Recommendations for the Treatment of Anti-Melanoma Differentiation-Associated Protein 5-Positive Clinically Amyopathic Dermatomyositis-Associated Rapidly Progressive Interstitial Lung Disease.

ABSTRACT

Objectives: The study aimed to develop evidence-based recommendations for the treatment of rapidly progressive interstitial lung disease (RPILD) associated with the anti-Melanoma Differentiation-Associated Protein 5 positive clinically amyopathic dermatomyositis (CADM) syndrome.

Methods: The task force comprised an expert group of specialists in rheumatology, intensive care medicine, pneumology, immunology, and internal medicine. The study was carried out in two phases: identifying key areas in the management of CADM-RPILD syndrome and developing a set of recommendations based on a review of the available scientific evidence. Four specific questions focused on different treatment options in several groups were identified. Relevant English-language publications through April 2018 were searched systematically for each topic using PubMed (MEDLINE), EMBASE, and Cochrane Library (Wiley Online). The experts used evidence obtained from these studies to develop a set of recommendations.

Results: A total of 134 studies met eligibility criteria and form the evidentiary basis for the recommendations regarding immunosuppressive therapy and complementary treatments. Overall, there is general agreement in the initial use of combined immunosuppressive therapy. Combination of high-dose glucocorticoids and calcineurin antagonists with or without cyclophosphamide is the first choice. In case of calcineurin inhibitors' contraindication or treatment failure, switching or adding other immunosuppressants may be individualized. Plasmapheresis, polymyxin B

hemoperfusion and/or intravenous immunoglobulins may be used as rescue options. ECMO should be considered in life-threatening situations while waiting a clinical response or as bridge to lung transplant.

Conclusions: Thirteen recommendations regarding the treatment of the anti-MDA5 positive CADM-RPILD were developed using research-based evidence and expert opinion.

Word count: 250

Keywords: Anti-Melanoma Differentiation-Associated Protein 5**,** Clinically Amyopathic Dermatomyositis, Rapidly Progressive Interstitial Lung Disease, glucocorticoid, cyclosporine, tacrolimus, cyclophosphamide, mycophenolate, rituximab, basiliximab, tofacitinib, intravenous immunoglobulins, plasmapheresis, polymixyn B hemoperfusion, Extracorporeal Membrane Oxygenation, Lung transplant.

Introduction

Idiopathic inflammatory myopathies are a heterogeneous group of systemic autoimmune diseases usually characterized with inflammatory infiltrates in the muscle biopsy. Several phenotypes are included, being dermatomyositis (DM) one of the best recognized[1]. The autoantibody profile allows to individualize the clinical presentations in DM patients being some manifestations linked to specific autoantibodies. This is the case of the clinically amyopathic dermatomyositis (CADM) with anti-melanoma differentiation-associated gene 5 (MDA5) antibodies[2]. Those are patients with the characteristic skin rash of the disease, with Gottron papules and heliotrope sign, but without muscle weakness, herein the name of clinically amyopathic DM. At least three different subsets of CADM positive to anti-MDA5 antibody can be identified[3-6], a

cutaneous form without muscle or lung involvement, a chronic form of cutaneous features with interstitial lung disease resembling the antisynthetase syndrome, and lastly the most severe form of cutaneous manifestations with rapidly progressive ILD (RPILD). Patients with CADM anti-MDA5 with RPILD usually have a bad prognosis, and more than 80% do not survive even after an early diagnosis or intensive immunosuppressive therapy[7]. Therefore, the aim of this study, with the participation of the different areas of knowledge implicated in its treatment (i.e. intensive care unit, rheumatology, pneumology, immunology and internal medicine) is to provide evidence-based recommendations on the different treatments until now used in these patients in order to define which will be the better treatment to offer, and to define an algorithm of actuation.

Recommendations' Questions

These recommendations address four clinical questions

1. Which is the effectiveness, efficacy, and safety of the different treatments administered in anti-MDA5 positive CADM-RPILD patients?

2. Which is the effectiveness, efficacy, and safety of the different treatments administered in anti-MDA5 positive patients with non-RPILD or other type of ILD such as usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), or cryptogenic organizing pneumonia (COP)?

3. Which is the effectiveness, efficacy, and safety of the different treatments administered in patients with inflammatory myopathy and RPILD negative to or with unknown status of anti-MDA5 antibodies?

4. Which is the effectiveness, efficacy, and safety of the different treatments administered in RPILD anti-MDA5 negative antibody patients with systemic autoimmune diseases other than dermatomyositis?

Methods

Study design. A qualitative synthesis of the scientific evidence currently available was performed. Consensus techniques of methodology were used to collect expert opinion based on the participants' clinical experience when only no or low-quality scientific evidence was available.

Study stages. This study has been developed according to the different stages for elaborating Clinical Practice Guidelines (CPG) in the Spanish National Health System[8]. The process was divided into six different stages.

Recommendations of the working group. The guidelines working group made up of 7 healthcare professionals from different disciplines in the area of myositis and progressive interstitial lung disease (rheumatology, internal medicine, intensive care medicine, immunology and pneumology). The expert group has been managed by a clinical and methodological coordination team. The different Scientific Societies involved were contacted agreeing to be represented in the development group.

Identification of key areas. The expert group defined the main objectives of the recommendations. They identified those clinical questions expected to have the greatest impact on the management of CADM-RPILD syndrome in MDA5 positive patients.

Analysis of scientific evidence. The research question was formulated according to the Population, Intervention, Comparison, Outcome (PICO) format. The question related to Lung transplantation was not framed in the PICO format, being based on a non-systematic review of the studies published on the topic. A systematic literature review was performed in PubMed (MEDLINE), EMBASE (Elsevier), and Cochrane Library (Wiley Online) until May 2018; subsequently the expert group identified some studies which had been published till July 2019 and were included in the evidence corpus. The

search strategy was constructed by an experienced medical librarian; included studies published in English, Spanish or French and were limited to studies in humans. The search strategy was developed initially in PubMed using controlled vocabulary and free text terms, and then it was adapted for each of the other databases to find publications about "lung diseases interstitial" and synonyms. Articles were excluded if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries and narrative reviews. Additional information about the search strategy can be consulted as on-line supplementary material (available in the Data Supplement).

Analysis and summary of scientific evidence. Evaluation of the quality of the studies and summary of the evidence for each question was performed using the critical reading tool of the Agency for Healthcare Technology Assessment of the Basque Country (OSTEBA)[9]. Furthermore, the determination of the evidence levels and the recommendations grade was based on SIGN methodology (Scottish Intercollegiate Guidelines Network)[8]. (Appendix 1).

Formulation of recommendations. Formulation of recommendations was based on the "formal evaluation" or "justified opinion" of SIGN[8]. To determine the strength of each one of the formulated recommendations, the development group has considered not only the level of evidence available but also the equilibrium between desirable and undesirable consequences of carrying out the recommendation. The good clinical practice recommendations have been formulated and agreed by consensus following a transparent methodology with a face-to-face meeting of the development group and a subsequent series of successive consultation rounds with a panel of experts. These recommendations have been divided into four complementary areas: general management, combination therapy, therapy for the refractory patient and other therapeutic options (Table 1).

External review. External reviewers have participated in the review of the second draft. The purpose of submitting the CPG to external review was to improve the overall quality, to ensure the appropriateness of recommendations, to disseminate the evidence, as well as to assess its applicability and feasibility.

Public Display. The draft of recommendations was subject to public comment by SER associate members and different interest groups (the pharmaceutical industry, other scientific societies, and patient associations). The objective was to collect scientific input on the methodology and recommendations put forth by the document.

