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Other CTD: Inflammatory Myopathies and Sjogren's (P Basharat and JFL Albayda, Section Editors)

Update on Treatment of Antisynthetase Syndrome: A Brief Review

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Abstract

Purpose of the review Antisynthetase syndrome (ASSD) is a rare, heterogeneous, systemic disease characterized by the clinical triad of arthritis, myositis, and interstitial lung disease (ILD) together with other accompanying findings, which often has a progressive and life-threatening evolution. The rarity of this condition and the lack of classification criteria make it hard to conduct studies on a homogenous cohort, resulting in the lack of standardized treatment regimens for this condition.

Recent findings To date, the evidence regarding the treatment of ASSD mostly derives from observational studies on polymyositis and dermatomyositis cohorts.
Summary Corticosteroids, calcineurin inhibitors, cyclophosphamide, and rituximab are the most widely used treatments for ILD and myositis, while few data are available for mycophenolate mofetil, methotrexate, and azathioprine. Data on arthritis are scarce, suggesting efficacy of corticosteroids, calcineurin inhibitors, and rituximab. A homogenous classification of these patients is necessary in order to produce good quality data on ASSD treatment.

Introduction

Antisynthetase syndrome (ASSD) is a rare connective tissue disease (CTD) associated with specific autoantibodies (anti-aminoacyl tRNA synthetase antibodies – ARS) addressed against different aminoacyl-tRNA synthetases and characterized by manifestations such as arthritis, interstitial lung disease (ILD), and myositis [1–3]. The most common ARS is the anti-Jo-1 (anti-histidyl-tRNA synthetase) [4]; other less common antibodies are the anti-PL-7 (threonyl), anti-PL-12 (alanyl), anti-EJ (glycyl), anti-OJ (isoleucyl), anti-KS (asparaginyl), anti-Zo (phenylalanyl), and anti-TYR (tyrosyl) [5–10]. Not all these antibodies are currently detected with commercially available kits. Arthritis, ILD, and myositis represent the classic triad of the disease, whereas Raynaud's phenomenon (RP), mechanic's hands (MHs), and fever are defined as accompanying findings for practical purpose [3, 11••]. ASSD onset may be "complete" (all triad manifestations) or "incomplete" (not all triad findings). We first showed that in incomplete ASSD, the occurrence of previously lacking triad findings during the follow-up is frequent [3, 11••, 12, 13]. By considering the heterogeneous presentation and evolution of the disease, the therapeutic approach may be challenging, depending on the prevalent and on the present manifestations of disease (e.g., myositis, ILD, arthritis, and skin involvement).

Clinical features overview – triad findings

Arthritis

Joint involvement is really common in ASSD, occurring in 40–80% of cases [3, 12, 14, 15]. In fact, arthritis may be the onset finding of the disease [16, 17], frequently occurring without the other triad or accompanying findings [1, 18]. The similarities with rheumatoid arthritis (RA) are very common, and the differential diagnosis may be troublesome [1, 19, 20], si nce ASSD-related arthritis may be poly-articular, symmetrical, and erosive, especially when occurring from disease onset [1, 15, 16, 21–24]. Moreover, the positivity for rheumatoid factor (RF) and/or anticitullinated peptide antibodies (ACPA) is possible in ASSD, and ACPA positivity seems to be associated with erosive and poly-articular arthritis even in this setting [20, 25].

Interstitial lung disease

ILD may affect ASSD patients with frequencies ranging from 60 to 80% [12, 14, 18, 26]. The most frequent CT findings are ground glass opacities and reticulations predominantly at lower lobes, mainly in the form of nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), or mixed patterns [27,

Table 1. Available treatments and their area of effectiveness

	Myositis	Interstitial lung disease	Joints	Skin	Dosage
Corticosteroids	◊	◊	◊	●	1–2 mg/kg/day or I.V. bolus (1 g/day for 3 days)
Calcineurin inhibitors	◊	◊	◊	●*	Cys 3 mg/kg/day; Tac initially 1 mg twice daily titrated until blood levels of 5–20 ng/ml
Cyclophosphamide	◊	◊		●	IV pulses 0.3–1.5 g/m2 or 10–15 mg/kg at weekly to monthly intervals for 6–12 months
Mycophenolate	●	◊		●	2–3 g/day
Rituximab	◊	◊	◊	●	1 g IV at day 0 and 14, then after 6 months
Methotrexate	◊		§		7,5–25 mg/week
Azathioprine	◊	●			1–3 mg/Kg/day
Hydroxychloroquine				●	200–400 mg/day
Intravenous Immunoglobulins	◊	◊		●	2 g/Kg over 2 to 5 days repeated every 4–8 weeks accordingly to clinical response

Legend.
not supporting data.
● currently used with data on polymyositis/dermatomyositis.
◊ currently used with data on ASSD.
* topical formulation
§ commonly used with data on other forms of arthritis (e.g., RA).

