

## **Glossary to be read in conjunction with the flowchart entitled: 'The Investigation, Management and Treatment of Interstitial Lung Disease (ILD) in Patients with Systemic Sclerosis (SSc)'**

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### **Background**

Systemic sclerosis (SSc) is a heterogeneous condition. Up to 65% patients with SSc develop interstitial lung disease (ILD) as seen on HRCT chest scan [Keir, Silver and Wells]. Studies have shown that this usually occurs in the early years; Steen et al reported that a decrease in forced vital capacity (FVC) occurred within 4-6 years of the onset of SSc [Steen 1994]. Severe ILD can be seen in patients with both limited and diffuse cutaneous SSc [Steen; White 2000]. A FVC less than 50% of predicted at baseline is highly predictive of mortality [Assissi Arthritis Rheum 2009]. Pulmonary complications, both ILD and pulmonary arterial hypertension (PAH), are now the main cause of disease-related mortality in patients with SSc [Steen 2007 ann rheum dis],[Tyndal AJ EUSTAR].

These best practice consensus recommendations are to be used in conjunction with the guidelines published by EULAR/EUSTAR and the very comprehensive guidelines published by the British Thoracic Society [Kowal-Bielecka O EULAR],[Wells AU and Hirani N].

We hope these recommendations provide a pragmatic approach to the treatment of ILD in patients with SSc. The working group for these recommendations particularly looked for an evidence base to the following questions:

1. To determine the best protocol for CT imaging of a patient with SSc and suspected ILD;
2. To determine the appropriate baseline (and subsequent investigations) for a patient with SSc and ILD;
3. To determine who to treat with ILD and SSc;
4. To determine the appropriate time to initiate treatment (early versus late);
5. To determine how to define change (either deterioration or improvement) and its effect on treatment in ILD in SSc;
6. To determine if PCP prophylaxis is required when using cyclophosphamide to treat ILD in SSc;
7. To evaluate the effect/safety of oral prednisolone versus IV methylprednisolone when using cyclophosphamide in the treatment of ILD in SSc patients;
8. To determine the role of non-pharmacological measures in the treatment of a patient with ILD and SSc;
9. To determine the role of haematopoietic stem cell transplant in a patient with SSc and ILD and;
10. To determine the role of lung transplant in a patient with ILD and SSc.

### **The Best Practice Consensus Recommendations:**

**1. Identifying patients with ILD** Patients with SSc and ILD are most likely to present to rheumatology or respiratory medicine but may be seen by other specialists e.g. dermatologists.

a. Most patients will present with dyspnoea, a dry cough or reduced exercise tolerance but sometimes patients may be asymptomatic and this should not preclude further investigation.

b. It is important to identify contributing factors that are related to a patient's SSc such as accessory muscle weakness, secondary to myositis, gastro-oesophageal reflux, and sicca symptoms causing xerotrachia that may also be affecting impaired respiratory function in SSc-ILD patients.

**2. The investigation of patients with potential ILD** There is a need to: a) identify if ILD is present; and b) assess the severity including the degree of disease activity (potentially reversible) and degree of damage (irreversible). The following tests are recommended as routine:

a. **Chest Xray (CXR)** A CXR is useful at baseline, although this is an insensitive method for the detection of lung involvement. The CXR may look normal but ILD is evident on a HRCT chest scan [Schurawitzki H]. However, a CXR may show other useful information e.g. a raised hemidiaphragm. Reporting of the CXR by a specialist i.e. thoracic radiologist is preferable.

b. **High resolution CT (HRCT) chest scan**

i. A HRCT chest scan is important in the routine detection & evaluation of ILD in SSc.

ii. SSc-ILD can be detected as a ground glass appearance with pulmonary fibrosis consistent with non-specific interstitial pneumonia (NSIP) pattern. Patients can develop honeycomb change (UIP pattern) [American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias].

iii. CT detection is not based on definitive validation, but has been found over two decades to be clinically useful [Wells Rheumatology 2008]. Reporting by a specialist i.e. thoracic radiologist is preferable. If this is not available, then consider discussing patient at the regional ILD MDT.

iv. Most radiology departments use standard protocols for patients with ILD and use helical CT or interval HRCT (interval HRCT is used more often if patient <40 years as helix CT has higher ionising radiation dose; the conventional HRCT radiation dose is approximately 12 times that of a PA and lateral CXR).

v. More than 90% UK thoracic radiology departments use prone HRCT either routinely to look for fibrosis, if fibrosis is suspected or if considered necessary after review of the supine CT [BSTI

HRCT Survey 2011, personal communication]. Dependent lung atelectasis is recognised to mimic early fibrosis [Swenson], [Aberle et al Radiology], [Aberle et al AJR], [Kashiwabara].