Conflicts of Interest

All members of the Expert Panel completed the disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

Overarching principles

Diagnostic accuracy and rationale of the different questions, methods of anti-MDA5 detection and brief description of the different therapies administered

Not generally accepted diagnostic criteria for patients with the anti-MDA5 syndrome do exist. Therefore, most studies included patients with definite or probably

DM, usually clinically amyopathic, and antibodies positive to MDA5 detected by means of home-made ELISA or blot, protein immunoprecipitation or commercial tests such as EUROIMMUNE. Altogether RPILD was considered when worsening of radiologic interstitial changes with progressive dyspnea and hypoxemia within 1 month after the onset of respiratory symptoms appeared. The diagnosis of ILD was established by chest X-ray and/or high-resolution CT scan showing reticular opacities, ground glass opacity (GGO) or honey-comb appearance[10].

One of the proposed strategies to treat properly these patients includes risk stratification. In this setting, it is important to evaluate those parameters that can act as an activity surrogate. Although a myriad of biomarkers has been described[11], ferritin is the most recognized factor. In Hoa et al (2017)[12] series of MDA5 (+) RP-ILD associated DM, levels of ferritin were in the range of 370-13,878 ng/ml (NV < 200 ng/ml). Blood values higher than 1,000 ng/ml, seem to be associated with a higher mortality in Caucasians and Asian ethnicities[13-15]; moreover, ferritin values run in parallel to the activity of the disease[16]. Beside the ferritin, Krebs von den Leugen-6 (KL-6), a type II pneumocyte glycoprotein has been postulated as a biomarker of ILD in different ethnicities[17, 18]. Nevertheless, although in anti-MDA5 (+) patients the value of KL6 is high, it does not correlate with activity, treatment response, or mortality[15, 16, 19, 20]. Finally, several articles focused on the level of the anti-MDA5 values which will be only measured by means of ELISA test. Higher values of anti-MDA5 antibodies correlate with a worst outcome[11, 15, 21, 22] and seem to be a good biomarker of relapse[16].

Given the probably scarce scientific evidence about the explored issue, the Expert Panel considered to analyze not only those patients with CADM-RPILD positive to anti-MDA5 antibodies but also other groups of related conditions which include DM patients with RPILD but negative for or with undetermined anti-MDA5 antibodies, other

autoimmune systemic diseases with RPILD, and also anti-MDA5 positive DM patients with non-RPILD, including those with a chronic form of ILD.

The different therapies that have been administered to these patients are described in Table 2.

Results

By the search strategy, 134, 134, 1164, and, 3132 references were respectively identified. Of these, 49, 8, 30, 13 full-text papers respectively were included in the systematic review. A detailed flow chart with the results of the literature search is shown in Appendix 2.

General Management

Recommendation 1: *Patients with CADM-associated rapidly progressive interstitial lung disease anti-MDA5 (+) should be treated with combination therapy as a first option. (Recommendation grade D).*

Scientific evidence on efficacy and safety of the drugs used for the treatment of anti-MDA5 (+) associated RPILD, come from observational studies and case reports. All the identified studies include a combined or progressive administration of immunosuppressive drugs with or without support therapies. The usual approach comprises a combined schedule of glucocorticoids (oral prednisone or prednisolone, intravenous methylprednisolone pulsed therapy, or both), immunosuppressive drugs (intravenous cyclophosphamide or calcineurin inhibitors such as cyclosporine or tacrolimus), and intravenous immunoglobulin as an adjuvant therapy[11-14, 16, 22-46] *(Level of evidence 3).*

Obtained data is mainly focused on mortality and prognosis factors that contribute to an interstitial pneumonia favorable outcome. In summary, all the studies gave support

to the combination therapy. Accordingly, and considering their clinical expertise, the elaborating group also supports combination therapy as the best available treatment in order to improve the clinical outcome and reduce the mortality in these patients.

Combination therapy

Recommendation 2: *A combination therapy which include glucocorticoids plus a calcineurin inhibitor (cyclosporine A or tacrolimus), or triple therapy adding intravenous cyclophosphamide to the previous schedule, are both considered good initial alternatives. (Recommendation grade D).*

Recommendation 2a: *Both, cyclosporine A and tacrolimus are considered equally good therapeutic options. The choice of any of them will depend on the safety profile and patients' characteristics (Recommendation grade √).*

Recommendation 2b: *Monitoring of calcineurin inhibitors blood levels are recommended in order to adjust posology and minimize toxicity (Recommendation grade √).*

A systematic review of the scientific evidence allowed us to identify several observational studies (case series) focused on the pharmacological combination therapy in patients with CADM-associated RPILD and anti-MDA5 positive antibodies.

Three retrospective studies[11, 14, 32] aimed to analyze the differences in clinical activity and pulmonary function parameters between patients with anti-MDA5 positive patients and RPILD who died or survived, and to determine the main prognostic factors.

The first study[11], included 20 RPILD anti-MDA5 patients, 12 of them received treatment with a combination of prednisolone and cyclophosphamide plus calcineurin inhibitors (triple therapy). Seven out of 12 (78%) died and the other 5 (46%) developed a favorable outcome and survived. Eight patients received treatment with a combination

of prednisolone and either cyclophosphamide or a calcineurin inhibitor (2 died and 6 survived).

At the second study[14] the authors identify 17 anti-MDA5 positive patients who develop RPILD among a series of 95 dermatomyositis patients. In this study only one (16%) out of 6 patients who received triple therapy (prednisolone, cyclophosphamide and calcineurin inhibitors) died. Among the other 11 who were treated with a combination therapy that include prednisolone plus either cyclophosphamide or calcineurin inhibitors, 3 (27%) died.

Finally, the third of the 3 retrospective studies previously mentioned[32] included 12 patients diagnosed with CADM anti-MDA5 positive who develop a RPILD. Eight of these patients received combination therapy with prednisolone and cyclosporine, and only 3 (25%) died. The other 4 patients received triple therapy (prednisolone, cyclophosphamide and cyclosporine), being the mortality of 75% (3 patients) *(Level of evidence 3)*.

Other study[16] analyzed 11 patients positive to anti-MDA5 with RPILD, who were also treated with triple therapy, being tacrolimus the calcineurin inhibitor used. A good clinical response was noticed and none of the patients died, although a non-significant trend to clinical relapse was observed in those patients who received a reduced number of intravenous cyclophosphamide cycles *(Level of evidence 3)*.

Hozumi et al, 2016[35] reported 15 patients diagnosed with dermatomyositis anti-MDA5 positive and ILD, 13 of them with anti-MDA5 positive and RPILD. Ten were treated with combination therapy that included prednisolone plus a calcineurin inhibitor (cyclosporine in 8 patients and tacrolimus in 2), and 5 received a triple therapy scheme

(prednisolone, cyclophosphamide and cyclosporine). Six out of 15 patients died, 5 of them due to respiratory failure and the other one of unknown cause *(Level of evidence 3)*.

Other 4 retrospective studies adding indirect evidence were identified. Patients reported in these studies were mostly but not all anti-MDA5 positive, and there was not specific information for this subgroup. Tanizawa et al *2011*[34] included 12 anti-MDA5 positive patients, five of whom developed RPILD. Seven out of the 12 patients died, five of them with RPILD, being six of them treated with triple therapy (glucocorticoid, cyclophosphamide and cyclosporine) and the other one with the combination of glucocorticoids and cyclosporine. *Ikeda et al 2015*[28] reported 10 patients positive to anti-MDA5 who developed ILD, 6 (60%) of them died, all with the RPILD phenotype, even though they received triple therapy. *Ma X et al 2016*[29], reported 7 MDA5 positive patients with RPILD, being treated with triple therapy that include mycophenolate, leflunomide, intravenous immunoglobulin, and some naturist therapies (i.e. Chinese herbs). Six out of 7 (85%) died. A study published by Nakashima, et al in 2016[31], compare a cohort of 14 MDA5 patients who develop RPILD and were treated with triple therapy (prednisolone, cyclophosphamide and cyclosporine) with a historical cohort who received standard therapy (not described). Mortality in the group treated with triple therapy was 25% in comparison with 31.4% of the historical cohort *(Level of evidence 3)*.

