Paradigmenwechsel in der Sarkoidosebehandlung weg von oralen Kortikosteroiden (OCS):

WASOG OCS-Erklärung zum Umgang mit Sarkoidose

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Hauptpunkte:

- Orale Cortikosteroide (OCS) sind die am häufigsten verschriebene Behandlungsmethode bei Sarkoidose.
- Eine OCS-Toxizität kann schnell auftreten, und die akuten Nebenwirkungen können sich kumulativ auswirken und bereits bei Prednisondosen von <5 mg täglich auftreten.
- Ziel des Umgangs mit Cortison bei Sarkoidose ist die Minimierung und der vollständige Verzicht auf orale Cortikosteroide.
- Dies kann durch eine kluge Abwägung der besten anfänglichen und nachfolgenden Behandlungsoptionen erreicht werden.

Einführung

Seit den 1950er Jahren warden, trotz der Verfügbarkeit von OCS-sparenden Alternativen, etwa 90 % der symptomatischen Patienten zunächst mit Prednison oder anderen OCS behandelt.(1, 2) Die Komplikationen der oralen Cortikosteroidtherapie (OCS) sind gut bekannt und umfassen sowohl akute Nebenwirkungen wie Diabetes, Gewichtszunahme, Bluthochdruck, Schlaf- und Stimmungsstörungen, Veränderungen der Körperkonstitution, Glaukom und Infektionen, als auch langfristige Toxizitäten wie Osteoporose, Osteonekrose und ein erhöhtes Risiko für Herz-Kreislauf-Erkrankungen.(3, 4) Viele Patienten bleiben jedoch jahrelang auf der täglichen Einnahme von Prednison in niedriger Dosis (<5 mg) sitzen, ohne dass nennenswerte Versuche unternommen werden, die Behandlung zu minimieren oder abzubrechen.

Im Frühherbst 2024 wurde das Team für den rationalen Einsatz oraler Cortikosteroide (OCS) bei Sarkoidose gegründet. Dieses Team setzte sich aus internationalen Experten verschiedener Fachrichtungen der Sarkoidosebehandlung, sowie Patienten und Patientenvertretern zusammen. Den Vorsitz führten Elyse Lower und Elliott Crouser. Zu den weiteren Mitgliedern gehörten Robert Baughman, Daniel Culver, Marc Judson, Catherine Bonham, Alicia Gerke, Jan Grutters, Chris Knoet, Filippo Martone, Katja Schillhorn, John Stone, Athol Wells und Andrea Wilson.

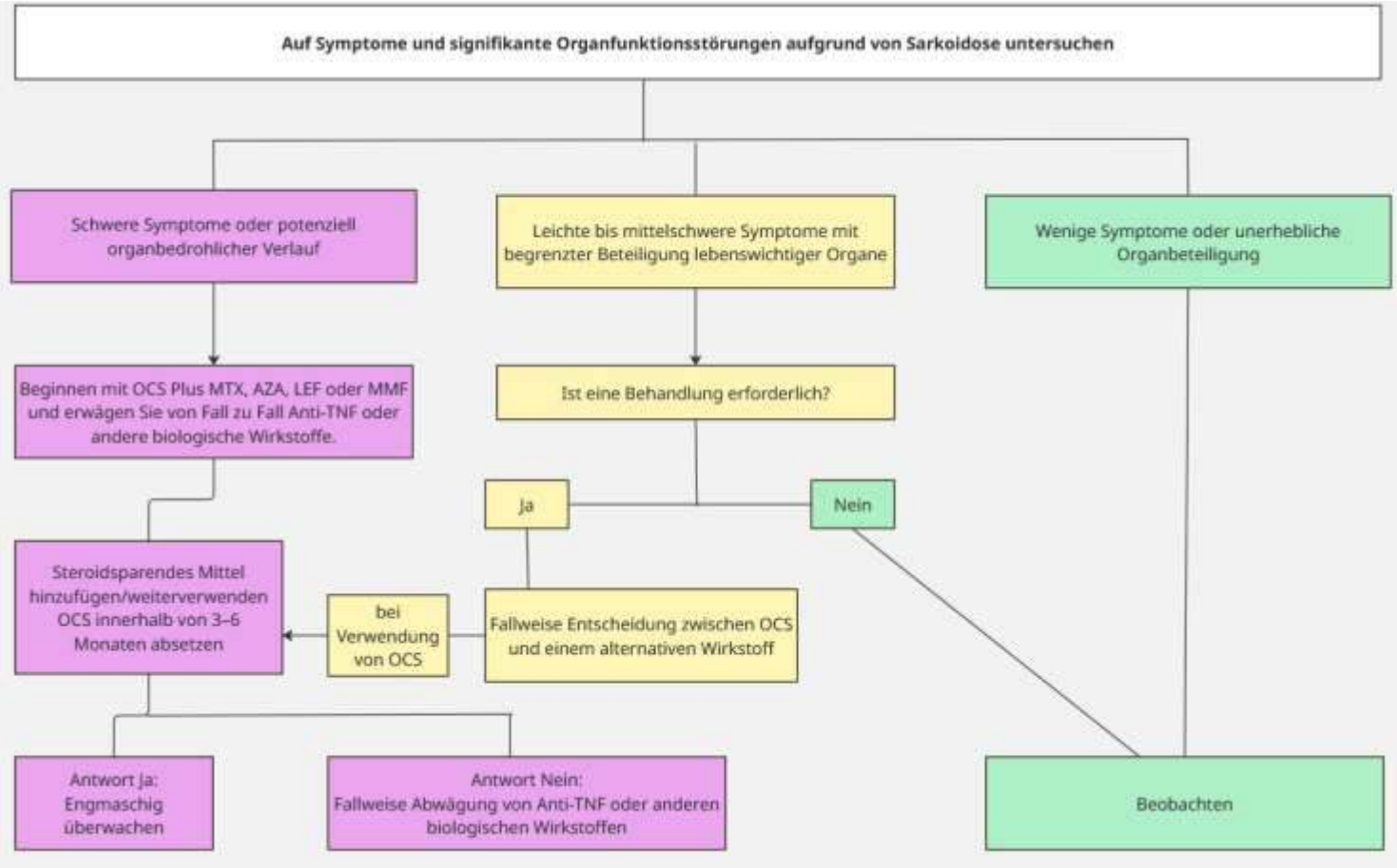
Die Herausforderung für einen verantwortungsvollen Umgang mit OCS basierte auf zwei Aussagen: Der eingeschränkte Einsatz von OCS sollte eher als Brücke zu weniger toxischen Therapien dienen, als als Eckpfeiler der Sarkoidosetherapie und Methotrexat kann bei einigen therapienaiven Patienten mit pulmonaler Sarkoidose eine Alternative zu OCS als Ersttherapie darstellen.

Das übergeordnete Ziel bestand darin, die Überdosierung und Überbehandlung bei der OCS-Therapie von Sarkoidose einzudämmen. Dies kann durch eine aggressive Reduzierung der OCS-Dosis mit dem Ziel einer vollständigen Absetzung, die Behandlung einiger Patienten mit anfänglich

steroidfreien Therapien und die Identifizierung von Symptomen wie Müdigkeit und Small-Fiber-Neuropathie erreicht werden, die wahrscheinlich nicht auf OCS ansprechen (5).