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- vi. HRCT chest scans can detect and assess severity of disease at baseline. ILD should be confirmed on HRCT chest scan before starting treatment.
- vii. There may be problems with comparing repeat scans as the sampling may be of slightly different areas on repeat scans.

A HRCT chest scan should definitely be performed if the patient is symptomatic or if declining lung function tests are observed. There is currently no consensus on whether to perform an HRCT chest scan as a screening test in all SSc patients versus only those who are symptomatic [Wells 2008] but this consensus group decided the following:

**Recommendation 1: Performing an HRCT chest scan at the time of presentation is strongly recommended as routine by this consensus group.**

- c. **Pulmonary/Lung function tests (PFTs)** should include at least spirometry and diffusing capacity of the lung (DLco). DLco should be corrected for haemoglobin at the time of the test (uncorrected low haemoglobins will produce a falsely low DLco).

NB Lung function tests are subject to variability e.g. within each assessment and between assessments due to variability of the equipment, varying proficiency of the technician and varying motivation of the patient [Millar et al]. The laboratory should be accredited and calibrate its equipment regularly as per national guidelines.

Forced vital capacity (FVC) has been validated as an outcome measure in a number of studies of ILD, including the two randomised, placebo controlled trials in SSc-ILD, the Scleroderma Lung Study (SLS) [Tashkin et al] and the FAST study [Hoyle et al]. In the SLS study, change in FVC correlated with parallel changes in the Mahler's transition dyspnoea index (TDI) [Khanna et al 2007] and with change in reticulation or 'fibrosis' score on CT [Goldin J et al].

Some PFT laboratories perform FVC and some a relaxed VC (RVC). Patients with significant ILD may find it difficult to perform FVC and experience distress/coughing during the assessment and thus giving a falsely low reading. So that a change in lung function can be monitored, it is important that a laboratory is consistent in which measurement it performs i.e. RVC or FVC.

Also of note some patients may initially have supranormal volumes e.g. 120% predicted, so a fall to 80% predicted would be significant in these patients.

DLco is a sensitive marker of ILD but also reflects pulmonary vascular impairment e.g. due to PAH, which is often present in SSc. The DLco

may therefore be disproportionately lower compared with a reduction in lung volumes.

Worsening of breathlessness in the context of stable or minor changes in lung function suggests the need for further assessment to exclude other causes of breathlessness including lower respiratory tract infection, pulmonary hypertension, a pulmonary embolus, pulmonary oedema/cardiac dysfunction, aspiration due to gastro-oesophageal reflux (see gastro-intestinal best practice recommendations), lung cancer, chest wall restriction and musculoskeletal changes, which may increase the work of breathing.

- d. **ECHO** – if the estimated pulmonary arterial systolic pressure (PASP) is greater than 50 mm Hg, or the patient is thought to have possible pulmonary hypertension and the estimated PASP is 40-50mm Hg, then the patient should be referred to the local PAH service for consideration of a right heart catheter to look for PAH (see SSc and PAH best practice recommendations).
- e. **Autoantibody testing** See flowchart
- f. **O<sub>2</sub> saturation**- look for desaturation on exercise, consider overnight oximetry. Of note, consideration should be given to the reliability of readings in SSc patients when using a finger probe in view of the frequent problems with peripheral circulation i.e. the presence of Raynaud's. Probes for the forehead can be used as an alternative.
- g. **6 minute walk test (6MWT)** – it is useful to perform this test at baseline so that a comparison can be made at a later date to help assess the significance of a decrease in lung function tests. Oxygen desaturation during the test is a good indicator of significant disease. A desaturation to less than 80% suggests cardio-pulmonary involvement.