Overall, published data are scarce and the level of evidence of the studies is weak. Hence, case reports were also included in the analysis, with a total of 53 anti-MDA5 positive dermatomyositis patients with RPILD. The outcome of the reported cases that were treated with combination therapy (glucocorticoids, plus either cyclophosphamide or cyclosporine, or a combination of both immunosuppressive drugs)[22-26, 30, 33], was good, and only 2 cases died[24, 30]. Other reported cases that used tacrolimus instead of cyclosporine[27, 36-38, 40, 41], also had a good prognosis, with the exception of two cases[40, 41]

and one out of the three reported cases in the *Koguchi-Yoshioka H, 2017* study[37] *(Level of evidence 3)*.

In summary, from the analysis of the reported cases, 21 patients (40%) died, and 32 (62%) improved after immunosuppressive therapy. Most cases received combination therapy with glucocorticoids (either oral prednisone or prednisolone or pulsed methylprednisolone), cyclophosphamide and/or a calcineurin inhibitor (cyclosporine or tacrolimus).

Two more published cases that include from the onset mycophenolate added to the combination therapy of glucocorticoid and calcineurin inhibitors were identified. One is the case number 9 from *Hoa, 2017*[12] who present a good outcome after being treated with mycophenolate, tacrolimus and glucocorticoids, and the other one (case 9) with RPILD reported by *Takada T, 2015*[39] develop a progressive course and died in spite of triple therapy with glucocorticoid, mycophenolate and cyclosporine *(Level of evidence 3)*.

The expert group, therefore, considers that data is lacking for a triple therapy recommendation which include mycophenolate plus glucocorticoid and calcineurin inhibitors from the onset.

Lastly, other studies have been identified that supply indirect information, considering that analyzed patients are those diagnosed with dermatomyositis and negative for or with unknown anti-MDA5 antibodies, which develop a RPILD. Combination therapy (glucocorticoid and calcineurin inhibitors from the onset) effectively reduce mortality in comparison with historical controls treated only with glucocorticoids, mainly in those patients with acute ILD (6.7% vs. 28.6%, p=0.043) and (31% vs. 68%, p=0,049)[11, 14]. Moreover, those dermatomyositis patients with acute or subacute ILD who

received triple therapy with glucocorticoids, cyclophosphamide and cyclosporine, have a survival of 50%[35, 39].

When tacrolimus was added to the standard immunosuppressive therapy (prednisolone and/or cyclophosphamide and/or cyclosporine), an improvement of pulmonary function parameters, creatine-kinase and MMT score and a reduction in glucocorticoid requirement were observed with an increase in disease-free survival (HR: 0.25; IC 95% 0.010-0.66, p=0.005)[28, 29] *(Level of evidence 3)*.

Considering these results, the expert group states that the first therapeutic option in anti-MDA5 positive patients with RPILD is a combination therapy including glucocorticoids plus the administration of a calcineurin antagonist, or alternatively a triple therapy with glucocorticoids, calcineurin inhibitors and pulses of intravenous cyclophosphamide. In those cases, in which cyclophosphamide is not feasible, the administration of mycophenolate may be a good option.

Otherwise, although studies performed in myositis patients with RPILD, negative for or with unknown anti-MDA5 antibodies, suggest that adding tacrolimus to other immunosuppressive drugs (glucocorticoids and/or cyclophosphamide and/or cyclosporine) may improve the outcome of these patients, the evidence is so scarce that does not allow to establish a preference for tacrolimus over cyclosporine.

It has to be said, that in most of the studies analyzing patients with RPILD and positive anti-MDA5 antibodies, cyclosporine A has been the most employed calcineurin inhibitor, and that the benefits of adding tacrolimus to other immunosuppressive drugs have not been specifically evaluated. The expert group considers that the choice of tacrolimus or cyclosporine will depend on the safety profile and the patient clinical background.

Recommendation 3: *When calcineurin inhibitors are not feasible, consider combination therapy with glucocorticoids and other immunosuppressive drugs such as cyclophosphamide and/or mycophenolate mofetil, or adding rituximab to any one of the previous schedules (Recommendation grade 3).*

Recommendation 3a: *The choice of one of these drugs will depend on the individual characteristics of the patient and the clinician experience (Recommendation grade √).*

Double therapy with glucocorticoid and cyclophosphamide is used in several retrospective studies and case reports. Two retrospective studies previously mentioned in recommendation 2[13, 14] describe 19 cases (8 and 9 patients, respectively) treated with a double therapy that combine glucocorticoid and cyclophosphamide or a calcineurin inhibitor, 14 patients of whom survived (6 and 8, respectively). The number of patients treated with the combination including cyclophosphamide is not specified. Besides, the case reported by Goussot 2014[26] received this double therapy and also survived *(Level of evidence 3)*.

The evidence about the efficacy and safety of mycophenolate in the treatment of RPILD associated to anti-MDA5 is scarce and indirect, based on 12 patients from case series and reports[42-46]. Mycophenolate was combined with other immunosuppressants resulting in three patients who died and nine with clinical improvement. Six out of nine patients who improved did not receive calcineurin inhibitors as part of the therapeutic strategy. Thus, three patients of Hoa 2017[12] were treated with glucocorticoids and mycophenolate (patients 3, 4 y 5) while three patients received triple therapy with cyclophosphamide[42], patient 8 of Hoa 2017[12] and one patient of Lee 2016[46], who also received adjuvant intravenous immunoglobulin. Two out of three patients who died received sequential treatment with several immunosuppressants which did not include calcineurin inhibitors[43, 44] *(Level of evidence 3).*

Looking at these results, the expert panel considers that when calcineurin inhibitors are not feasible, either double therapy with glucocorticoid and cyclophosphamide or mycophenolate or triple therapy with the three of them with or without intravenous immunoglobulin might also be a valid therapeutic option.

Regarding rituximab, 13 treated patients with RPILD associated to anti-MDA5 have been reported. Six of them did not receive calcineurin inhibitors as part of the combined therapy with cyclophosphamide with or without mycophenolate[12, 42-44, 47]. Of these, four patients died[12, 43, 44] and only two improved[42, 47] *(Level of evidence 3)*. According to these data, the expert panel considers that adding rituximab to the combination of glucocorticoid and cyclophosphamide must be taken with caution.

Therapy for the refractory patient

Recommendation 4: *In patients with CADM-associated rapidly progressive interstitial lung disease anti-MDA5 (+) who do not respond to combination therapy with glucocorticoids plus immunosuppressive drugs, clinicians have to take into account the following alternatives:*

- *Adding one of these immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, rituximab, basiliximab or tofacitinib) to the current therapy (Recommendation grade D)*
- *Change one immunosuppressant for another (Recommendation grade √)*

Although definition of a refractory patient can differ from a study to another, it is generally accepted as a lack of response after administration of the classical therapeutic schedule following recommendations 2 and 3. Some studies have defined treatment failure in these patients when they fulfill the following conditions at least 1 week after the institution of triple therapy: deteriorating respiratory symptoms; increasing alveolo-arterial O_2 tension difference (A-aDO2); newly-emerging or expanding GGO/consolidation on chest imaging; increasing ferritin levels, and the personal

impression of clinical worsening of the patient under triple therapy by the attending physicians[48].