Eine OCS-Toxizität kann sehr früh oder sehr spät im Behandlungsverlauf auftreten. Bereits wenige Stunden nach der ersten OCS-Gabe können Patienten einen Anstieg des Blutzuckerspiegels und des Blutdrucks, sowie Stimmungs- und Schlafstörungen erleben. Das Infektionsrisiko steigt innerhalb weniger Tage nach Beginn der OCS-Gabe deutlich an und dieses Problem kann selbst bei sehr niedrigen täglichen Prednison-Dosen auftreten. Nach Wochen bis Monaten der Behandlung können Gewichtszunahme, Hautveränderungen, Knochenschwund und gastrointestinale Beschwerden auftreten. Leider kann eine jahrelange Therapie, selbst bei niedriger täglicher Prednison-Dosis, zu Osteoporose, Osteonekrose und einem erhöhten Risiko für kardiovaskuläre Ereignisse führen.

Die WASOG-Leitlinie zum Umgang mit oralen Kortikosteroiden (OCS) bei Sarkoidose beinhaltet einen algorithmischen Behandlungsansatz, der auf dem Schweregrad der Erkrankung und den Symptomen basiert (Abbildung 1). Der Gesamtansatz konzentriert sich auf die Minimierung, Vermeidung und das Absetzen von OCS sowie auf die Aufklärung der Patienten.



Ein vorgeschlagener Ansatz zur Behandlung der Sarkoidose. Adaptiert nach Wells et al.(5)

Minimalisierung: Wenn eine initiale orale Kortikosteroidtherapie zur raschen Linderung organbedrohender oder schwerwiegender Symptome der gesundheitsbezogenen Lebensqualität

erforderlich ist, sollten diese Medikamente vorsichtig in niedriger Dosierung und über einen kurzen Zeitraum verschrieben werden. (6) Steroidsparende Medikamente wie Methotrexat, Azathioprin, Leflunomid oder Mycophenolat sollten frühzeitig in Betracht gezogen werden, um die Steroiddosis zu reduzieren. Methotrexat ist das einzige Medikament mit qualitativ hochwertiger Evidenz in der Sarkoidosetherapie. (7) Biologika können ebenfalls eine sinnvolle Ergänzung darstellen, wobei Infliximab der einzige Wirkstoff mit qualitativ hochwertigen Belegen in der Sarkoidose-Behandlung ist. (8)

Einstellung: Bei Patienten, die länger als zwei bis sechs Wochen orale Kortikosteroide (OCS) benötigen, ist eine schrittweise Dosisreduktion mit dem Ziel der vollständigen Absetzung der OCS anzustreben. Dies kann mehrere Reduktionsversuche im Laufe der Zeit und eine enge Absprache zwischen Patient und Arzt erfordern.

Vermeidung: Bei Patienten mit leichten bis mittelschweren Symptomen und begrenzter Beteiligung lebenswichtiger Organe kann die Erkrankung mit topischen Therapien wie Steroidcremes oder lokalen Steroidinjektionen behandelt werden. Auch Methotrexat kann als initiale Therapieoption in Betracht gezogen werden. In einer aktuellen Studie zu pulmonaler Sarkoidose verlief die Linderung der Symptome und die Verbesserung der Lungenfunktion unter Methotrexat langsamer als unter Prednison; die Gesamtansprechraten unterschieden sich jedoch nicht zwischen den beiden Behandlungsregimen. (9)

Für die Zukunft: Es ist von entscheidender Bedeutung, sowohl Patienten als auch medizinisches Fachpersonal über den verantwortungsvollen Umgang mit oralen Kortikosteroiden zu informieren. Ein kürzlich veröffentlichtes Patienteninformationsblatt unterstützt die in dieser Publikation enthaltenen Konzepte. (5)

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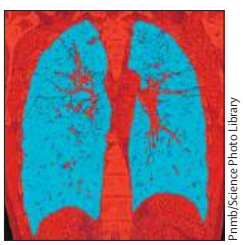
Towards a new treatment era in sarcoidosis



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Athol U Wells and colleagues make an important and timely argument in their Position Paper:[1] it is time to reconsider the central role of oral corticosteroids in sarcoidosis management. For clinicians who manage immune-mediated diseases in other specialities, this moment feels familiar. We have seen what happens when long-term steroid use becomes routine—the gradual accumulation of toxicity and the quiet acceptance of dependency. The time has come for sarcoidosis to move beyond that model.

Many chronic immune-mediated diseases have already undergone this transformation away from a dependency on corticosteroids. The traditional treatment pyramid, starting with steroids and adding disease-modifying agents only after failure has largely been replaced by early, targeted intervention. This shift was driven by the recognition that chronic low-dose steroid use is not benign and that early introduction of steroid-sparing agents improves long-term outcomes, a point that Wells and colleagues articulate with clarity.

However, there are challenges facing sarcoidosis that differ from other immune-mediated diseases such as rheumatoid arthritis or Crohn's disease. Sarcoidosis is distinct in that up to half of cases resolve spontaneously,[2] complicating decisions about the early initiation of steroid-sparing agents. Yet holding back from treatment risks missing a window of benefit for those with potentially progressive disease, a difficulty heightened by the absence of reliable biomarkers to identify such patients. Further complicating this picture is the scarcity of evidence on which treatments should be used. Despite motivation to move from steroid-centred management towards a model built on mechanism and precision, evidence for what these treatments should include remains sparse.

Modern immunology offers an extraordinary range of therapeutic options. Biological and targeted synthetic agents have transformed the management of immune-mediated disease: they are safe, effective, and far more precise than the corticosteroids they replace. Although cost considerations have restricted access to some agents, these therapies have already redefined what is possible.

The real challenge is disease specificity. Inflammation is not a single process. Different cytokine pathways drive different diseases.[3] IL-6 inhibition improved outcomes in rheumatoid arthritis yet proved ineffective in psoriasis and inflammatory bowel disease, whereas IL-23 inhibition improves outcomes in psoriasis and inflammatory bowel disease but is ineffective in rheumatoid arthritis. For sarcoidosis, the key question is which immune pathways are central to pathogenesis and therefore therapeutically targetable. Increasingly, attention has turned to the myeloid compartment, macrophages, and dendritic cells that orchestrate granuloma formation and sustain chronic inflammation. The concept of a myeloid reset, in which these cells are reprogrammed or replaced to restore immune homoeostasis, whether through cellular depletion, metabolic reprogramming, or phenotypic switching, might ultimately prove to be as important as targeting individual cytokines.

An increasing number of clinical studies are shaping the therapeutic landscape, although the signal remains fragmented.[4] Identifying the dominant biological mechanisms and matching them to effective therapies, must be the next step.

The results from two major sarcoidosis trials, neither of which met their primary endpoints, have been disappointing but nonetheless informative.[5-7] These outcomes might simply reflect suboptimal selection of therapeutic targets. However, an alternative explanation deserves consideration: are trials focusing on the wrong outcome measures? Forced vital capacity is notoriously insensitive to change in established disease, as it primarily reflects fixed fibrosis rather than active inflammation,[8] although it can be more responsive earlier in the disease course.[9] Patient-reported outcomes offer valuable insight into lived experience but fail to capture disease activity, inflammation, or tissue damage. Steroid-sparing endpoints are confounded by variation in practice and clinician preference. The absence of standardised tapering protocols and subjective definitions of acceptable disease control complicate interpretation, and small dose adjustments at the lower end can have disproportionate biological effects, making results difficult to compare across patients.

Progress in the treatment landscapes of other diseases has often followed the development of robust outcome

measures. In vasculitis, validated composite indices, such as the Birmingham Vasculitis Activity Score,[10] have transformed trial design and comparability, enabling rapid therapeutic progress. Sarcoidosis urgently needs an equivalent framework.

