15 mg/d or more, AZA 1–2 mg/kg/d, LFN 20 mg/d | TNFi: IFN 3–5 mg/kg (IV) week 0, 2, 6 then each 4–8 weeks/ADA 40 mg (SC) each 14d, or each 7d if severe | Consider CYC, MMF, RTX, TCZ, JAKi, clinical trials | 18,161,162 |
| Sarcoïdosis arthritis | Impaired quality of life, proven arthritis | Corticosteroids 20–40 mg/d for at least 4 weeks then tapering to 5–10 mg/d (maintenance regimen) on 1–6 months. Maintain 5–10 mg/d for 1–3 months then slow tapering depending on clinical benefit | Increasing symptoms despite CS, or issues with CS tapering (if CS cannot be lowered under 10 mg/d). | HCQ, MTX, AZA, LFN | TNFi | Switch biologic (TCZ, RTX) or JAKi or clinical trial | 163 |
| Heart sarcoidosis | Proven cardiac sarcoidosis (PET CT, MRI + extracardiac granuloma or cardiac granuloma alone) | Corticosteroids max 30 mg/d and consider association with MTX in first line | Progression on MRI or PET-CT | MTX | TNFi (prefer IFX) | CYC, IVMP | 82,164,165 |

(Continued)
| Organ Involvement | When to Treat | First-Line Treatment | When to Use Second-Line Treatment | Second-Line Treatment | Third Line | Fourth Line | References |
|-------------------|---------------|---------------------|-----------------------------------|-----------------------|------------|-------------|------------|
| Eye involvement   | Anterior uveitis | Topical steroids + cycloplegics | Persistent uveitis or recurrent flares | Consider peri or intraocular CS | ND | ND |          |
|                   | Unilateral intermediate or posterior uveitis without complications | Consider peri or intraocular CS | Persistent uveitis | (± IVMP) + systemic CS 1 mg/kg/d for 3 to 6 weeks | If CS > 7 mg/d or unacceptable CS side effects, consider MTX or AZA | TNFi, MMF or LFN. If failure, consider RTX, TCZ or clinical trial | 49,62,166,167 |
|                   | Severe intermediate or posterior uveitis with ON or ME or ORV or both eye involvement | (± IVMP) + systemic CS 1 mg/kg/d for 3 to 6 weeks | CS > 7 mg/d or unacceptable side effects of CS | MTX or AZA | TNF, MMF or LFN | If failure, consider TCZ or JAKi |
| Skin involvement  | Lupus pernio   | Localized cutaneous sarcoidosis | Extended cutaneous disease or esthetic/functional threatening skin sarcoidosis | | | |          |
|                   | Intraleisonal triamcinolone, DXC, HCQ, TNFi, TLD | Non-severe lesions | Severe lesions (thick, major extension, inflammatory) | First line | Second line | Third line | 48,129,130,145,150,168,169 |
|                   | Topical CS can be used. If systemic treatment needed, prefer HCQ, DXC, MTX, TLD. If refractory, TNFi or JAKi may be used | Topical treatments (dermocorticoids, topical tacrolimus, topical retinoids) | Intraleisonal triamcinolone (thick plaques), laser, dynamic phototherapy | Consider systemic therapy (prefer HCQ, DXC, MTX, TDM) | Consider other drugs before IS: systemic CS, pentoxifylline, apremilast, acitretin | Consider TNFi. JAKi may be considered |
| Nasopharyngeal involvement | Disturbing symptoms, cartilage perforation, ... | Local CS can be used but systemic CS are often needed | Refractory disease or unacceptable side effects or contra indication to CS | Consider HCQ, MTX, AZA | Consider TNFi | Other IS (CYC), clinical trials, ... | 170 |
Recently, Sharp et al reported four patients with multi-drug-resistant sarcoidosis treated with TCZ (one case of pulmonary sarcoidosis, one of cutaneous sarcoidosis, one of sarcoidosis with arthritis and fatigue, and one of upper respiratory tract involvement). Three patients were treated with TCZ infusion and one patient was treated with subcutaneous TCZ. One patient developed breast cancer under TCZ.

In ocular involvement, TCZ may be helpful in patient with uveitis refractory to TNFi. In 2016, Silpa-Archa et al reported improvement of inflammatory ocular disease in a case series of 17 patients. Among the 17 patients, one had ocular multidrug-resistant sarcoidosis, which improved under TCZ therapy with no major side effects. TCZ is also known to be effective in refractory inflammatory cystoid macular edema (CME) no matter its etiology.