Evidence based analysis have identified several drugs used as a rescue therapy in refractory patients with anti-MDA5 positive dermatomyositis-associated RPILD. Rituximab has been added to the standard immunosuppressive therapy (recommendations 1 and 2) in patients with RPILD impairment[12, 43, 44, 47, 49-53]. Eight out of 13 reported patients died, even though rituximab have been added[12, 43, 44, 49, 53], and 5 improved[12, 47, 50, 51], although in a single case relapse did not involve lung[42] *(Level of evidence 3)*.

As previously reported, recommendations 2 and 3 gather the available evidence (case reports) about the use of mycophenolate in combination with other immunosuppressive drugs. Only a single patient refractory to the initial triple therapy that finally improved after adding mycophenolate has been identified[45] *(Level of evidence 3)*.

A single study was detected that showed the efficacy of basiliximab (an anti-CD25/sIL-2R monoclonal antibody) in 3 out of 4 patients who were refractory to immunosuppressive therapy which include prednisone, cyclosporine, and intravenous immunoglobulin[54] *(Level of evidence 3)*.

Another option in the case of failure to the conventional triple therapy is to switch one immunosuppressant for another. Nevertheless, at least in the case of calcineurin inhibitors, Yoshida et al 2016[55] described the case of a patient refractory to triple immunosuppressive therapy who died despite switching cyclosporine by tacrolimus. *(Level of evidence 3)*.

Finally, two studies have found a good response adding the Janus kinase inhibitor tofacitinib (5 mg twice daily) to conventional triple therapy in six refractory cases. Kurasawa et al (2018)[48] reported a survival rate of 60% in tofacitinib-treated patients (three out of five) compared to none out of six historical controls with similar poor-

prognostic factors. However, 80% of tofacitinib-treated patients presented varicella-zoster virus reactivation and 100% developed cytomegalovirus infection. Kato el al (2019)[56] reported a case of refractory ILD with pneumomediastinum responsive to tofacitinib add-on therapy *(Level of evidence 3)*.

Considering these results, the expert group suggests that in refractory cases to standard triple immunosuppressive therapy (recommendations 2 and 3), addition to a new immunosuppressant or switching one for another may be considered valid therapeutic alternatives.

Recommendation 5: *In patients who do not respond to combined immunosuppressive drugs, the use of the following alternative rescue therapies, either separate or in a sequential manner, might be considered:*

- *Polymyxin B hemoperfusión (Recommendation grade D)*
- *Plasmapheresis (Recommendation grade D)*
- *Intravenous immunoglobulins (Recommendation grade √)*

Use of non-pharmacologic therapies such as polymyxin B, plasmapheresis or intravenous immunoglobulin (IVIg) administration is accepted as a rescue therapy in these patients. Adsorption and elimination of inflammatory cytokines, mediators and activated leukocytes, as well as removing anti-MDA5 antibodies could be the rationale of its efficacy.

A retrospective study[57] aimed to evaluate the efficacy of polymyxin B hemoperfusion analyzed 14 clinically amyopathic dermatomyositis associated RPILD patients (10 with anti-MDA5 antibodies). All patients prior to polymyxin were treated with standard triple therapy including prednisolone, cyclophosphamide and calcineurin inhibitors (cyclosporine or tacrolimus). Polymyxin administration was performed by using a polymyxin B-immobilized fiber column and conventional equipment for

hemoperfusion and hemodialysis circuit. Nine out of 10 (90%) of anti-MDA5 positive patients died, and only one case survived *(Level of evidence 3)*.

Takada et al reported in a retrospective study 2 out of 13 patients diagnosed with CADM and positive anti-MDA5 antibodies refractory to combined immunosuppressive therapy in whom polymyxin hemoperfusion was performed; one of them survived.

Four more patients refractory to conventional immunosuppressive therapy have also been published[58-61] reporting a significant improvement when polymyxin hemoperfusion was added. Ichiyasu et al[62] reported 3 cases of CADM with RPILD who respond to polymyxin B hemoperfusion after a previous failure of triple combination immunosuppressive therapy (cyclophosphamide pulses, cyclosporine and glucocorticoids), although the anti-MDA5 status is not reported. The same author reported a study of 77 patients diagnosed with RPILD, 41 being treated with polymyxin B hemoperfusion in comparison with 36 from an historical control group. They found a 90-day reduced mortality in the polymyxin group vs the historical group (41.5% vs 66.7%, p=0.019). Half of the patients studied were diagnosed with connective tissue disease, and 12 with dermatomyositis with unknown MDA5 status. All received concurrent immunosuppressive therapy[63]. Moreover, Furosawa[61] published a series of 24 patients with an acute exacerbation of interstitial pneumonia, 12 of them were dermatomyositis, who were negative for anti-MDA5 antibodies. Data reported in this study have shown a better outcome of those patients in whom polymyxin hemoperfusion was performed, although it did not reduce the mortality. Nevertheless, only one out of 5 dermatomyositis patients in whom polymyxin hemoperfusion was performed died in comparison with 6 out of 7 who did not receive this therapy (p=0.045). Therefore, direct hemoperfusion using a polymyxin B-immobilized fiber column after triple standard immunosuppressive therapy, even in patients negative to anti-MDA5 antibodies, may

support, in an indirect way, the usefulness of this technique as a rescue therapy in this clinical setting *(Level of evidence 3)*.

Considering this data, and that a third (5 out of 14, 35%) of RPILD anti-MDA5 positive patients who received polymyxin hemoperfusion as an add-on therapy to the triple immunosuppressive therapy survived, the expert group made a favorable recommendation.

Ten patients treated with plasmapheresis[7, 43, 49, 59, 64] have been identified. All the reported cases included this therapy as additional treatment to triple conventional combined/progressive immunosuppressive schedule. Only 2 patients survived, and one of this received also polymyxin hemoperfusion[59, 64] *(Level of evidence 3)*.

Considering the data reported above, the expert group suggests that plasmapheresis may be included as a part of the schedule approach in patients with anti-MDA5 positive and RPILD.

Intravenous immunoglobulin rescue therapy is usually administered as an adjuvant therapy. A total of 22 patients with anti-MDA5 positive rapidly progressive ILD associated DM were recruited from published case reports, more than half of them (13 out of 22, 59%) were alive at the end of the therapy, which was usually combination of different immunosuppressive drugs and glucocorticoids. Ma X, et al (2016)[29] in a single study reported 7 out of 11 anti-MDA5 positive patients with pneumomediastinum and rapidly progressive ILD. No data on the specific outcome in those 7 patients was reported.

The Expert Panel agreed on that although there is not enough data to support that IVIg are useful as a direct therapy for anti-MDA5 positive rapidly progressive ILD associated DM, it should be considered as a potential useful adjuvant treatment *(Recommendation grade √)*.

***Recommendation 6**: Assistance with extracorporeal membrane oxygenation (ECMO) should be considered in patients with life threatening severe and refractory respiratory insufficiency in order to maintain the patient alive while waiting for a clinical response to intensive and combined immunosuppressive treatment or as a bridge to lung transplantation (Recommendation grade √).*

Extra-corporeal Membrane Oxygenation (ECMO), a method of life support used to oxygenate the blood is a technique aimed to provide prolonged cardiac and respiratory support in those patients with respiratory failure. ECMO assistance can maintain lung and heart function during days or weeks. Nevertheless, it is a complex procedure and consumes high human and technical requirements that only are feasible to be performed in high specialized centers. It is considered the very last therapeutic option when standard therapy had failed, and always as bridge to a definitive solution of the original cause of respiratory failure.