Future trials must be grounded in outcome measures that capture the true clinical and biological spectrum of sarcoidosis. A dedicated task force has made important progress towards the goal of improving outcome measures for sarcoidosis, outlining key principles for trial design and publishing recommendations for pulmonary and cardiac disease-specific endpoints.[10] Although these recommendations represent substantial advances, an ideal endpoint should reflect the disease's heterogeneity, potentially within a composite index, recognising that almost any organ can be involved. They must distinguish active inflammation from irreversible fibrosis; predict meaningful outcomes such as survival, organ function, and quality of life; show sensitivity to change; and meet regulatory standards to support licensing and clinical adoption. Until such measures are established, promising therapies risk being evaluated against endpoints that cannot capture their true effect.

Wells and colleagues should be commended for framing this shift so clearly. Reducing corticosteroid reliance is not an aspiration, it is a clinical imperative. Yet meaningful progress will depend on more than substituting drugs. It will require collaboration across disciplines, agreement on what constitutes disease activity, and validation of measures that can guide both clinical care and regulatory approval.

The experience of other immune-mediated diseases shows that such transformation is possible, sarcoidosis now has the same opportunity. This Position Paper provides both the rationale and the momentum. The task is to convert recognition into coordinated action and, in doing so, usher in a new era of precision medicine in sarcoidosis care.

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A paradigm shift in corticosteroid therapy for sarcoidosis: a World Association of Sarcoidosis and Other Granulomatous Disorders Position Paper, endorsed by the Americas Association of Sarcoidosis and Other Granulomatous Disorders

Athol U Wells, Elyse E Lower*, Robert P Baughman, Daniel A Culver, Marc A Judson, Catherine A Bonham, Alicia K Gerke, Jan C Grutters, Chris Knoet, Filippo Martone, Katja Schillhorn, John H Stone, Andrea B Wilson, Elliott D Crouser*

For over seven decades, oral corticosteroids have been the cornerstone of sarcoidosis management. Oral corticosteroids suppress sarcoidosis inflammation rapidly, but long-term oral corticosteroids result in toxicity and some patients are unable to taper oral corticosteroids without experiencing disease flare ups. The routine use of oral corticosteroids as first-line therapy, as recommended in sarcoidosis guidelines, could have unintentionally promoted the long-term use of oral corticosteroids. We believe that oral corticosteroids should no longer be considered as first-line therapy in all patients with sarcoidosis requiring treatment. Furthermore, we view long-term use of oral corticosteroids in sarcoidosis as an undesirable outcome. When initial oral corticosteroids are required, we propose that oral corticosteroids be used as bridging therapy, ideally for no longer than 3–4 months. There is an urgent need to address the widespread use of long-term maintenance therapy with oral corticosteroids in patients with sarcoidosis, and we advocate the systematic withdrawal of steroid therapy with replacement, if necessary, by other immunosuppressive agents.

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Introduction

Sarcoidosis is an enigmatic disease with major uncertainties pertaining to cause, pathophysiology, and optimal therapy. Since the 1950s, oral corticosteroids have been used as first-line therapy for virtually all sarcoidosis phenotypes.[1] However, despite the availability of oral corticosteroid-sparing alternatives, up to 90% of symptomatic patients are prescribed prednisone or other oral corticosteroids as initial therapy[2] and many patients remain on oral corticosteroids for years.[3] In many cases, minimal tapering of the steroid dose is attempted.[4] Unfortunately, most of those patients, including those maintained on low-dose therapy, experience both short-term side-effects and long-term toxicities, some of which are insidious.[5–8] Mortality can be twice as high in patients with sarcoidosis treated with oral corticosteroids than in untreated patients with sarcoidosis.[9] The medical community has long known that oral corticosteroid therapy is associated with comorbidities such as diabetes, glaucoma, hypertension, changes in body habitus, sleep disturbance, and moodiness. The cumulative toxicity of prolonged low-dose maintenance therapy includes reduced quality of life, worsening cardiac disease, increased risk of osteoporotic fractures, the precipitation of hypertension and diabetes, and increased rates of acute and chronic infections.

We emphasise that this Position Paper should be seen strictly as a position statement addressing the widespread overuse of oral corticosteroids in the management of sarcoidosis. Our primary intention is to alert those managing sarcoidosis to the toxicity of oral corticosteroids, including low-dose oral corticosteroids (which are often erroneously viewed as a safe long-term treatment approach), which is an increasing and crucial issue for patients, funders, and the medical community. We also provide detail on the optimal approach to oral corticosteroid withdrawal to support an immediate strategy of oral corticosteroid minimisation. However, this Position Paper is not a guideline, covering all aspects of sarcoidosis management, although we hope that it will serve as a bridge to guideline updates, following prospective evaluation of both existing steroid-sparing agents and novel therapies in the context of systematic oral corticosteroid minimisation. At present, we advocate that existing approaches to the use of steroid-sparing

Key messages

- The over-use of oral corticosteroids in the short-term and long-term management of sarcoidosis should be viewed as a crisis
- The concept of safe low-dose oral corticosteroids in the long term has now been definitively discredited
- Initial oral corticosteroids continue to be required when there is severe major organ involvement or when severe symptoms require rapid alleviation, but a second agent should be introduced, ideally at initial treatment, to minimise oral corticosteroid usage
- In other scenarios requiring treatment, alternatives to oral corticosteroids should be considered
- In patients on long-term oral corticosteroids, immediate steroid withdrawal is a pivotal goal with replacement by an alternative agent if necessary

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agents, which are widely applied in current clinical practice and detailed in the guideline on the management of sarcoidosis,[1] should now be applied much more proactively to oral corticosteroid minimisation. This Position Paper is a combination of a narrative review, expert opinion, and crucial input from patient-group leaders, although informed by the formal literature review of oral corticosteroids usage, undertaken in the 2021 guidelines.[1]

Current steroid-sparing agents include methotrexate, azathioprine, leflunomide, mycophenolate, hydroxychloroquine, biological drugs (including tumour necrosis factor [TNF] inhibitors), and other emerging agents.[1,10] Strategies to minimise oral corticosteroid usage have reduced steroid-associated complications in other inflammatory diseases. For example, oral corticosteroids usage has been systematically downgraded in the treatment of connective tissue disease-related interstitial lung disease.[11]

First-line therapy with oral corticosteroids remains highly appropriate in some patients with sarcoidosis. Granulomatous inflammation responds more quickly to corticosteroids than to other agents,[12,13] and high-dose corticosteroid therapy remains essential for the initial treatment of sarcoidosis crises affecting the eyes, heart, and brain. Compared with biological agents, oral corticosteroids are inexpensive and readily available. Oral corticosteroids have been widely evaluated in observational studies and clinical trials and represent both the past and current foundational comparator in clinical trials of novel agents.[14] For these reasons, the 2021 multinational treatment guidelines recommend oral corticosteroids as initial therapy.[1]

Widespread concerns about major steroid-associated comorbidities strongly suggest a restricted use of oral corticosteroids as a bridge to other less toxic treatments, rather than as the cornerstone of long-term sarcoidosis therapy. A pivotal study supports that the use of methotrexate can be an alternative to oral corticosteroids as initial therapy in some treatment-naive patients with pulmonary sarcoidosis.[15] However, the initial methotrexate dosing and tapering strategies and the choice of steroid-sparing agent have not been standardised.[1] Other therapies, less studied than methotrexate, are widely used, especially when there is intolerance to methotrexate. Furthermore, from our combined experience as clinicians and patient-group leaders, we have found that, in many cases, oral corticosteroids can be withdrawn or their use minimised without recourse to alternative treatments.

The goal of our multispecialty steroid stewardship team is to curb excesses in both the dose and duration of oral corticosteroid treatment for sarcoidosis. Achieving these goals will require aggressive tapering of oral corticosteroids with the goal of complete withdrawal, treatment of some patients with steroid-free regimens from the outset, and identifying para-sarcoidosis symptoms, such as fatigue and small fibre neuropathy, that usually do not respond to oral corticosteroids.[1,16,17] These aims apply equally to the possible use of oral corticosteroid-free initial therapy and to minimising oral corticosteroids usage, both initially and in the longer term.