28]. ILD deeply affects prognosis of ASSD patients [29], though thier survival is better than Idiopathic pulmonary fibrosis (IPF) one's [30, 31].

Myositis

Muscle involvement prevalence ranges from 60 to 80% of cases [4]. Myositis onset could be defined as classic (muscle strength deficit) or hypomyopathic (instrumental/laboratory evidence of muscle impairment without strength deficit), thus suggesting the need for an underlying muscle involvement investagation also when patients are not symptomatic. Regarding muscle biopsies, perifascicular necrosis seems to be a very common histology finding in ASSD, and anti-OJ patients are more keen to present a severe muscle involvement during the disease course [32].

Accompanying findings

The most important accompanying findings are RP, MHs, and fever. The prevalence of these manifestations is reported to be about 50% of cases [15, 18]. None of these manifestations may be considered specific for ASSD, since RP is transversal to the entire family of CTDs [33] and MHs have been reported also in PM-Scl-positive patients [34]. Recently, some authors reported another cutaneous finding typical for ASSD, the hiker's feet [35]. Accompanying findings may be useful inpatients' follow-up because, in incomplete ASSD, the onset of new accompanying findings strongly

increases the risk for of occurrence of the remaining triad findings (80% vs. 50.5%). In the same cohort, the median time of occurrence of a new triad manifestation was 14 months (independently from the presence of accompanying findings) [11••].

Treatment overview

Literature data driving ASSD treatment are poor and mostly based on case series or on small cohorts of patients. Furthermore, the majority of studies has been addressed to ILD treatment, with only few reports focusing on joint and muscle involvement. Although corticosteroids are the established first-line therapy [36], the risk of disease flare during prednisone tapering is very high [2, 36]. On this basis, the use of other immunosuppressants is very common and frequently recommended from the onset [36]. In this regard, one of the main issue is to establish which treatment regimen would be more appropriate according to the clinical presentation of ASSD. In the next paragraphs, we will report the available treatments focusing on their related area of effectiveness accordingly to literature data (Table 1); we will also report the experience of the descriptive and retrospective cohort of American and European NEtwork of Antisynthetase Syndrome (AENEAS), which is an international collaborative group aiming at collecting data on ASSD from all over the world in order to increase our knowledge on its clinical presentation and evolution.

Corticosteroids (CS)

CS are the mainstay of ASSD therapy [37]. Prednisone is generally administered at the dosage of 1–2 mg/kg/day orally, up to a maximum of 80–100 mg daily, while intravenous (I.V.) methylprednisolone (1 g/day for 3 days) could be used in most severe cases (e.g., refractory muscle and lung involvement) [36, 38]. As borrowed from polymyositis and dermatomyositis, the oral dose of prednisone is maintained for 4 weeks and then gradually tapered to 5–7.5 mg/day, trying to stop the treatment after 6–12 months [36]. However,since ASSD-related ILD is frequently refractory to GC monotherapy or relapsing during steroid tapering, the early association with other immunosuppressant should be considered. In the AENEAS cohort, CS are ongoing in the 96% of cases, thus showing the difficulties in corticosteroids' withdrawal [39].

Calcineurin inhibitors (CIB)

The use of cyclosporine (Cys; 3 mg/kg/day) and tacrolimus (Tac; initial dose 1 mg twice daily titrated until the target blood levels of 5–20 ng/ml are reached) in ASSD is mainly supported by case series and small cohorts generally focusing on ILD [2, 40–45]. The largest studies available are from Spain [40], Italy [2], and USA [42] including, respectively, 15, 17, and 13 patients with ASSD-ILD, treated with Cys or Tac for refractory ILD (41 cases) or as a first-line therapy (4 cases). Lung function and HRCT scans were stable or improved in 43 out of 45 cases. The treatment was maintained long-term, and, at least for Cys, the effectiveness was maintained also at low dose. Of note, CIB were found to be effective also for articular and muscular manifestations of ASSD, according to

two cohort studies [2, 42] Only one report showed ineffectiveness of cys in seven ASSD–ILD patients, but without reporting pulmonary function tests or lung HRCT scoring [46]. In the overall AENEAS cohort, CIB are ongoing in the 20% of patients.

Cyclophosphamide (CYC)

Data on CYC in ASSD are scanty and not conclusive. In fact, although some studies reported improvements in muscular strength/function, CK levels, Vital Capacity, DLCO, and HRCT opacities after CYC [46–49], other studies did not confirm the effectiveness of this therapeutic approach [46, 50••, 51]. However, CYC is worldwide used in clinical practice (generally IV pulses 0.3–1.5 g/m2 or 10–15 mg/kg administered at weekly to monthly intervals for 6–12 months) to stabilize ASSD-ILD, and the prevalence of ongoing CYC pulses is about the 25% of patients in AENEAS cohort.