The use of ECMO in refractory anti-MDA5 positive dermatomyositis patients that develop RPILD is absolutely exceptional and has been described in only 4 studies. In a retrospective study[7] reported 6 patients with refractory respiratory failure who received veno-venous ECMO as an organ support and all (100%) of them finally died. Alqatari, 2018[49] y Gorka 2015[65] reported 2 cases that developed a poor outcome and died. However, Broome 2008[66] and Leclair 2018[67] reported the case of a middle-aged man with anti MDA5-associated RPILD refractory to immunosuppressants which was treated with ECMO for 52 days as bridge to successful bilateral lung transplant *(Level of evidence 3)*.

The expert group considers that the use of ECMO as a life support may be effective in anti-MDA5 positive patients who develop RPILD while a complete response to combination immunosuppressive therapy has not yet been achieved or as a bridge to lung transplantation.

***Recommendation 7**: Lung transplantation should be considered as a therapeutic option in patients with refractory RPILD associated to anti-MDA5. Early referral for transplant eligibility assessment is recommended at the time of ILD diagnosis (Recommendation grade √).*

In patients with interstitial lung disease associated with connective tissue disease, lung transplantation is contraindicated at many centers because of the impact of pre-existing conditions on post-transplant outcomes. Potential contributors to poor outcomes include gastroesophageal reflux (thought to cause *bronchiolitis obliterans* syndrome), renal disease (as it complicates management of immunosuppressive and antimicrobial agents commonly used after transplantation), and extra-pulmonary disease such as myositis (which complicates management of immunosuppression and rehabilitation after transplantation and the risk of malignancy association). Less than 1% of all lung transplants worldwide between 1995 and 2015 were given to patients with connective tissue disease associated with lung disease[68]. However, recent studies suggest that post-transplant outcomes in these patients do not differ significantly from those in patients with non-connective tissue disease[69-71].

Data on lung transplantation in anti-MDA5 positive CADM associated RPILD are scarce and limited to case series and reports. Selva-O'Callaghan et al (2005)[72] reported two cases of unsuccessful lung transplantation of undetermined cause in patients with DM-associated RPILD complicated with pneumomediastinum, subcutaneous emphysema and acute alveolar injury. Stored serum samples of these patients at the beginning of the disease were analyzed several years after, being positive for anti MDA 5 antibodies (author personal communication). On the other hand, Shoji T et al (2013)[73] reported a case of bilateral living-donor lobar lung transplantation with uneventful

postoperative course and able to perform daily activities without oxygen seven months postoperatively. More recently, the case reported by Leclair et al (2018)[67] underwent bilateral lung transplantation after prolonged venovenous ECMO, having resumed his normal life with a survival period to date of twelve years in remission *(Level of evidence 3)*.

Therefore, the expert group strongly recommends that patients with ILD associated to antiMDA5 should be referred early to centers with experience in the evaluation and management of lung transplantation in connective tissue diseases.

Other treatment options

Recommendation 8: *Azathioprine, methotrexate and leflunomide are not recommended for the treatment of RPILD associated to anti-MDA5 (Recommendation grade √).*

The evidence about the efficacy and safety of azathioprine in RPILD associated to anti-MDA5 is scarce and results uneven with only five reported cases. Thus, two cases received azathioprine as part of a sequential therapy with non-calcineurin inhibitors immunosuppressants (cyclophosphamide, mycophenolate and rituximab) and did not survive[43, 44]. However, case 5 of the Hoa series *2017*[12] who developed pleural effusion improved after adding azathioprine to glucocorticoid and tacrolimus double therapy. Finally, azathioprine monotherapy plus glucocorticoid resulted in ILD improvement in one case[74] and fatal outcome in another[75] *(Level of evidence 3)*.

Information about the use of methotrexate in anti-MDA5-associated ILD has only been found in seven patients with the non-RP form. In all these cases, methotrexate was used as part of the combined treatment with other immunosuppressants (mycophenolate, hydroxychloroquine, azathioprine, or rituximab). All patients presented a good clinical course without progression of the pulmonary involvement[5, 76]. Both, the scarce number

of patients and the association with other immunosuppressants make difficult to evaluate the real effect of methotrexate in the observed outcome *(Level of evidence 3)*.

Leflunomide has only been evaluated in seven patients with anti-MDA5-associated RPILD[29]. It was used in combination with chinese herbs and other immunosuppressants, including glucocorticoid, cyclophosphamide, calcineurin antagonists, mycophenolate and intravenous immunoglobulins, thus being very difficult to evaluate, in this context, the role of this drug in the fatal outcome of 6 of the 7 patients (85%) *(Level of evidence 3)*.

Taking into account both, the results of all these studies and the clinical experience, the elaborating group considers that azathioprine, methotrexate and leflunomide should not be recommended in the management of RPILD in these cases.

Recommendation 9: Infliximab is not recommended in MDA-5 associated RPILD treatment *(Recommendation grade √)*.

Regarding de use of infliximab in inflammatory myopathy-associated RPILD, only a retrospective case series of fourteen non-MDA5 treated patients in combination with the conventional immunosuppressant therapy has been identified[6]. Ten out of them did have the clinical amyopathic form. All the fourteen patients were initially treated with methylprednisolone combined with cyclophosphamide in seven, mycophenolate in one, tacrolimus in three, cyclosporine in one, methotrexate in another one and immunoglobulins in five. All of them received infliximab at a dose of 5 mg/kg/i.v. at week 0, 2, 6 and every eight weeks. The ten patients (71%) treated in the early phase did have a favorable response while the other four (29%) who received infliximab after the respiratory failure, died *(Level of evidence 3)*.

Despite this data, the expert panel has taken into account the clinical evidence showing that anti-TNF agents may cause serious ILD and, therefore, cannot recommend infliximab use in the therapeutic management of these patients' ILD.

Recommendation 10: *Although pirfenidone has been added to conventional immunosuppressant treatment in CADM-associated subacute interstitial pneumonia with data of pulmonary fibrosis, the expert panel may not recommend its use in patients with RPILD associated to anti-MDA5 (Recommendation grade √).*

Data on the use of antifibrotic agents comes from a prospective study[46] that included 30 patients with CADM-associated RPILD treated with pirfenidone in addition to conventional immunosuppressive treatment (glucocorticoid, cyclosporine and mycophenolate) compared with a historical cohort of 27 patients treated with conventional therapy. In the pirfenidone-treated group, 22/30 patients were MDA5 positive versus 4/27 patients of the control group. Overall, mortality in the pirfenidone-treated group was lower although did not reach statistical significance compared with the control group (36.7% vs. 51.9%, p=0.223). Subgroup analysis in patients with acute ILD (<3 month) (n=30) showed identical mortality for case and control groups (50% vs. 50%, respectively; p=0,386). However, in patients with subacute ILD (3 to 6 month) (n=19), the mortality in pirfenidone-treated patients was lower than that of the control group (90% vs. 44%, p=0,045). Subgroup analysis describing only MDA-5 patients was not performed. No serious adverse events have been described *(Level of evidence 3)*.

Based on all the previous recommendations, the expert panel proposes two flow charts for the diagnosis and treatment (Figures 1 and 2, respectively) of RPILD in patients with anti MDA5 antibodies.