Rationale for oral corticosteroid and steroid-sparing usage in sarcoidosis

Existing guidelines recommend usage of oral corticosteroids only for disease manifestations that are associated with risk of major morbidity or mortality or that compromise health-related quality of life (HRQoL).[1,14] These agents have a rapid onset of action and low cost, unlike other immune modulating treatments.[18] Both oral corticosteroids and corticotrophin were developed many decades ago as treatment for autoimmune and immune-mediated diseases, including sarcoidosis.[19,12] The long-term risks of oral corticosteroids were not fully appreciated until years later, and new data continue to emerge indicating that even low long-term doses of 5 mg/day prednisone are potentially toxic.[20]

There is low to moderate quality evidence that oral corticosteroids can produce short-term improvements in chest imaging and pulmonary function in patients with non-fibrotic pulmonary sarcoidosis. The European Respiratory Society (ERS) Clinical Practice Guidelines identified six clinical trials for pulmonary sarcoidosis that show that oral corticosteroids improved lung manifestations and lower risk of deterioration during short-term follow-up.[1] Long-term functional and radiographic improvement was found to be minimal, despite 12–18 months of steroid therapy[21,22] A high relapse rate after oral corticosteroid discontinuation has also been reported.[8,13,14] These data suggest that oral corticosteroids suppress sarcoidosis but do not hasten resolution of underlying disease activity. To sustain clinical improvement with oral corticosteroids alone, many patients with sarcoidosis require long-term therapy, which is associated with major potential toxicity.[3]

Many alternative drugs to oral corticosteroids that have been prescribed for sarcoidosis were used originally in chronic autoimmune diseases, such as rheumatoid arthritis. Unlike higher doses of methotrexate, which are cytolytic (eg, used as chemotherapy), low-dose methotrexate suppresses inflammation through the production of adenosine as a consequence of inhibition of the folinic acid pathway, and adenosine inhibits many inflammatory and immune reactions.[16] Methotrexate is steroid sparing in sarcoidosis[6,23,24] and is an alternative for some patients as first-line therapy.[15,25]

A minority of patients are intolerant of methotrexate due to severe leukopenia, liver toxicity, or impaired clearance of its biologically active metabolites in acute or chronic renal disease.[17] Therefore, routine renal and haematological monitoring is recommended.[26] Based on several retrospective studies, azathioprine, leflunomide, and mycophenolate mofetil, have been recommended.[1]

These agents could be equivalent to methotrexate as steroid-sparing agents,[27–32] although no final conclusions can be drawn on their relative efficacy and toxicity in the absence of prospective data. However, azathioprine and mycophenolate mofetil are associated with a higher risk of serious infections.[27,33] Hydroxychloroquine, an antimalarial drug, can be effective for mild skin disease, hypercalcaemia, or arthralgias attributed to sarcoidosis,[34–36] but studies to date have not found it generally useful for pulmonary sarcoidosis.[36,37] Despite previous negative clinical trials, hydroxychloroquine is being studied in two new clinical trials, QUIDOSE (NCT05247554) and CAESAR (NCT05841758).

For patients who are unable to reduce oral corticosteroids with steroid-sparing drugs, biological agents have been recommended.[1] The monoclonal anti-TNF antibody, infliximab, was effective for treating pulmonary sarcoidosis in two double blind, placebo-controlled trials.[38,39] Several studies have reported the effectiveness of anti-TNF monoclonal antibody therapy for advanced pulmonary and extra-pulmonary disease.[40–43] Similar to oral corticosteroids, there is a high relapse rate with anti-TNF monoclonal antibody therapy discontinuation.[44,45] A substantial proportion of patients with sarcoidosis treated with infliximab or adalimumab eventually discontinue treatment due to adverse events or contraindications, such as cancer or serious infections.[40,46,47]

The ERS guidelines recommend that other agents be considered on a case-by-case basis. Rituximab has been reported effective for refractory sarcoidosis.[46,48,49] The JAK inhibitors have been successfully used for sarcoidosis, especially cutaneous disease.[50,51] Since 1952, repository corticotropin injections for treatment of sarcoidosis has been approved only in the USA. The risk of corticosteroid side-effects from repository corticotropin injection therapy is currently unknown.

Morbidity and mortality rates

Despite the widespread use of prednisone and other agents, the mortality rate in patients with sarcoidosis is higher than in the general population.[52] Furthermore, the sarcoidosis-specific mortality rate in the USA, Canada, Japan, South Korea, and England has increased over the past 30 years.[53–57] In the USA and Europe, this increase is due to respiratory failure, whereas in Japan, cardiac involvement is the leading cause,[58,59] with increasing detection a likely contributor for all regions. The age-adjusted mortality rate is 12 times higher in Black patients with sarcoidosis compared with white patients with sarcoidosis, and the rise in death rate and overall number of deaths are highest in Black women.[53,60–62] Hispanic patients with sarcoidosis tend to have lower mortality than patients of other races and ethnicities.[63] Compared with other demographics, Black patients with sarcoidosis die younger.[60] In the Black Women's Health Study from the USA, the death rate was 2·44 times higher in Black women with sarcoidosis compared with Black women without sarcoidosis, and 25% of these deaths were directly related to sarcoidosis.[64] Socioeconomic and geographical factors are also associated with worse outcomes.[65–69] In one study, lower incomes, an absence of insurance, and self-reported African American ethnicity were associated with increased sarcoidosis comorbidities.[66] These findings might partly be due to barriers to care but are also likely to reflect differences in treatment practice or susceptibility to comorbid conditions.[68]

Data from the USA have shown that hospitalisation rates and the associated morbidity of patients with sarcoidosis are increasing.[61,65] However, the rate of sarcoidosis as the primary admission diagnosis remains unchanged, which might reflect increased complications and co-morbid conditions.[44,65] These trends are most prominent in Black people, females, and older individuals.[61,67] Furthermore, a population study identified oral corticosteroid usage as an independent predictive factor for sarcoidosis-associated hospitalisation[61] and a large Canadian population-based cohort study found that all-cause hospitalisation in patients with both active and chronic sarcoidosis was associated with prednisone use.[70] It is unclear if these associations are the result of continued oral corticosteroid treatment being associated with more advanced disease or are related to the development of serious oral corticosteroid-related comorbidities and adverse events.

In one study, regardless of disease stage, oral corticosteroid usage was associated with higher mortality rates in referral centres compared with non-referral centres.[71] Aggressive oral corticosteroid prescribing by sarcoidosis specialists might be a contributing factor, however the reasons for this need further study.[28] In a survey of 14 global sarcoidosis referral centres, 1022 of 1445 (71%) of patients had received prednisone or other oral corticosteroids.[2] In addition, Black patients are treated with higher doses of oral corticosteroids and for longer time periods than other patient groups receiving oral corticosteroids,[5,72,73] which might partly account for increased morbidity in this group.