**The following tests can be considered and are appropriate in some cases but are not recommended as routine:**

- a. **Lung biopsy** – This rarely adds diagnostic or prognostic information in the setting of SSc-ILD, and is associated with potential complications. Therefore it is rarely performed in SSc patients (usually only when a wide differential diagnosis remains for the cause of ILD) and only after discussion at a regional ILD MDT meeting to determine if it will be clinically useful. If a lung biopsy is indicated, then the HRCT chest scan should be used for guidance regarding the site to biopsy and more than 1 biopsy is recommended.
- b. **Bronchoalveolar lavage (BAL) and induced sputum** – These tests add very little to prognostic information. However a relatively high rate of infection has been described in patients with SSc-ILD so if infection needs to be excluded and there is no spontaneous expectoration, then induced sputum and BAL may be useful.
- c. **Exhaled NO** – There is currently insufficient evidence for use of eNO in routine practice.

### 3. Management of patients with ILD

#### a. Monitoring

- i. **SSc-ILD patients can be allocated to the following groups:**
  - 1) active/progressive disease that needs treating;
  - 2) very careful watching for suggestion of deterioration;
  - and 3) routine surveillance.
- ii. **Surveillance** – annual lung function should be performed but more frequent tests e.g. 4-6 monthly are indicated if:
  - 1) patient is developing loss of lung volume and/or a fall in transfer factor;
  - 2) patient becomes breathless or develops a persistent cough, patient has evidence of extensive disease on HRCT chest scan (i.e. >20% involvement of lungs) [Goh et al]; or
  - 3) patient on immunosuppressive treatment for SSc-ILD. Patients of particular concern are those in whom the (F)VC has dropped by more than 10% and/or DLco has dropped by more than 15% compared with baseline values.
- iii. **The role of the ILD MDT meeting** – these should include respiratory physicians, thoracic radiologists, pathologists, cardiothoracic surgeons, rheumatologists with an interest in connective tissue diseases, nurse specialists and the palliative care team. The meetings provide an ideal forum where SSc-ILD patients can be discussed. These meetings can occur at a local level but some patients may need to be discussed at a tertiary referral centre.
- iv. SSc-ILD patients require an annual ECHO to **monitor** for new onset PAH.

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#### b. Who to treat

**Active (progressive and/or extensive) disease** Treatments are sometimes offered late in the disease course and treatment response is consequently often poor [Saketkoo J of Rheum 2011]. Early versus late treatment is now proven to be of benefit in several rheumatological conditions e.g. rheumatoid arthritis, SLE and vasculitis. This analogy is probably applicable to patients with SSc-ILD. thus patients should be considered for treatment as early as possible as there may be a window of opportunity, when disease is most active and potentially reversible before damage has occurred and the changes are irreversible. Indicators of active disease may be rapidly progressive decline in lung function e.g. falling (F)VC by a clinically meaningful value i.e. >10% per annum/or compared with baseline values (95% chance the change is real) and/or > 15% fall DLco per annum/or compared with baseline values (95% chance the change is real) [Pellegrino R], or changes on the HRCT chest scan e.g. extensive disease on HRCT chest scan affecting  $\geq 20\%$  lungs.

It is good to decide a priori when to treat i.e. what will be the 'progression threshold' e.g. X% fall in lung function over a defined period of time. Predictors of worsening from SLS-I study were FVC%  $\leq$  70% and/or of fibrosis on baseline HRCT scan [Tashkin]. Similar findings were also reported by Goh et al [Goh 2008]. If it is not clear that a patient has active disease that needs treating, then repeat lung function tests are indicated in 4 months to provide a comparison.

- c. **The treatment** Therapy needs to be targeted to the individual patient i.e. the same prescribed course of treatment will not be adequate/appropriate for everyone. The potential risks versus benefits need to be fully discussed with patients. The aim of treatment should be improvement, or at least stabilisation of lung function. IV cyclophosphamide is often used for induction and then mycophenolate mofetil as maintenance therapy. Close monitoring is required to assess response and detect potential toxicity. IV cyclophosphamide is potentially toxic and is classified as a chemotherapy agent and should be given according to national guidelines e.g. it has to be administered by chemotherapy trained nurses [chemotherapy]. The presence of ILD may be just one manifestation of several e.g. worsening skin thickening, inflammatory myositis, that may sway the physician to consider treatment with IV cyclophosphamide.