Currently, few data support the use of TCZ in sarcoidosis. Preliminary data indicate that anti-IL-6 therapy could be an interesting therapeutic approach to treat multi-drug-resistant sarcoidosis, but further studies must be carried out.

Paradoxically, new-onset sarcoidosis during TCZ treatment has been described in four case-reports. In three cases, there was what was presumed to be TCZ-induced sarcoidosis, observed during treatment for RA, at least 1 year after the start of the treatment. Del Giorno et al recently reported TCZ-induced sarcoidosis in a 74-year-old woman treated for giant cell arteritis, which occurred 8 months after TCZ initiation. In all these cases, there was skin involvement, associated with bilateral hilar lymphadenopathy in 3 patients. No clinical trial is underway to evaluate TCZ in this indication.

**JAK Inhibitors**

There are currently three JAK inhibitors approved by the FDA (Food and Drug Administration) and EMA (European Medicines Agency): ruxolitinib for the treatment of myeloproliferative disorders, tofacitinib in RA, psoriasis and ulcerative colitis, and baricitinib which is indicated for the treatment of RA.

Sarcoidosis pathophysiology involves several cytokines, such as IL12/23, IL-17, IL-6, and IFNγ, which signal through the JAK-STAT pathway. In a transcriptomic analysis, Rosenbaum et al showed that the STAT1 pathway is activated in granulomatous diseases.

On Medline, 6 case reports are available. Among those patients, two were treated for concomitant polycythemia vera. Those 2 patients experienced improvement.

### Abbreviations:

- AUA: azathioprine
- AZA: azathioprine
- CS: corticosteroids
- CT: computed tomography
- CYC: cyclophosphamide
- DLCO: diffusing capacity of the lung for carbon monoxide
- DXC: doxycycline
- FVC: forced vital capacity
- HCQ: hydroxychloroquine
- IFX: infliximab
- IS: immunosuppressants
- IV: intravenous
- IVMP: intravenous methylprednisolone pulse
- JAKi: Janus kinase inhibitor
- LFN: leflunomide
- MMF: mycophenolate mofetil
- MRI: magnetic resonance imaging
- MTX: methotrexate
- NT: not tested
- PET: positron emission tomography
- PSL: prednisone
- SC: subcutaneous
- TCZ: tocilizumab
- TLD: thalidomide
- TNFi: tumor necrosis factor-alpha inhibitor.
of lung involvement under ruxolitinib. Levraut et al recently reported a case of sarcoid-like systemic granulomatosis refractory to MTX, TNFi, anakinra, antimalarial drugs, AZA, MMF, and CYC that improved under ruxolitinib. Damsky et al reported a case of refractory cutaneous sarcoidosis previously unsuccessfully treated with topical steroids, hydroxychloroquine, MTX, tacrolimus, ADA, and apremilast. Once switched to tofacitinib, the patient improved her CSAMI score (Cutaneous Sarcoidosis Activity and Morphology Instrument). For skin biopsy samples, phosphoSTAT1 (Signal Transducer and Activators of Transcription) and phosphoSTAT3 immunostaining was done. During tofacitinib treatment, the entire phosphoSTAT1 and -3 staining vanished. During the treatment, downregulation of the mRNA of the JAK/STAT pathway (such as IL-6 and IFN-γ) was shown on skin samples, during the treatment.

There are currently two trials recruiting for evaluating tofacitinib in sarcoidosis. NCT03793439 is a Phase 1 trial, which will evaluate the CS-sparing effect of tofacitinib in pulmonary sarcoidosis. NCT03910543 is an open-label trial assessing the efficacy of tofacitinib in granuloma annulare and cutaneous sarcoidosis.

Safety data are reassuring since severe adverse events with JAK inhibitors are rarely reported. An increased incidence of herpes zoster infection was noticed in RA trials. The FDA recently alerted on the increased risk of thromboembolic events under tofacitinib at higher dosages. Given the good safety profile of JAK inhibitors, they could represent an interesting alternative for refractory sarcoidosis in case of TNFi failure or contraindication. Further studies and randomized clinical trials are still needed to confirm this.

**Ciclosporin A**

Ciclosporin A (CisA) is an immunosuppressive agent targeting calcineurin, first used in organ transplants. Few data are available concerning the use of CisA in sarcoidosis. One randomized clinical trial was conducted in 1997 by Wyser et al to assess the efficacy of CisA in pulmonary sarcoidosis. Unfortunately, there were significantly more serious adverse events in the CisA group versus placebo (especially serum creatinine elevation). No statistically significant improvement was noted in the CisA group versus placebo. Bogabathina et al reported on a case of severe and refractory cardiac involvement that improved after CisA administration. Regarding T-cell involvement and potential efficacy of mTOR inhibition, CisA may theoretically be useful in sarcoidosis, although too little data are currently available to support its use.