Both sarcoidosis and oral corticosteroid treatment is associated with many comorbidities. It is important to realise that these adverse events and complications could be a consequence of either the disease or the oral corticosteroid treatment. For example, the disease associated sequelae pulmonary fibrosis and pulmonary hypertension are strong predictors of mortality.[74–75] In contrast, obstructive sleep apnoea is more prevalent in patients with sarcoidosis than the general population.[76] The addition of oral corticosteroids further increases the risk of obstructive sleep apnoea.[77]

After a sarcoidosis diagnosis, the risk of cardiovascular morbidity might increase.[78,79] Controlled data indicate that patients with sarcoidosis have an increased arterial pulse wave index, suggestive of early atherosclerosis.[80]

In the US Nationwide Inpatient Sample, 188 438 (31%) of 609 051 hospitalised patients with sarcoidosis had cardiovascular comorbidities including heart failure, conduction disorders, cardiomyopathy, and pulmonary hypertension.[81] It is possible that the increased cardiovascular morbidity in sarcoidosis is related to the use of oral corticosteroids and other immunosuppressants. In a Swedish study, myocardial infarction increased by 40% in patients with sarcoidosis receiving immunosuppressive treatment including oral corticosteroids.[82] Even prednisone doses of less than 5 mg/day increase cardiovascular risk in other immune-mediated diseases including systemic lupus erythematosus, rheumatoid arthritis, vasculitis, and inflammatory bowel disease.[20]

Respiratory infection is a frequently cited cause of death in patients with sarcoidosis.[59] In a French analysis of death certificates, the rates of infection (including for tuberculosis) were higher in patients with sarcoidosis than what is expected in the general population.[59] There is an increased infection rate in patients with sarcoidosis treated with immunosuppressants including oral corticosteroids.[59,83–86] Unsurprisingly, infection rates increase with higher oral corticosteroid doses.[73] Patients receiving oral corticosteroids experienced more fungal infections, such as cryptococcosis, compared with patients receiving other immunosuppressants, and fungal infections can be particularly severe in patients with structural lung disease.[87,88]

Extra-pulmonary sarcoidosis can lead to substantial morbidity and mortality. Despite its relatively low frequency, cardiac sarcoidosis is a major cause of sarcoidosis death.[9,89,90] Likewise, neurosarcoidosis is an important source of morbidity and increased mortality.[91,92] Oral corticosteroids are recommended as initial therapy in cardiac sarcoidosis and neurosarcoidosis.[1] The addition of methotrexate and infliximab, or both, can be steroid sparing for both cardiac sarcoidosis[93–95] and neurosarcoidosis.[42,92]

Oral corticosteroid toxicity

The adverse effects of oral corticosteroids, ranging from minor and short-lived to severe and life-altering, can be as rapid as the positive impact on inflammation. Within hours of oral corticosteroids administration, untoward effects are evident on glucose control, blood pressure, mood, and sleep.[96] Within days of starting high-dose oral corticosteroids, patients have an increased risk of infection. Even low doses of daily prednisone (<5 mg/day) are associated with a substantially increased risk of infection.[97] Within weeks to months of starting treatment, the most common side-effects include substantial weight gain, acne, and cutaneous striae. Within months to years of starting treatment, a loss of bone mineral density and higher fracture risk leads to osteoporosis and pathological bone fracture, with an increase in fracture risk disproportionate to the change in bone mineral density.[98] Corticosteroid use was associated with a 50% increase in bone fractures in one cohort of patients with sarcoidosis.[99] Although most clinicians acknowledge the potential for oral corticosteroid toxicity, in clinical practice the reality of the adverse effect of oral corticosteroids on patients' lives is often ignored in the interest of controlling the underlying disease or overlooked because some of the most devastating effects (eg, osteonecrosis, osteoporosis, and infection) might not be obvious at the time of a clinic visit.

The high incidence of oral corticosteroid toxicity, over even a short time (eg, 13 weeks), was shown in a clinical trial population by use of the Glucocorticoid Toxicity Index in antineutrophil cytoplasmic antibody-associated vasculitis.[100] The Glucocorticoid Toxicity Index measures change in oral corticosteroid toxicity over time in nine domains: BMI, glucose tolerance, lipid metabolism, blood pressure, infection, bone mineral density, skin toxicity, neuropsychiatric impact, and muscle weakness.[101] Although the protocol prescribed the discontinuation of oral corticosteroids in all patients within 5 months, the incidence of oral corticosteroid toxicity was 94% at 13 weeks, with toxicity common in multiple domains. Toxicity incurred by 13 weeks generally persisted at 26 weeks, at which time 206 (67%) of 307 patients had toxicity in one to six of these domains. The Glucocorticoid Toxicity Index has been used in more than 30 disease indications to measure oral corticosteroid toxicity, including phase 3 clinical trials in antineutrophil cytoplasmic antibody-associated vasculitis, giant cell arteritis, polymyalgia, systemic lupus erythematosus, and pemphigus vulgaris.

Data on oral corticosteroid toxicity in sarcoidosis clinical trials remain scarce, but substantial experience confirms the magnitude of oral corticosteroid toxicity in clinical practice. In a large cohort of patients with sarcoidosis who were monitored longitudinally using a mobile phone app, 244 (46%) of 526 patients who were prescribed immune modulating treatments reported adverse drug side-effects, most patients who reported these side-effects were receiving oral corticosteroids.[102] The table details the common adverse oral corticosteroid toxicities in five cohorts reporting oral corticosteroid toxicity in patients with sarcoidosis from three randomised control trials and two observational cohorts. To date, these are the largest studies with adequate follow-up detailing oral corticosteroids toxicity.

Weight gain with glucocorticoid use in patients with sarcoidosis[8] occurs within a few months of starting treatment.[105] The average weight gain after 12 months of glucocorticoid therapy has ranged from 9·5 to 26·2 pounds.[6,105,106] In one study, weight gain significantly correlated with the cumulative dose of prednisone.[106]

In 105 patients newly diagnosed with sarcoidosis, followed for several years at a university sarcoidosis clinic, patients treated with oral corticosteroid were twice as likely to experience diabetes, hypertension, weight gain,

hyperlipidaemia, low bone mineral density, and ocular toxicity compared with patients not treated with corticosteroids.[5] Furthermore, a dose response was observed for oral corticosteroid toxicity and confirmed in other sarcoid cohorts.[19,76] In one study, approximately one third of patients treated with oral corticosteroids for up to 1 year experienced one or more side-effects, including weight gain, increased appetite, easy bruising, depression, moodiness, and insomnia, with increased prevalence in those receiving more than 10 mg of prednisone daily.[103] Patients with sarcoidosis receiving higher cumulative doses of oral corticosteroids require more health-care visits per year and more non-sarcoidosis-attributed emergency department visits per year than those treated with lower cumulative doses.[73]

Guidelines have been developed for the management of oral corticosteroid toxicities, including during pregnancy and osteoporosis, associated with long-term oral corticosteroid treatment. These guidelines cover the use of corticosteroid sparing therapy, corticosteroid tapering, and monitoring.[1,107,108]

Oral corticosteroid-sparing therapies should be considered for patients with sarcoidosis with persistent symptomatic disease. In a randomised clinical trial comparing methotrexate plus oral corticosteroids to placebo plus oral corticosteroids, patients on methotrexate required lower oral corticosteroid doses and experienced less weight gain than those on placebo plus oral corticosteroids.[6] The benefits of oral corticosteroid-sparing therapy were also shown in a review of 56 patients with sarcoidosis, some treated exclusively with methotrexate. Those treated with oral corticosteroids had more frequent side-effects that were more severe and rated as more bothersome (using an 11-point scale) than patients not treated with oral corticosteroids.[104] In a retrospective review of patients with cardiac sarcoidosis treated with oral corticosteroids, the addition of infliximab was associated with less toxicity and lower oral corticosteroids doses.[95] Beyond specific toxicities, chronic oral corticosteroid usage might adversely impact the HRQoL of patients with sarcoidosis. In an analysis of 114 patients with sarcoidosis followed for 1 year, patients receiving cumulative oral corticosteroid doses of more than 500 mg/year had a lower HRQoL, as measured by the Sarcoidosis Assessment Tool,[109] than those receiving oral corticosteroid doses of 500 mg/year or less.[7] Lower HRQoL was also associated with oral corticosteroid use in a cross-sectional study of three university sarcoidosis clinics.[110]