Summary and Conclusions

Medical literature searching discloses a generally poor prognosis and bad outcome in patients with CADM who are positive to anti-MDA5 antibodies and develop a rapidly progressive ILD. The rarity of the syndrome precludes performing randomized clinical trials in order to know which the best treatment for this catastrophic situation will be. These recommendations are based in observational studies, mainly cohort studies and case reports, therefore the level of scientific evidence is not higher than 3. We have completed them summing up the experience of the clinicians from different specialties who participate in the task force (clinical recommendations by the expert panel).

Taking into account these limitations, there is a consensus to treat these patients from the onset with a combination therapy that, besides the glucocorticoids, includes immunosuppressive drugs such as calcineurin inhibitors, and following the experience from Asian cohorts, adding cyclophosphamide as a third drug. Nevertheless, this combination therapy approach did not always suffice for obtaining a good outcome and to date, more than half of the patients develop a fatal course. Then, adding on or switching immunosuppressants could play a role; monoclonal antibodies such as basiliximab, rituximab, or new immunosuppressive drugs such as mycophenolate mofetil or JAK-2 inhibitors (tofacitinib) may be a good option. Moreover, tofacitinib combined with glucocorticoids has recently shown to be a promising therapy in the early stage of anti-MDA5 positive CADM-ILD[77] as the six month survival after ILD onset was significantly higher in tofacitinib-treated patients (18 of 18, 100%) than that of the historical controls who met the same criteria and received conventional therapy (25 of 32, 78%) (p=0.04). Further studies are warranted in order to determine its role in anti MDA5 positive RPILD initial therapy. In addition to the immunosuppressive treatment and given the bad outcome that usually develop these patients, some rescue therapies such as

plasmapheresis, intravenous immunoglobulin or polymyxin B hemoperfusion are also indicated when the patient doesn't behave properly in terms of respiratory failure. Lastly, extracorporeal membrane oxygenation as a strategy to allow time for immunosuppressive therapy to be effective or as a bridge to lung transplantation is an option to take more and more into account.

Future research

Multicenter prospective studies are mandatory to gather enough number of patients that allow performing randomized clinical trials, tuning up definitions of improvement and outcome, and the proper use of reliable biomarkers in order to define the risk strategy and the best therapeutic option at any moment will undoubtedly contribute to the better outcome and improvement of this severe syndrome. On the other hand, a consortium that allows going deeper in the knowledge of the intrinsic mechanisms or epidemiological issues will be of paramount importance for the understanding of this syndrome.

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Table 1. Recommendations for the treatment of anti-MDA5 positive CADM-RPILD*

	Set of Recommendations	RG**
	General management	
1	Patients with CADM-associated rapidly progressive interstitial lung disease anti-MDA5 (+) should be treated with combination therapy as a first option.	D
	Combination therapy	
2	A combination therapy which include glucocorticoids plus a calcineurin inhibitor (cyclosporine A or tacrolimus), or triple therapy adding intravenous cyclophosphamide□ to the previous schedule, are both considered good initial alternatives.	D
2a	Both, cyclosporine A and tacrolimus are considered equally good therapeutic options. The choice of any of them will depend on the safety profile and patients' characteristics.	√
2b	Monitoring of calcineurin inhibitors blood levels are recommended in order to adjust posology and minimize toxicity.	√
3	When calcineurin inhibitors are not feasible, consider combination therapy with glucocorticoids and other immunosuppressive drugs such as cyclophosphamide□ and/or mycophenolate mofetil†, or adding rituximab† to any one of the previous schedules.	D
3a	The choice of one of these drugs will depend on the individual characteristics of the patient and the clinician experience.	√
	Therapy for the refractory patient	
4	In patients with CADM-associated RPILD anti-MDA5 (+) who do not respond to combination therapy with glucocorticoids plus immunosuppressive drugs, clinicians have to take into account the following alternatives:	
	- Adding one of these immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, rituximab, basiliximab or tofacitinib[ĵ]) to the current therapy.	D
	- Change one immunosuppressant for another	√
5	In patients who do not respond to combined immunosuppressive drugs, the use of the following alternative rescue therapies, either separate or in a sequential manner, might be considered:	
	- Polymyxin B hemoperfusion	D
	- Plasmapheresis	D
	- Intravenous immunoglobulins	√
6	Assistance with ECMO should be considered in patients with life threatening severe and refractory respiratory insufficiency in order to maintain the patient alive while waiting for a clinical response to intensive and combined immunosuppressive treatment or as a bridge to lung transplantation.	√
7	Lung transplantation should be considered as a therapeutic option in patients with refractory RPILD associated to anti-MDA5. Early referral for transplant eligibility assessment is recommended at the time of ILD diagnosis.	√

	Other treatment options	
8	Azathioprine, methotrexate and leflunomide are not recommended for the treatment of RPILD associated to anti-MDA5.	√
9	Infliximab is not recommended in MDA-5 associated RPILD treatment	√
10	Although pirfenidone has been added to conventional immunosuppressant treatment in CADM-associated subacute interstitial pneumonia with data of pulmonary fibrosis, the expert panel may not recommend its use in patients with RPILD associated to anti-MDA5.	√

*Level of evidence was 3 in all the recommendations. Avoid its administration in young female or male who are willing to have offspring. † Avoid its administration in women prone to be pregnant due to the risk of fetal embryopathy. ∫ There is not available data on the safety of combined therapy with biologic agents and tofacitinib. Abbreviations: R, Recommendation. RG, Recommendation Grade based on SIGN methodology, see Appendix 1. RPILD, Rapidly Progressive Interstitial Lung Disease. MDA5, Melanoma Differentiation-Associated protein 5. Anti-MDA5, anti-MDA5 antibodies. ECMO, Extracorporeal Membrane Oxygenation.
** Appendix 1.

Table 2. Reported therapies in anti-MDA5 positive CADM associated RPILD

Therapy	Dose, schedule and route of administration
Prednisone/prednisolone[1]	0.5-1 mg/kg/day p.o.
Pulsed methylprednisolone[1]	500 mg-1 gr/day (x3 consecutive days) i.v.
Cyclosporine A[2]	2-5 mg/kg/day p.o. or i.v.
Tacrolimus[3]	0.06-0.075 mg/kg/day p.o.
Cyclophosphamide	0.5-1 gr/m^2/2-4 weeks i.v.
Azathioprine[4]	2-3 mg/kg/day p.o.
Leflunomide[5]	10-20 mg/day p.o.
Methotrexate[6]	Up to 25 mg/week p.o. or s.c.
Mycophenolate mofetil	1-3 g/day p.o.
Basiliximab	20 mg/week (x2) i.v.
Infliximab	5 mg/kg i.v. at week 0, 2, 6 and every 8 weeks
Rituximab	350-375 mg/m^2/week (x2-4) i.v. or 1 gr/2 week (x2) i.v.
Tofacitinib	5 mg b.i.d. p.o.
Pirfenidone	267 mg t.i.d. p.o.
Immunoglobulin	0.4 mg/kg/5 days i.v.
Polymyxin B and plasmapheresis	Hemoperfusion with polymyxin B at a flow rate of 100 ml/h for 3 h/day (x2) and plasmapheresis with 3.5 l of 5% seroalbumin replacement followed by intravenous immunoglobulin

[1] Corticosteroids as initial or induction/rescue therapy. [2] To achieve a trough level of 150-250 ng/mL. [3] To achieve a trough level of 5-10 ng/mL. [4] Depending on TPMT activity. 5 Dose not reported. [6] Not administered in MDA5 associated RPILD. P.o.: per os. i.v.: intravenous. bid: twice in a day. tid: three in a day.

Figure 1. Diagnosis of RPILD in patients with anti MDA5 antibodies.