Two randomised controlled trials have been performed using cyclophosphamide in SSc-ILD patients: the Scleroderma lung study -1 (SLS-1) [Tashkin] and the FAST study [Hoyles]. EULAR/EUSTAR guidelines recommend 'cyclophosphamide should be considered for the treatment of SSc-related ILD'.

### 1. Immunosuppression

#### a. Examples of induction protocols

- i. IV cyclophosphamide 15mg/kg 3-4 weekly for 6 pulses but reduce pulse dose in elderly (over 70 years) and in patients with renal impairment to 10 mg/kg. The HRCT chest scan and pulmonary function tests should be repeated after 6 pulses to determine if there is improvement, stabilisation or further decline and thus inform the next stage of treatment. Sometimes high dose IV cyclophosphamide (e.g. 22.5 mg/kg for 4 pulses) is tried in very severe disease and if the patient has not responded to the usual induction regimen, however the patient will be more at risk of significant neutropenia. There is evidence in other connective tissue diseases of oral cyclophosphamide causing more toxicity e.g. infections and leucopenia [Adu], [Yee].

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**Recommendation 2: If cyclophosphamide is indicated for the treatment of SSc-ILD, then the IV route of administration is recommended. Oral cyclophosphamide is not recommended by this consensus group.**

ii. Mycophenolate mofetil (MMF) 500 mg daily increasing to 2g per day in two divided doses over 2 – 4 weeks. Sometimes the dose is increased to 3g/day.

**b. Maintenance therapy**

The following are potential treatment options:

MMF (aiming for 2g per day and sometimes 3g per day in severe cases);

azathioprine (aiming for 2.5mg/kg/day provided no known potential risk of bone marrow suppression i.e. TPMT test suggests normal homozygote); or

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IV cyclophosphamide at less frequent intervals e.g. 6-12 weekly but one needs to be aware of the cumulative dose and potential increased risk of long term toxicity with a cumulative dose of 30g or more of cyclophosphamide.

Pulmonary function tests will need to be performed at regular intervals e.g. 4-6 monthly to ensure stabilisation is maintained. If there is deterioration, then there may need to be escalation of treatment.

On discontinuation of immunosuppression, a deterioration in lung function has sometimes been observed [Griffiths et al, Tashkin]

**c. Corticosteroids** - any use of corticosteroids requires very careful monitoring of renal function – serum creatinine, blood pressure and urine dipstick (including urine protein creatinine ratio if dipstick positive for protein) to detect potential renal crisis at a very early stage.

The effectiveness of corticosteroids in combination with cyclophosphamide for the treatment of ILD in SSc patients is inconclusive. The two published RCTs used oral corticosteroids, some observational studies have used IV methylprednisolone and some studies have used cyclophosphamide alone.

Adverse events do not appear to be more frequent when using corticosteroids in combination with cyclophosphamide.

Oral prednisolone (less than 20mg once daily) or IV methylprednisolone (up to 10mg/kg) with pulses of IV cyclophosphamide are used by different centres in the UK.

**d. Consider co-prescription of the following drugs when using cyclophosphamide:**

**proton pump inhibitors**, especially if patient has oesophageal reflux and using corticosteroids;

**mesna** is used by many centres when patients are receiving IV cyclophosphamide to reduce the risk of haemorrhagic cystitis. An example of a protocol is as follows: 400 mg mesna taken orally 1 hour before the start of the cyclophosphamide infusion and then 2 more doses are taken 2 hours and 6 hours after completing the infusion.

**bone prophylaxis** use according to local/national guidelines but particularly consider if using concomitant corticosteroids;

**PCP prophylaxis** - now known as pneumocystis jiroveci, formerly pneumocystis carinii. There are no RCTs, only case series and observational data, to guide recommendations in SSc patients who are receiving cyclophosphamide. The BSR guidelines for use of IV cyclophosphamide and corticosteroids in ANCA-associated vasculitis recommend use of co-trimoxazole 960 mg three times per week. Some centres within the consensus group use co-trimoxazole but the consensus of the group was that PCP incidence appeared to be very low in SSc-ILD patients who were receiving IV cyclophosphamide.

low dose of an **ACE inhibitor** e.g. lisinopril 2.5 mg daily, especially if a patient has diffuse disease and is receiving IV methylprednisolone with the aim to potentially reduce the risk of renal crisis is used by some centres but there is no universal consensus on this. Some data suggests that prior use of ACE inhibitors may make them less effective if a patient develops a renal crisis [reference- 3 observational studies]. The key fact may be that hypertension, even borderline hypertension, needs to be treated aggressively if corticosteroids are being contemplated or perhaps in this scenario corticosteroids should be avoided.