Strategies to eliminate the use of oral corticosteroids

As noted in the figure, several oral corticosteroid-sparing agents have been investigated in sarcoidosis, with methotrexate the most frequently studied drug. The first randomised clinical trial challenged the steroid primacy in 24 patients with acute pulmonary sarcoidosis, comparing prednisone plus placebo to prednisone plus methotrexate.[6] After 6 months, patients receiving methotrexate and prednisone required approximately 50% lower prednisone doses compared to patients receiving prednisone plus placebo (8 mg/day *vs* 16 mg/day), with similar outcomes and fewer glucocorticoid toxicities. A 2025 multicentre Dutch trial randomised patients with pulmonary sarcoidosis to initial therapy with prednisone or methotrexate.[15] After 24 weeks, both groups experienced similar improvement in symptoms and pulmonary physiology with more rapid improvement noted in the oral corticosteroid group. In a retrospective review of patients with pulmonary sarcoidosis treated with either methylprednisolone (97 patients) or methotrexate (46 patients) as initial therapy, it was found that methotrexate was equally effective as methylprednisolone with less toxicity.[111] Although these studies have some limitations,[112] they provide support for using methotrexate as first-line therapy in patients with pulmonary sarcoidosis who do not require urgent treatment effects.

The onset of action for anti-inflammatory therapy varies. Oral corticosteroid therapy often leads to symptomatic improvement within 2 weeks of starting treatment,[105] and the full benefit for pulmonary disease is generally evident by 4 weeks.[105] Patients treated with infliximab experience objective radiographical and physiological improvement within 6 weeks of starting

	Baughman (2002)[103]*	Dhooria (2023)[8]	Khan (2017)[5]	Kahlmann (2021)[104]	Kahlmann (2025)[15]
Number of patients	22	43†	105	50	69
Duration of observation	12 months	6 months	101 months (median)	24 months (median)	28 weeks
Diabetes	NR	12%	12%	NR	NR
Acne and skin problems	NR	35%	NR	8%	NR
Hypertension	NR	28%	32%‡	NR	NR
Weight gain	32%	63%	45%‡	48%	43%
Increased appetite	27%	NR	NR	18%	NR
Moodiness	27%	9%	NR	NR	13%
Gastro-oesophageal reflux disease	11%	19%	NR	NR	12%
Easy bruising	40%	9%	NR	NR	NR
Insomnia	33%	16%	NR	20%	42%
Depression	27%	NR	NR	NR	NR
Cushingoid	NR	81%	NR	NR	14%
Striae	NR	16%	NR	NR	NR
Infection	NR	14%	NR	NR	1%
Osteoporosis	NR	9%	15%	6%	NR
Hyperlipidaemia	NR	NR	14%	NR	NR
Ocular problems	NR	NR	20%	NR	NR
Oedema	NR	NR	NR	20%	NR
Palpitations	NR	NR	NR	10%	NR

NR=not reported. *Toxicity reported most or all of the time. †40 mg arms. ‡Only hypertension and weight gain were significantly different from controls.

Table: **Proportion of patients treated with oral corticosteroids in prospective trials reporting adverse events**

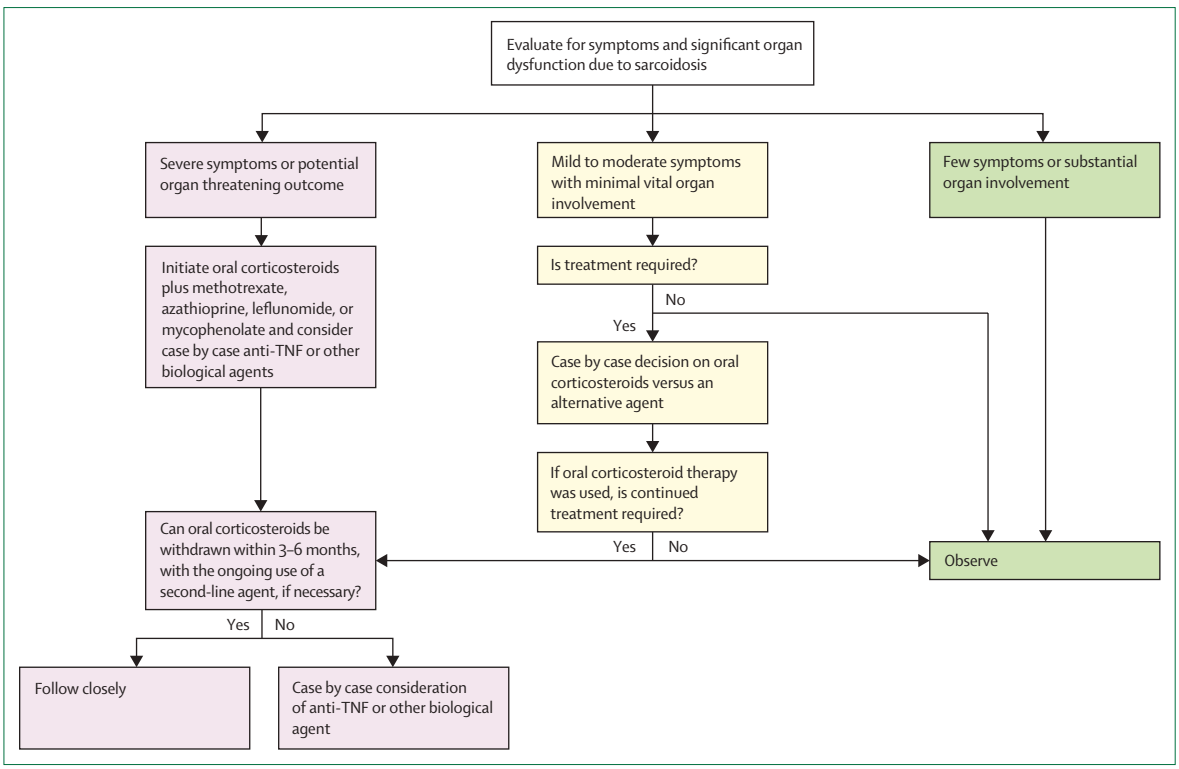

Figure: **Approach to treatment of sarcoidosis and ways to reduce oral corticosteroid use and duration**
Patients receiving oral corticosteroid therapy should be evaluated every 1–3 months for oral corticosteroid withdrawal. TNF=tumour necrosis factor.

treatment.[38] Patients treated with methotrexate might require up to 6 months to achieve objective improvement, although it often results in symptomatic improvement more quickly.[6] The initial and subsequent increase in dosing depends mostly on patient tolerance and haematological and hepatic toxicity.[26] In addition, to avoid premature steroid cessation in the setting of delays in efficacy from a second-line therapy, a combination of oral corticosteroids plus a steroid-sparing agent as initial therapy might be logical after discussion with the patient.[1] Patients might also experience acute, short-term worsening (eg, bronchitis) for which rescue oral corticosteroids are prescribed.[113,114] In some patients, only 2 weeks of corticosteroid treatment might be required.[115] Acute worsening could be caused by infectious,[113] environmental,[116] or other unknown factors.[114]

Based on ERS guidelines[1] and previously discussed studies, the figure provides an algorithm for treating patients with symptomatic disease and those at risk for death or loss of organ function. For those with organ or life-threatening disease, the combination of oral corticosteroids plus a steroid-sparing agent should be considered as initial therapy. The figure also includes strategies for initiating and withdrawing oral corticosteroids. There are four scenarios for different initial therapy (panel 1) including monotherapy with oral corticosteroids or with an alternative agent, both options for patients with mild to moderate symptoms and minimal vital organ involvement. For example, some patients with Lofgren's syndrome might never require systemic therapy and in HLA-DRB1*03-negative patients, steroid treatment is associated with worse outcomes and should be avoided.[118] Examples of scenarios for short-course oral corticosteroid monotherapy are also listed in panel 1, these include patients who present with isolated seventh cranial nerve involvement, who might respond to a short course of oral corticosteroids with a low rate of relapse.[119]

Some patients might have contraindications to methotrexate or prefer to consider alternative agents. Although the ERS Guidelines list leflunomide, azathioprine, and mycophenolate as other second-line agents, methotrexate is the only agent with high-quality clinical evidence in sarcoidosis treatment and it is preferred by most patients. However, there are no randomised clinical trials comparing methotrexate to the other listed steroid-sparing alternatives. Decisions on which steroid-sparing or steroid-replacing agent to use should be undertaken in conjunction with a patient-centred discussion.