**mTOR Inhibitors**

Some data are available on mTOR activity in sarcoidosis. Recently, Calender et al showed that mTOR signaling and autophagy signaling are overexpressed in sarcoidosis. This was consistent with previously published data in mice.

In 2011, Manzia et al described a case of a liver transplant recipient with sarcoid-like granulomatosis which improved on introduction of rapamycin after CisA failure.

SAVE 1 and -2 studies were, respectively, phases I and II clinical trials assessing the safety and efficacy of intravitreal or subconjunctival sirolimus, administered either at 440 µg monthly or 880 µg every 2 months in patients with non-infectious uveitis. In those studies, the proportion of ocular sarcoidosis represented, respectively, 27% and 1% of the population. This treatment was well tolerated in both clinical trials. In SAVE 2, the 440-µg dosage seemed to be more efficient than 880-µg dosage. Both dosages were able to achieve vitreal haze resolution. The SAKURA study was a Phase III clinical trial reporting on the efficacy of intravitreal sirolimus for non-infectious uveitis. Twenty-nine patients out of 347 (8.4%) were treated for ocular sarcoidosis. Unfortunately, there are no available data for the sarcoidosis subgroup.

Further investigations must be carried out before recommending mTOR inhibition in sarcoidosis even though available data are encouraging.

**IL-1 Blockade Therapy**

No case reports are available concerning the use of IL-1 blockade therapy. On the contrary, cases of sarcoid-like side reactions are reported. Despite that, a Phase 2 clinical trial is ongoing to assess safety and efficacy of anakinra in adult cardiac sarcoidosis (ARAMIS trial NCT03018834). The MAGiC-ART trial (NCT04017936) is also an ongoing phase 2 study evaluating the IL-1 blockade in treating cardiac sarcoidosis.

**Thalidomide**

Thalidomide is an immunomodulating agent that is known to reduce IFN-γ secretion and enhances IL-4 and IL-5 production, thus optimizing a Th1 to Th2 switch. This drug is usually prescribed for cutaneous sarcoidosis. In 2014, Droitcourt et al showed in a randomized controlled trial (RCT) that thalidomide was not superior to placebo in treating cutaneous sarcoidosis, to the contrary of
a previous trial published in 2012. Some authors reported improved cutaneous and mucosal involvement under thalidomide. Available data are still not sufficient to recommend using thalidomide in treating sarcoidosis even though case reports may be encouraging. New molecules similar to thalidomide, such as lenalidomide, may represent a well-tolerated alternative to thalidomide.

Apremilast
Apremilast is a specific phosphodiesterase 4 (PDE4) inhibitor. This specificity allows higher dosages with fewer side effects than pentoxifylline, a non-specific PDE4 inhibitor (cf infra). In 2012, Baughman et al described the efficacy of apremilast in treating chronic cutaneous sarcoidosis. Among the 15 patients treated with apremilast at 20 mg twice daily, 14 patients had improved induration scores after 4 and 12 weeks. Three months after apremilast discontinuation, 3 patients underwent a cutaneous relapse: the increase in CS dosage only moderately improved cutaneous induration.

Except for this publication, there are no case reports available today for recommending its use in sarcoidosis even if its safety profile may be of interest.

Ustekinumab
Ustekinumab is a human monoclonal antibody targeting the IL-12/23 pair. In a randomized double-blinded and controlled versus placebo trial in 2014, Judson et al showed that ustekinumab was neither associated with improved respiratory function tests nor improved organ involvement in the 60 patients studied.

Abatacept
Abatacept is a fusion protein of CTLA4 (cytotoxic T-lymphocyte-associated protein 4) and immunoglobulin known as CTLA4-Ig. The mechanism of action is based on the downregulation of T lymphocyte-induced immune response by CTLA4.

Currently, there are no studies or case reports on abatacept use in sarcoidosis. A clinical trial (NCT00739960) was conducted to assess abatacept efficacy versus placebo but its results have not been published since its completion date.

Other Treatments and Adjunctive Therapies
Repository Corticotropin Injections
Except for CS, repository corticotropin injections (RCI; or ACTHAR® gel) are the only treatment approved by the US FDA for “sarcoidosis” indication whereas this therapeutic option is not used in Europe. RCI seems to represent a good alternative to CS in case of CS-resistant disease or CS side effects, but until recently, there were only a few retrospective studies supporting its use in sarcoidosis. Very recently Chopra et al published a large retrospective case series of 302 patients treated with RCI. A total of 288 (95%) patients improved their status at 3 months according to physicians' evaluations. A total of 116 (38%) improved lung function and reduction or discontinuation of CS was possible in 32% of the patients. At present, there is no completed prospective studies confirming its use in sarcoidosis even though such trials are underway (Table 4).