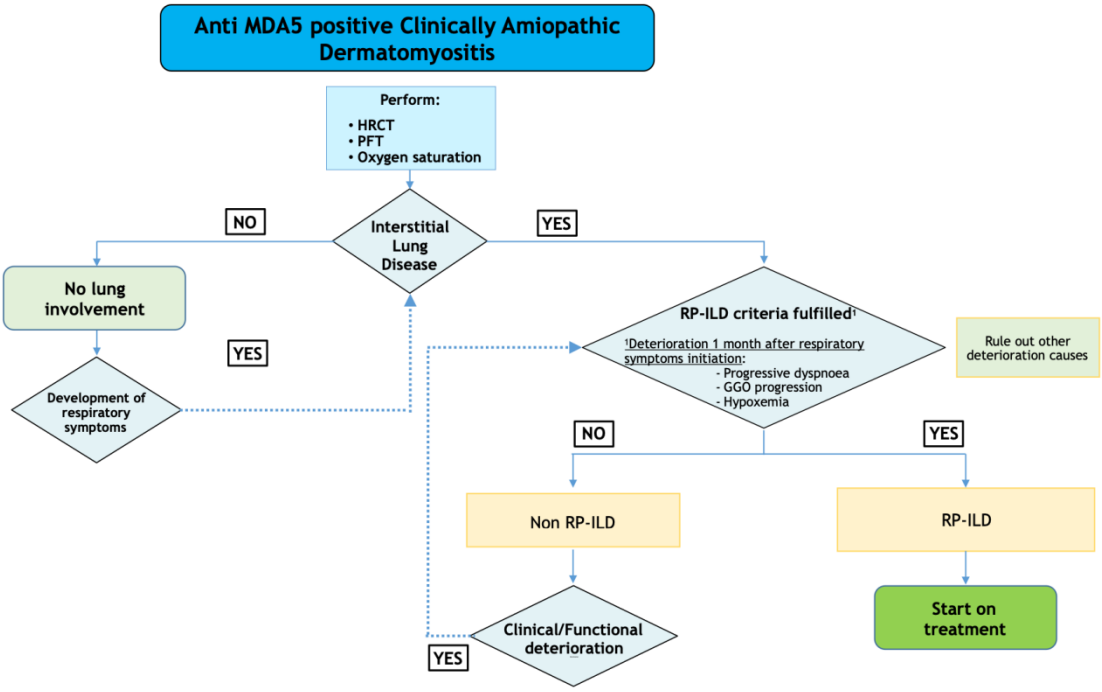
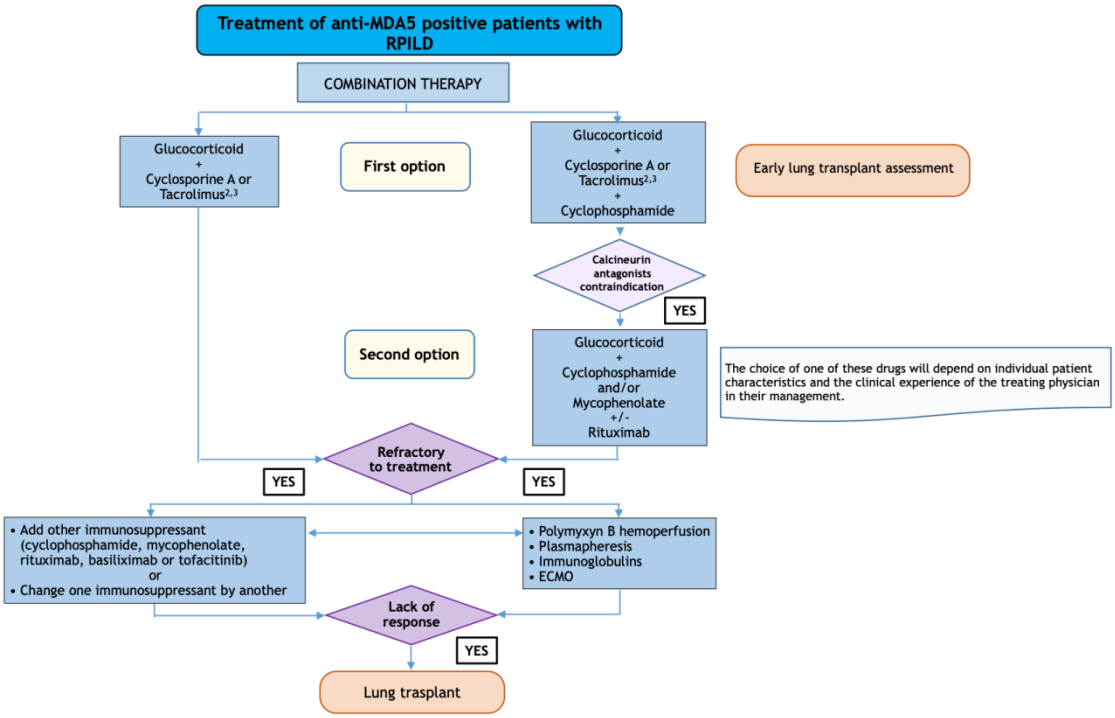


Figure 2. Treatment of RPILD in patients with anti MDA5 antibodies.



Appendix 1. Levels of evidence and grades of recommendation

SIGN Levels of evidence and grades of recommendation[8]

	Levels of evidence
1++	High quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with little risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high bias risk.
2++	High quality systematic reviews of cohort or case-control studies. Cohort or case-control studies with very low risk of bias and with high probability of establishing a causal relationship.
2+	Well conducted cohort or case-control studies with low risk of bias and a moderate probability of establishing a causal relationship..
2-	Cohort or case-control studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies such as case reports and case series.
4	Expert opinion.

Studies classified as 1- and 2- must not be used in the process of developing recommendations due to their high potential for bias.

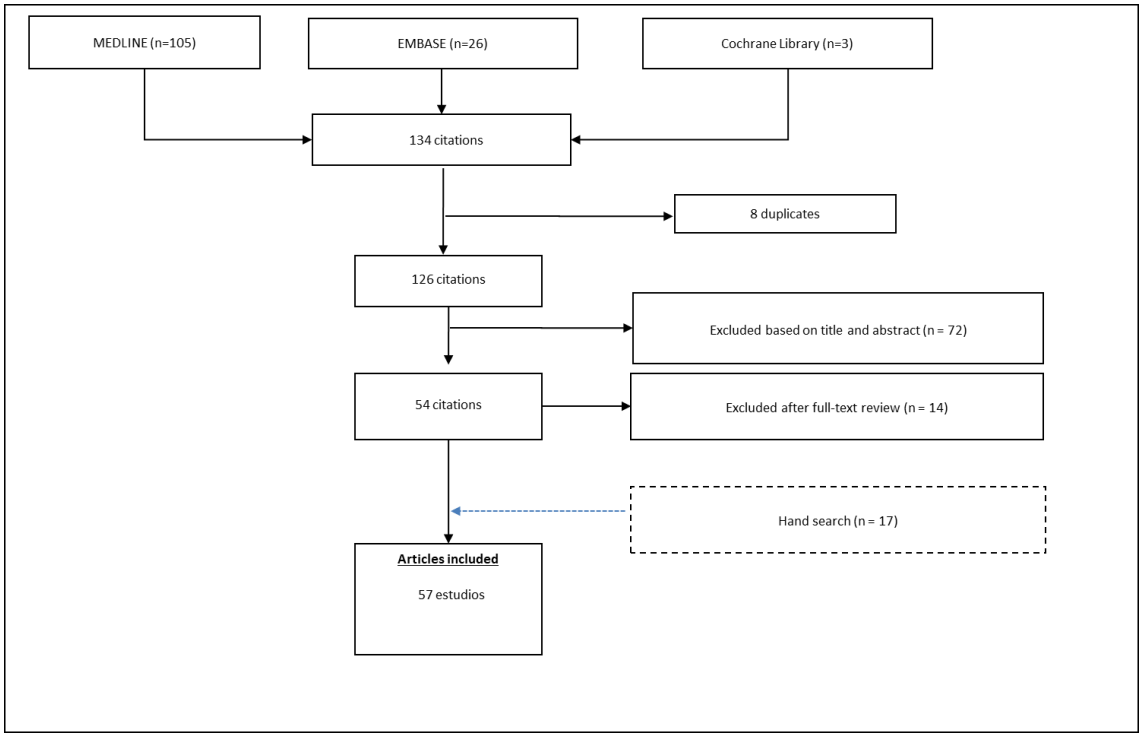
	Grades of recommendation
A	At least one meta-analysis, systematic review or clinical trial rated as 1++ directly applicable to the target population of the guide; or a body of evidence consisting of studies rated as 1+ and showing overall consistency of results.
B	A body of evidence consisting of studies rated as 2++, directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 1++ or 1+.
C	A body of evidence consisting of studies rated as 2+ directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 2++.
D	Evidence level 3 or 4; or evidence extrapolated from studies rated as 2+.