Depending on disease severity, there is ample precedent for steroid-free induction therapy in several rheumatological diseases, including rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus.[120–122] In the setting of severe life or organ-threatening manifestations (eg, myocarditis), higher

dose oral corticosteroids or intravenous corticosteroids are recommended to achieve faster response times.[123] Similarly, the Neurosarcoidosis Consortium has recommended intravenous methylprednisolone for severe neurosarcoidosis, based on extrapolation from clinical practice in multiple sclerosis.[124]

For patients using oral corticosteroids for more than 2 weeks, tapering is desirable with a goal of total steroid discontinuation.[108] In some cases, many attempts are necessary, with prednisone daily dose reductions as small as 1 mg, often at 1–2-month intervals.[125,126] All patients on corticosteroid monotherapy are candidates for discontinuation of corticosteroid therapy. The figure provides a roadmap for patient–physician decision making. It is important to remember that the patient is the driver for decisions regarding symptomatic relief.

In a minority of patients, complete cessation of oral corticosteroids will not be reached at the first attempt; this applies both to the use of oral corticosteroid bridging therapy at initial treatment and to steroid withdrawal in patients on long-term oral corticosteroids. However, if complete cessation of oral corticosteroids cannot be reached initially, the minimum oral corticosteroid requirement should be rechallenged, repeatedly if necessary, at 6–12-month intervals. It is important that a proactive approach to the withdrawal or minimisation of oral corticosteroids includes the informed involvement of the patient with full awareness of the importance of oral corticosteroid cessation, regardless of how long it could take.

Anecdotal reports indicate that tapering oral corticosteroids can result in non-specific oral corticosteroids withdrawal symptoms including worsening fatigue, arthralgias, mood changes, and generalised pain. However, to date there are no prospective studies in sarcoidosis. Although usually self-limited, these symptoms can be temporarily disabling. Strategies to minimise side-effects related to oral corticosteroid tapering include patient education on withdrawal symptoms, slower tapering when low oral corticosteroid doses are reached, and the use of alternative therapies, such as nonsteroid anti-inflammatory agents and serotonin re-uptake inhibitors. Fatigue with oral corticosteroid tapering can be treated with neurostimulants,[125,126] exercise,[127] mindfulness,[128] and other integrative strategies.[1]

Symptomatic adrenal insufficiency is a feared complication of tapering.[108] Although rare, this phenomenon can occur even in patients treated with low prednisone doses of 5 mg/day or in those on treatment for less than 1 month.[129] Common features of adrenal insufficiency include fatigue, nausea, orthostatic symptoms, hypotension, and electrolyte derangements including hyponatraemia and hypoglycaemia.[130] Adrenal insufficiency can be diagnosed by a random morning cortisol level (<5 µg/dL is diagnostic and 5–10 µg/dL is uncertain) or a cosyntropin stimulation test with a serum cortisol level less than 18 µg/dL, 30 min after administration of 250 µg cosyntropin.

Biochemical testing for adrenal insufficiency is not recommended for patients who are asymptomatic and treated with oral corticosteroids or those with stable fatigue. When adrenal insufficiency is confirmed, the prednisone-equivalent oral corticosteroid dose should be increased to at least 10 mg/day.[131]

Panel 1: Induction therapy scenarios for oral corticosteroids and steroid-sparing agents

The following are general strategies that can be applicable for most patient scenarios. Each treatment decision should be individualised according to the specific clinical situation.[117]

No oral corticosteroids (observation and symptomatic therapy, eg, non-steroidal anti-inflammatory drugs)
Patients with:
- Löfgren's syndrome
- Non-bothersome cutaneous sarcoidosis
- Non-organ threatening biochemical, physiological, or radiographical abnormalities (eg, mild transaminitis or asymptomatic pulmonary disease)
- Elevated biomarkers, including fluorodeoxyglucose uptake (treatment of isolated cardiac fluorodeoxyglucose uptake without other cardiac manifestations is controversial)

Short-course oral corticosteroid monotherapy
Patients with:
- Bothersome acute sarcoidosis presentations failing non-steroidal anti-inflammatory drugs
- Acute flares in sarcoidosis activity
- Seventh cranial nerve paralysis

Steroid-sparing agents with oral corticosteroid tapering
Patients with:
- Organ-threatening disease, eg, substantial cardiac, neurological, ocular, or severe pulmonary disease (refer to the European Respiratory Society Guidelines for details; definition of organ-threatening is situational, dependent on a variety of clinical features[1])
- Progressive fibrotic disease
- Calcium abnormalities causing symptoms or renal dysfunction
- Conditions where rapid control is desired by the patient (eg, severe symptoms)

Steroid-sparing agents without oral corticosteroids
Patients with:
- Substantial organ impairment that is not rapidly progressing
- Mild to moderate symptomatic disease that is not organ-threatening
- Bothersome cutaneous sarcoidosis
- Comorbidities that substantially worsen with oral corticosteroids (eg, diabetes or obesity)

See Online for appendix

***Panel 2*: Public health initiatives to minimise oral corticosteroid usage**

- Update both health-care providers and patients on side-effects of oral corticosteroids and options for oral corticosteroid-sparing treatments.
- Ensure that patients have access to health-care providers with sarcoidosis expertise who can address adherence concerns, determine patient eligibility for steroid-sparing therapies or biologics, and carefully monitor use and toxicities of oral corticosteroids and steroid-sparing agents
- Educate health-care providers that optimal sarcoidosis therapy involves not only disease control but maximizing patient quality of life
- Support health-care providers in the development of oral corticosteroid-sparing strategies that include shared decision-making about oral corticosteroid risks
- Solicit government agencies to modernise public health policies and materials to reflect the importance of oral corticosteroid-sparing interventions
- Petition payers to adopt appropriate and timely access to non-steroid treatment options

***Panel 3*: Statements regarding sarcoidosis management (approved unanimously in voting by group members)**

1. All decisions regarding oral corticosteroid usage should take into account the priorities and values of the fully informed individual patient
2. For patients with asymptomatic sarcoidosis with low risk of death or disabling loss of major organ function from sarcoidosis, there is no indication for oral corticosteroids
3. Group members would favour alternatives to initial oral corticosteroids in patients with symptomatic sarcoidosis with low risk of death or disabling loss of major organ function from sarcoidosis
4. Group members would use initial treatment with oral corticosteroids if symptoms are severe or based on patient preference (eg, need for a rapid treatment effect) or there is severe cardiac, neurological, or other organ threatening disease
5. When oral corticosteroids are used as initial therapy for severe symptoms requiring urgent relief or risk of death or disabling organ loss, group members would favour initial combination therapy with a steroid-sparing agent to expedite oral corticosteroid cessation within 3–6 months
6. For severe cardiac, CNS, or symptomatic patients on oral corticosteroids and a steroid-sparing agent for more than 3 months with persistent disease, group members would consider, case by case, an anti-tumour necrosis factor antibody or other biological agent for oral corticosteroid minimisation
7. For most patients with sarcoidosis receiving oral corticosteroids for longer than 3 months and in many cases, for years, group members view total oral corticosteroid discontinuation as a primary treatment goal; group members would introduce steroid-sparing alternatives, with the goal of total cessation of oral corticosteroids