Mycophenolate mofetil (MMF)

To date, only few reports showed the effectiveness of MMF on ASSD. In a large cohort of idiopathic inflammatory myopathies (IIMs) including only five ASSD, the treatment with MMF (2-3 g/day) significantly improved FVC% and DLCO after a long-term therapy [52]. The effectiveness on connective tissue diseaser (CTD)-related has been shown also in other small case series [53–58], and reported also for myositis [58–62] and skin involvement [58, 63, 64]. However, the prevalence of ASSD patients in these cohorts is unclear, given the absence of established classification criteria. In the AENEAS collaborative cohort (828 ASSD patients), the prevalence of ongoing MMF therapy is 16%, thus confirming the increasing trend in the prescription of MMF in this condition.

Rituximab (RTX)

Rituximab is an effective treatment for ASSD , particularly lung involvement. In a subanalysis of the RIM trial (Rituximab In Myositis), Aggarwal et al. evidenced that ARS positivity (30/195 patients) predicted the achievement of IMACS's definition of improvement with an HR of 3.08 as compared to seronegative patients [65]. In a recent literature review, *Fasano* et al identified 458 IIMs patients treated with RTX [66•], including 100 ASSD, 40 treated for ILD, 51 for myositis, 1 for arthritis, 7 for ILD and myositis, and 1 for the complete triad [51, 67–79], confirming the effectiveness of the treatment. Subsequent studies confirmed the efficacy of rituximab for both ILD and myositis, with a rate of response of about 80%, particularly in case of anti-Ro positivity [47, 50••, 80–83]. Of note, RTX was generally administred at 1 g at day 0 and 14, but great discrepancies were present for maintenance scheme or associated immunosuppressants. The therapy was generally well tolerated, with infection being the most common adverse effect, occurring in 5 to 20% of cases. In the AENEAS collaborative cohort, the prevalence of ongoing RTX therapy is 13%, thus confirming the central role of RTX in ASSD.

Other treatments

Methotrexate (MTX) and azathioprine (AZA) are the most commonly used therapies in polymyositis and dermatomyositis [84], but data on ASSD are very

limited. In fact, the only significant study has been published recently [85•]. The study compared the efficacy and the safety of AZA and MTX in a very large cohort of patients. In the 102 analyzed patients, the authors did not observe significant differences in the rate of improvement for both muscle strength and CK serum levels, as well as in prednisone tapering, between the two groups. Also the prevalence of drug-related side effects was similar between the two treatment regimens, although two patients on MTX developed a possible drug-related pneumonitis. Data on *hydroxychloroquine* are completely lacking, although the drug is the reference therapy for skin manifestations of dermatomyositis, as evidenced in one in the few clearly established guidelines on idiopathic inflammatory myopathies [86]. Generally, the drug is used according to the available guidelines on IIMs management [86]. *Intravenous immunoglobulins (IVIg)* in ASSD are used as a second-line therapy in case of refractory muscle disease, although some authors suggested the effectiveness also in case of ILD [53, 59, 87–89, 90•, 91]. They are commonly 3 administred at monthly infusion of 2 g/kg divided over 2 to 5 days, with great variability in the duration of the therapy accordingly to disease severity. Another second-line therapy option is *double-filtration plasmapheresis* that can be used of refractory lung and muscle involvement in association with conventional immunosuppressants [92]. Some literature data reported also the effectiveness of *tocilizumab* [93] and *leflunomide* [94], but data available are for now very scanty. Finally, *anti-TNF-alpha agents* have been considered by some authors as a potential trigger factor for the development of ASSD [95–97]. However, many of these patients were ARS positive since arthritis onset or not tested for ARS, thus suggesting that ASSD developement could have represented the natural evolution of their disease rather than a side effect of anti-TNF alpha therapy.

Conclusion

ASSD is a complex disease from both the clinical and therapeutic points of view. In fact, the heterogeneity of clinical spectrum time course may complicate therapeutic approach, with the consequent need of immunosuppressants changes [18]. Furthermore, treatment guidelines of ASSD are still lacking [86], mainly due to the lack of established classification criteria [98, 99] leading to different patients' classification and treatment according to different specialist referrals [4, 100]. Another unmet need is a deeper insight on the pathological pathways involved in ASSD developement, which seem to be very heterogeneous and unclear, since the most intriguing results have been obtained by drugs acting against both T (Cys and Tac) and B cells (RTX). It appears clear that better quality studies are necessary to improve our knowledge of the disease. In this regard, the developement of established classification criteria for ASSD could be the first step to accomplish in order to obtain evidence-based treatment regimens and improve patients' progosis.

Compliance with ethics guidelines

Conflict of interest

The authors declare no conflicts of interest relevant to this manuscript.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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- •• Of major importance

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This large observational study showed that ASSD may change over time, with the occurrence of new triad manifestation during the follow-up, especially when accompanying features are present.

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