Pentoxifylline
Pentoxifylline is a non-specific phosphodiesterase 4 inhibitor used to reduce pro-inflammatory cytokine secretion, such as TNF-α. In 1997, Zabel et al treated 23 patients with pentoxifylline. Among them, 11 patients improved their lung function test. Three patients with CS-resistant disease were able to decrease their daily prednisone intake. In 2009, Park et al showed that adverse events of pentoxifylline at doses used to correctly treat thoracic sarcoidosis may limit its benefits. Pentoxifylline may possibly be useful in sarcoidosis-induced fatigue.

Antimycobacterial Therapy
In 2013, Drake et al showed in a phase 1 single masked study that oral concomitant antimycobacterial therapy (AMBT) with levofoxacin, ethambutol, azithromycin, and rifampicin in a population of 30 patients with chronic cutaneous sarcoidosis lesions resulted in a mean decrease in lesion diameter of −8.4 mm compared to an increase of 0.07 mm in the placebo group (p = 0.05) thereby suggesting objective efficacy for AMBT in chronic cutaneous sarcoidosis. In 2014, the same authors conducted a phase Ib clinical trial assessing the efficacy of specific AMBT in pulmonary sarcoidosis. Through it, AMBT was associated with significant improvement of FVC and an increase for the 6-minute walk test. These data, beyond the interesting pathophysiological considerations they highlight, need to be confirmed in larger trials.

Antifibrotic Agents
Pirfenidone and nintedanib are the two available and approved drugs for treating idiopathic pulmonary fibrosis when lung transplantation is contraindicated. There is no data in available medical literature recommending those
of nintedanib on various interstitial lung diseases-associated pulmonary fibrosis (including sarcoidosis) has demonstrated benefits on FVC decline. Of note, a clinical trial assessing the efficacy of pirfenidone in progressive fibrotic sarcoidosis is currently underway (NCT03260556).

**Adjunctive Therapies**

In addition to symptomatic treatment (e.g., antiepileptics, antiarrhythmics, prostacyclin for pulmonary hypertension, ursodeoxycholic acid for hepatic sarcoidosis, etc.), adjunctive therapy can be used in refractory sarcoidosis for specific localizations. Cardiac transplantation should be considered for patients with severe intractable heart failure refractory to medical therapy. In neurosarcoidosis, there have been rare reports of radiation therapy for CNS sarcoidosis but always in the context of other treatment failures.

Beyond objective clinical symptoms, fatigue and parasympathetic manifestations such as sarcoid myopathy or neuropathy can represent a therapeutic challenge. Nasopharyngeal obstruction and thus sleep apnea may increase fatigue. In most cases, anti-inflammatory drugs are ineffective. Other molecules (dexamethasone, methylphenidate, armodafinil) can be useful. Small fiber neuropathy (SFN) may be a major concern for the patients and the clinicians in terms of pain management and quality of life. Several case series reported the efficacy of intravenous immunoglobulins (IVIg) in SFN. IVIg were also reported to be effective in other manifestations such as sarcoid myopathy or neuropathy.

**Conclusion**

Refractory sarcoidosis and multidrug-resistant sarcoidosis are challenging conditions with no clear guidelines available. Even if no clear definition of refractory sarcoidosis can be found in medical literature, we chose to define it as a disease which does not respond to CS and conventional immunosuppressants. We considered this definition to fit the best with a situation many clinicians are facing. Checking for a differential diagnosis, assessing adherence, and testing for anti-drug antibodies should be done systematically before classifying patients as non-responders. At present, TNFi are the most commonly used immunosuppressants in severe or refractory sarcoidosis. Multidrug-refractory sarcoidosis should be referred to a clinician accustomed to refractory sarcoidosis management. In this context, switching from a TNFi to another or re-treating with a previously used immunosuppressant can sometimes be useful. New therapeutic approaches are on the horizon. Among them, JAK inhibitors appear promising although few clinical trials are currently carried out on this therapeutic approach to sarcoidosis. New tools to predict response and adverse events are required so as to optimize the risk/benefit ratio in a more personalized type of medicine.

**Disclosure**

Dr Yvan Jamilloux reports personal fees from Sobi, outside the submitted work. Professor Pascal Sève reports personal fees from Abbvie, Chugai, Pfizer, and Sobi, during the conduct of the study. The authors report no other conflicts of interest in this work.

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