√ [1]	Recommended practice based on clinical experience and the consensus of the editorial team.

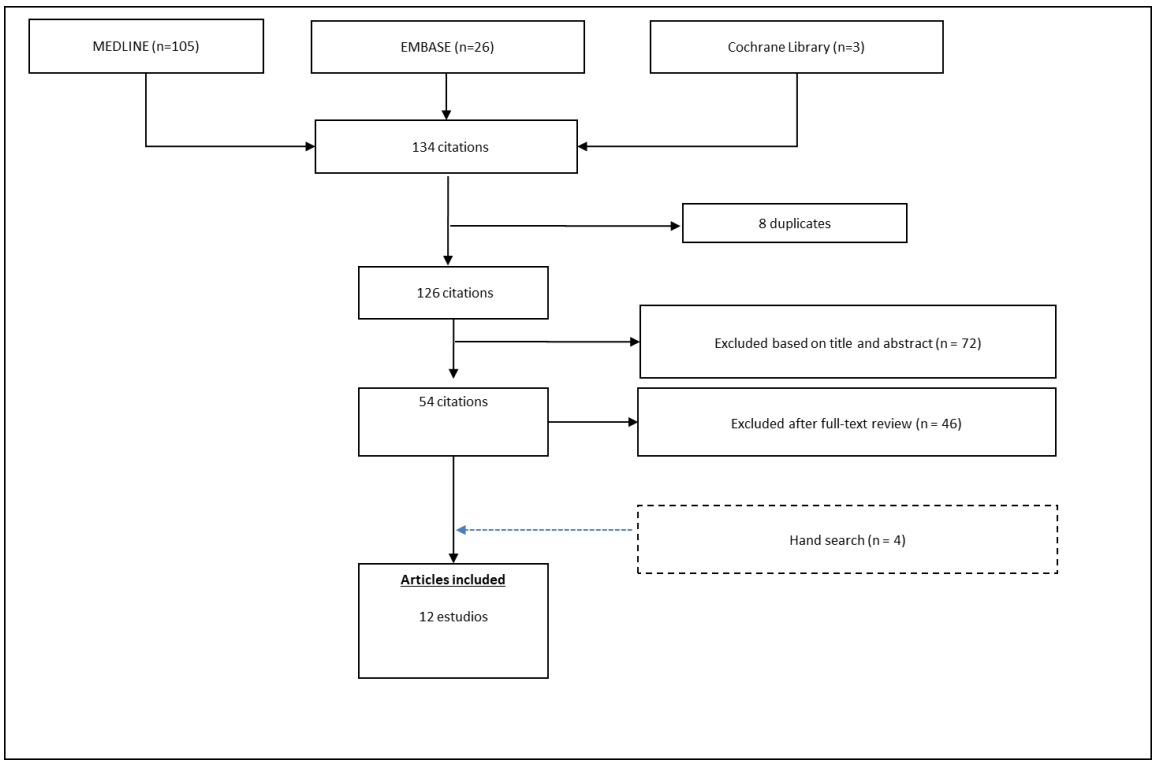
1. At times, the development group finds important practical aspects that must be highlighted and for which no scientific evidence has been found. In general, these cases are related to some aspects of the treatment that nobody would normally question and they are evaluated as points of “good clinical practice”.

Appendix 2. Flow chart with the results of the literature search

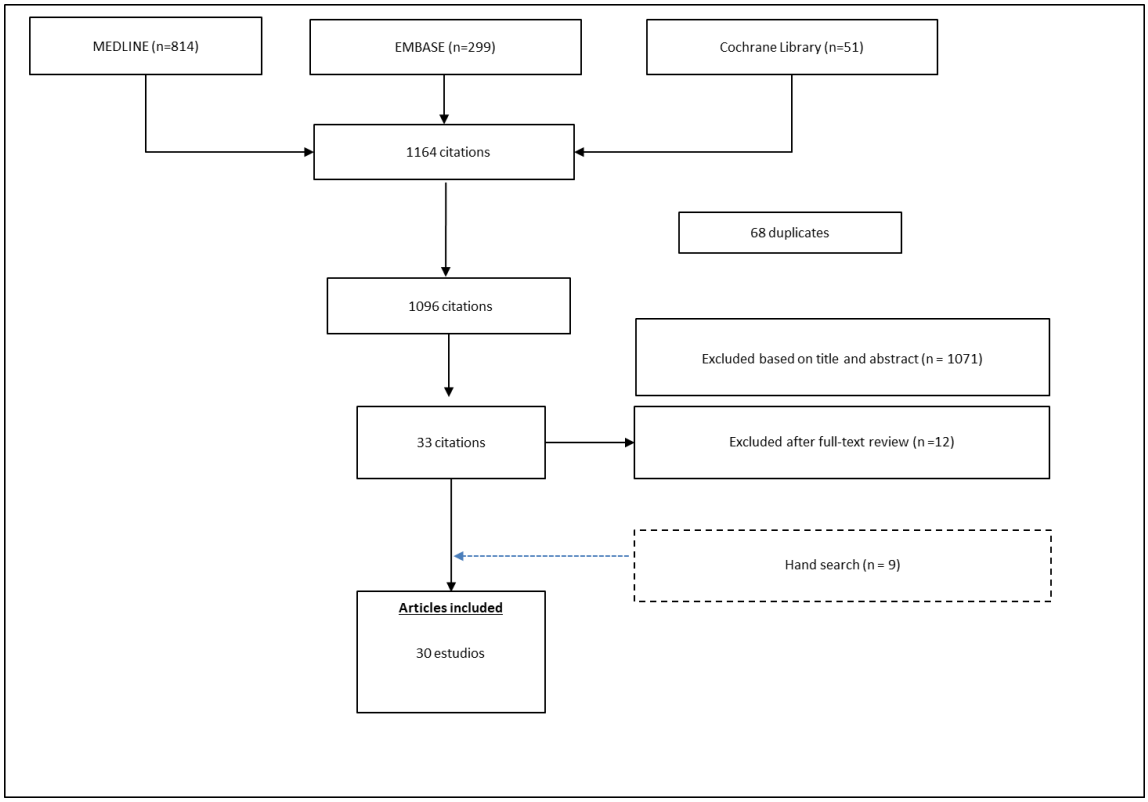
Question 1.



Question 2.



Question 3.



Question 4.