Patient and clinician management partnerships

All phases of oral corticosteroid therapy should be a shared decision between the patient and health-care provider. This conversation needs to start at treatment initiation and should include the benefits of oral corticosteroid treatment, the risks of acute side-effects, and long-term oral corticosteroid toxicity. In patients with symptomatic disease, ongoing granulomatous inflammation does not necessarily lead to functional impairment.[132]

It is essential that patients are empowered to pursue the goal of oral corticosteroid elimination and to this end, a fact sheet is provided to facilitate decision-making during consultations between doctors and patients (appendix pp 1, 2). This document, developed by the patient representatives (CK, FM, KS, and ABW) in the group, in collaboration with EEL and RPB, will need to be translated and adapted according to cultural differences, for worldwide use.

In order to reach effective patient–clinician dialogue, a clear understanding of key concepts is required. First, is the indication for treatment is only symptomatic (without major concerns about organ failure or life expectancy)? This distinction is often blurred in the minds of both clinicians and patients. When it is clearly understood that sarcoidosis is not dangerous in an individual patient, a focussed discussion is possible about whether symptoms, in themselves, require treatment. Second, not all symptoms are necessarily due to sarcoidosis. For example, symptoms might be due to osteoarthritis or atypical migraines. Third, not all sarcoid symptoms are likely to respond to oral corticosteroids or other anti-inflammatory therapies. Arthralgia, cough, and other symptoms associated with reversible inflammatory disease are generally treatment responsive but fatigue and small fibre neuropathic pain are seldom alleviated by oral corticosteroid therapy. Fourth, symptom severity is a judgement made by patients, based on individual awareness of the impact of sarcoidosis on quality of life. Sometimes, symptoms not deemed severe by clinicians have high priority for individual patients and merit intervention for this reason alone. Conversely, some patients might prefer to live with symptoms without therapy. These decisions should be supported by clinicians with a plan to review the ongoing impact of sarcoidosis on quality of life. Fifth, initial treatment for symptoms is negotiable for the type, dose, and duration of therapy. For example, because a patient might express major concerns regarding oral corticosteroid toxicity, the initial use of a steroid-sparing agent alone should be considered. Patient buy-in is essential and it needs to be anticipated that some patients will require rapid alleviation of symptoms that can only be achieved by use of oral corticosteroids. In a patient with an urgent need for rapid alleviation of symptoms, initial oral corticosteroids plus a steroid-sparing agent can be prescribed, in this scenario, oral corticosteroids should be continued until the steroid-sparing agent is effective.

Clinician and patient partnerships are important regarding initial treatment decisions on whether to introduce oral corticosteroids based both on disease severity and individual patient values. The wish by patients to avoid oral corticosteroids altogether should be strongly supported whenever possible. However, when there is severe major organ involvement or a patient

Search and selection strategy criteria

The formal literature search covered 1953–2021. Papers published between 1953 and 2017 were processed in the formulation of 2021 guideline GRADE recommendations, with the literature search updated in 2021 to ensure that relevant studies were not omitted. Selected terms were used post-2021 to ensure that subsequent relevant publications were included in the statement. Terms used with regard to pulmonary sarcoidosis consisted of "lung sarcoidosis", "pulmonary sarcoidosis", "lung sarcoid", and "pulmonary sarcoid" with same spectrum used for cardiac sarcoidosis, neurosarcoidosis, ocular sarcoidosis, and cutaneous sarcoidosis. Terms searched for corticosteroid therapy included "corticosteroid", "glucocorticoid", "dexamethasone", "prednisone", "prednisolone", "budesonide", "fluticasone", "methylprednisolone", "hydroxycorticosteroid", "corticotrophin derivative", "corticosterone", "triamcinolone", "triamcinolone acetonide", "betamethasone", "medrol", "methylprednisolone sodium succinate", and "beclomethasone". Terms searched for efficacy and adverse events, paired with treatment terms, included "drug therapy", "drug efficacy", "drug substitution", "withdrawal", "drug analysis", "drug comparison", "adverse drug reaction", "drug treatment failure", and "treatment outcome". Terms searched for alternative agents included "immunosuppressive agent", "immunosuppressive", "methotrexate", "azathioprine", "tumor necrosis factor" "cyclophosphamide", "leflunomide", "mycophenolic acid", "cyclosporin", "chlorambucil", "infliximab", "etanercept", "adalimumab", and "golimumab". Key conclusions were formulated by all group members, with initial e-mail discussion followed by a lengthy Zoom discussion, in which the wording of all statements was reviewed for its accuracy, precision, and to accommodate individual reservations. It was stressed that in subsequent formal voting, abstention, or disagreement was highly appropriate when necessary. Formal voting was then sent in confidence to a single group member (EEL) with, as it transpired, unanimous agreement on all statements. These are not termed recommendations, to avoid confusion with formal guideline recommendations made using GRADE methodology. We see these statements as providing guidance, worded as conclusions on the current practice by clinician-group leaders conclusions, endorsed by patient-group leaders.

requires rapid symptomatic relief that is not achievable with alternative agents, initial oral corticosteroids are unavoidable. However, it is essential that the importance of limiting the duration of oral corticosteroids to bridging therapy should be understood from the outset by both patients and medical personnel.

Future initiatives to minimise oral corticosteroid usage

Pivotal initiatives, broadly consisting of public health initiatives, are shown in panel 2.

It is essential that future prospective research be undertaken as rapidly as possible, directed specifically towards the goal of oral corticosteroid minimisation. This aim requires both optimal use of existing alternative therapies and the validation of novel agents in routine clinical practice. Both domains lie beyond the scope of the current position statement but, we believe, should be an essential component of future guideline update.

There is also a need, given the enormous importance of oral corticosteroid minimisation to patients, that steroid reduction be considered as a pivotal endpoint in trials of new therapies undertaken in patients currently receiving oral corticosteroids.[133] Optimal endpoint selection in sarcoidosis trials is a complex area and is addressed in an imminent World Association of Sarcoidosis and Other Granulomatous Disorders Task Force statement. As with other endpoints, steroid reduction protocols in a trial setting pose problems that lie beyond the scope of the current document. However, trial designs without protocolised steroid reduction have failed to show robust differences between treatment and placebo, probably due to ongoing disease suppression by background oral corticosteroids.[1] In current sarcoidosis trials, steroid reduction is a pivotal endpoint. These include trials of efzofitimod (NCT05415137), namilumab (NCT05314517), and XTMAB-16 (NCT05890729). During the current era, with oral corticosteroid usage in sarcoidosis highly prevalent, oral corticosteroid reduction is likely to be viewed by regulatory agencies as a key surrogate marker for how patients feel, function, and survive. Statements regarding sarcoidosis management, focused on minimising corticosteroid usage, are shown in panel 3.

Contributions

All authors contributed to manuscript generation. AUW, EEL, RPB, DAC, MAJ, CAB, AKG, JCG, JHS, and EDC, working in pairs, produced separate sections that were then centrally edited and modified by email input from all group members. CK, FM, KS, and ABW provided patient group input and took part in a discussion with their input incorporated in text. All authors reviewed the manuscript critically and approved it and generated, refined, and voted on the statements providing broad guidance to clinicians.

Declaration of interests

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