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#### e. Research therapies/studies

##### **Haematopoietic Stem cell transplantation (HSCT)**

HSCT has been shown to result in a rapid and sustained improvement of skin thickening, improvement of (F)VC and HRCT chest scan abnormalities, but not DLco, in several phase 1-2 trials including a recent small randomised, controlled trial [ASSIST].

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Unpublished data from the phase 3 ASTIS-trial demonstrate a survival benefit for diffuse cutaneous SSc (dcSSc) patients treated with HSCT when compared to those treated with IV cyclophosphamide [van Laar et al, EULAR 2012 late-breaking abstract] with effects of HSCT on skin thickening and lung function (VC but not DLCO) also being superior [ACR 2012 late-breaking abstract].

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All studies on HSCT in SSc have involved autologous PSCT but there was heterogeneity in the mobilisation/conditioning protocols, eligibility criteria (not all had lung disease), duration of follow up and endpoints used. There have been several reports of cardiopulmonary toxicity from conditioning (probably total body irradiation or ATG-related).

HSCT may be considered for poor-prognosis dcSSc patients including those with mild to moderate interstitial lung disease.

**Scleroderma Lung Study 2:** a multicentre RCT comparing oral cyclophosphamide for one year followed by placebo for one year versus mycophenolate for 2 years is underway in the USA.

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**Rituximab:** no RCT data in SSc-ILD, only observational studies with variable results.

**Anti-fibrotic drugs** e.g. pirfenidone, NICE appraisal determination for idiopathic pulmonary fibrosis published in March 2013 but limited data available in patients with SSc.

**Drugs that have previously been tested but found to be ineffective include:** penicillamine, the anti-TNFs and bosentan

**Monitoring the effect of treatment** Using descriptors being developed for CTD-ILD RCTs e.g. 'lack of damage', 'stabilisation', 'no deterioration', 'time to clinical worsening' [Saketkoo J of Rheum 2011].

**2. Best supportive care/MDT Treatment** - all patients with ILD should be offered best supportive care (BSC) [Wells and Hirani 2008], in addition to any disease targeted therapies. BSC is a proactive approach including patient information and support, symptom directed treatments and early palliative therapies. BSC should also include avoidance, dose reduction or withdrawal of therapies that do harm with no perceivable benefit. BSC in SSc-ILD should also address smoking cessation support, pulmonary rehabilitation, nutritional support, oxygen therapy and influenza/pneumococcal vaccination.

**Education and support** From the time of diagnosis patients should be offered tailored, clear and accurate information regarding the diagnosis, treatment options and prognosis [Wells and Hirani 2008]. This includes appropriate written information such as patient information leaflets [Raynaud's and Scleroderma Association, Scleroderma Society and our leaflet].

Patients should have regular review and access to the multidisciplinary clinical team which should include a Nurse Specialist "key worker". The anticipated role of the Nurse Specialist would include ensuring all aspects of best supportive care and palliative care continue to be addressed as well as being involved in ongoing review of the patients and interaction with the patients, their families and carers.

**Oxygen** Long term oxygen therapy (LTOT) has been recommended for patients with interstitial lung disease who have resting hypoxaemia. It is recommended that the same criteria used for patients with COPD i.e. persisting resting hypoxaemia ( $\text{PaO}_2 < 7.3\text{kPa}$  on air, or below  $8.0\text{kPa}$  with clinical evidence of pulmonary hypertension) are followed. LTOT should be prescribed for at least 16 hours per day [Wells & Hirani 2008].

Ambulatory oxygen may be appropriate for patients with LTOT who remain active outside the home and for individuals who demonstrate exertional desaturation and are demonstrated to be less breathless/have improved exercise capacity on formal ambulatory oxygen testing. Short burst oxygen therapy may be suitable for patients who demonstrate hypoxia but do not require LTOT or ambulatory oxygen. Patients with established SSc-ILD should therefore be screened for exertional hypoxaemia and be assessed for ambulatory and short burst oxygen therapy. Ideally this should be by a specialist oxygen assessment service.

**Smoking** A recent retrospective cohort study of Canadian patients [Hudson 2011] with SSc confirmed smokers to have more respiratory symptoms and impaired lung function though did not specifically comment on the prevalence of SSc-ILD. Smokers in this study demonstrated increased Raynaud's, digital ulceration and increased gastro-oesophageal reflux symptoms as well as respiratory symptoms leading the authors to conclude that smoking cessation in patients with SSc should be prioritised. All patients with SSc-ILD should be offered opportunistic smoking cessation advice from healthcare professionals and this advice should be recorded in the case notes. All smokers should have access to specialist smoking cessation

services including the prescription of nicotine replacement therapy, bupropion and varenicline.

**Palliative care** It is important that symptomatic patients with SSC-ILD have their symptoms palliated. This will require the involvement of the clinical team as well as specialist palliative care services. It is important that the clinical team, patients and their carers do not view palliative care as being confined to end of life care. The model best suited to the management of SSC-ILD is that involving individualised integrated palliative care [Lanken 2008]. In this model the patient receives palliative care from the outset of symptoms and concurrently with disease centred management. The intensity of palliative care increases/decreases to reflect the needs of the patient and their carers, often increasing towards the end of life. Symptoms, including breathlessness, cough, fatigue, depression and anxiety should be actively managed.

**Recommendation 3: All patients with SSC-ILD should be offered best supportive care in addition to disease targeted therapies.**

### 3. Lung transplantation

SSC-ILD and/or SSC-PAH are rare indications for lung transplant in international registries (account for 0.5% transplants performed). The multi-systemic nature of SSC can affect early and late post transplant outcomes but acceptable post transplant outcomes have been identified for SSC patients, when compared to patients with IPF or iPAH regarding lung function, morbidity and mortality rates. A successful transplant can be life-changing but the process can be emotionally draining. Careful patient selection is therefore required and it is emphasised that patients are assessed on an individual basis. .

**The following are disease-specific criteria used for consideration of lung transplantation:**

severe ILD (FVC < 40% predicted, DLco < 40% predicted). Patient has received maximum medical therapy;

oxygen dependent, 6MWD desaturation less than 88%;

a careful assessment for gastro-intestinal (particularly for gastro-oesophageal reflux and malabsorption), renal, cardiac and dermatological manifestations (modified Rodnan skin score  $\leq 2$  is required on the chest wall). Active digital ulceration, particularly with breakdown or necrosis which carries a risk of severe infection, an active vasculitic process, progressive myopathy or neuropathy, or multiple digital amputations are contra-indications to transplantation.

**The following are relative contra-indications:**

extra-pulmonary organ failure (cardiac, renal, liver);

creatinine clearance of < 50 mls/min/ m<sup>2</sup> ;

age >65 for single lung transplant, age > 60 for bilateral lung transplant, age > 55 for heart-lung transplant;

severe obesity (BMI > 30 kg/m<sup>2</sup>) or low BMI < 18 kg/m<sup>2</sup>; and

severe or symptomatic osteoporosis.

#### **4. Research agenda**

There are many unanswered questions in the management and treatment of patients with SSc and ILD. These are some of the areas identified by the group for further assessment:

1. RCT to compare the effectiveness and safety of oral prednisolone versus IV methylprednisolone versus placebo in patients receiving IV cyclophosphamide
2. RCT comparing the effectiveness of treating patients as soon as ILD detected versus those whose FVC has dropped by 10% and /or DLco by 15%
3. To evaluate the effectiveness of targeted IV cyclophosphamide to stabilise/improve and then maintenance with MMF in patients with evidence of worsening on lung function tests
4. To compare the use of VC versus FVC
5. To look at the impact of pulmonary rehabilitation on this group of patients

We have established a network of centres to participate in RCTs comparing novel therapies in this group of patients.

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